Clinical trial results:
Immunogenicity and Safety Study of a Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13) at 3, 5, 11 to 12 Months of Age in Healthy Infants in Europe.

Summary

EudraCT number	2012-001054-26
Trial protocol	SE FI
Global end of trial date	10 January 2014

Results information

Result version number	v1 (current)
This version publication date	08 February 2016
First version publication date	14 February 2015

Trial information

Trial identification

Sponsor protocol code	A3L38

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1122-2235

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43, emmanuel.feroldi@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43, emmanuel.feroldi@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001201-PIP01-11
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	12 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the Hexaxim vaccine to the licensed Infanrix hexa vaccine, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates to all antigens contained in both investigational and control vaccines, 1 month after a 2+1-dose schedule.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Prevenar 13 was co-administered with both the investigational and control vaccines in order to document the concomitant administration with the investigational vaccine as compared to its co-administration with the licensed vaccine.

Evidence for comparator:

Infanrix hexa was chosen as the comparator vaccine as it was the only licensed hexavalent vaccine in Europe at the time of study start and was licensed but not used in Sweden and Finland.

Actual start date of recruitment	01 November 2012
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	Sweden: 43
Country: Number of subjects enrolled	Finland: 511
Worldwide total number of subjects	554
EEA total number of subjects	554

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	554

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 01 November 2012 to 12 March 2014 in 11 centers in Finland and 2 centers in Sweden.

Pre-assignment

Screening details:

A total of 546 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Neither the Investigator, the subject's parent(s)/legally representative(s), nor the Sponsor knew the vaccine administered. The product preparation and administration, and the assessment of safety were performed by 2 different individuals in separate rooms. The Investigator or delegate included subjects and evaluated the immediate safety post- vaccination. The nurse/vaccinator prepared and administered the vaccine in a separate room and had sole access to the product accountability forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	DTaP-IPV-HB-Hib+Prevenar 13

Arm description:

Subjects who received 3 doses of DTaP-IPV-HB-Hib vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.

Arm type	Experimental
Investigational medicinal product name	Hexaxim
Investigational medicinal product code	DTaP-IPV-HepB-PRP-T
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular injection into the anterolateral area of the right thigh, 3 doses at 3, 5, and 11 to 12 months of age.

Arm title	Infanrix hexa+Prevenar 13

Arm description:

Subjects who received 3 doses of Infanrix hexa vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.

Arm type	Active comparator
Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection, Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular injection into the anterolateral area of the right thigh, 3 doses at 3, 5, and 11 to 12 months of age.

Number of subjects in period 1[1]	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13
Started	271	275
Completed	266	267
Not completed	5	8
Consent withdrawn by subject	4	6
Adverse event, non-fatal	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects enrolled at baseline (N=546) represents subjects who were vaccinated at V01 and included in the Full Analysis Set.

Baseline characteristics

Reporting groups	
Reporting group title	DTaP-IPV-HB-Hib+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of DTaP-IPV-HB-Hib vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	
Reporting group title	Infanrix hexa+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of Infanrix hexa vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	

Reporting group values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13	Total
Number of subjects	271	275	546
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	271	275	546
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: days			
arithmetic mean	89.6	89	
standard deviation	± 3.2	± 3	-
Gender categorical			
Units: Subjects			
Female	130	142	272
Male	141	133	274

End points

End points reporting groups

Reporting group title	DTaP-IPV-HB-Hib+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of DTaP-IPV-HB-Hib vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	
Reporting group title	Infanrix hexa+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of Infanrix hexa vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	

Primary: Percentage of Subjects with Seroprotection or Vaccine Response Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects with Seroprotection or Vaccine Response Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)[1]

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a diphtheria micrometabolic inhibition test; Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay; Anti-Polio types were measured by neutralization assay; Anti-hepatitis B (Hep B) Ab were measured by the VITROS ECi/ECiQ Immunodiagnostic System; and Anti-polyribosyl ribitol phosphate (PRP) Ab were measured using a Farr-type radioimmunoassay. Seroprotection was defined as Anti-Diphtheria and anti-Tetanus Ab concentrations ≥ 0.1 international units (IU)/mL, Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil), Anti-Hep B Ab concentrations ≥ 10 mIU/mL, and Anti-PRP Ab concentrations ≥ 1 µg/mL. Vaccine response for PT and FHA was defined as Post-Dose 3 Ab concentrations ≥ 4 × Lower Level Of Quantitation (LLOQ), if pre-Dose 1 Ab concentrations < 4 × LLOQ; Post-Dose 3 Ab concentrations ≥ pre-Dose 1 Ab concentrations, , if pre-Dose 1 Ab concentrations ≥ 4 × LLOQ.

End point type	Primary

End point timeframe:

1 month post-Dose 3

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria	100	99.2		
Anti-Tetanus	100	100		
Anti-PT	98	99.6		
Anti-FHA	100	99.6		
Anti-Polio 1	100	100		
Anti-Polio 2	100	100		

Anti-Polio 3	99.6	99.6		
Anti-Hep B	96.4	99.6		
Anti-PRP	93.5	85.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Vaccine Antibodies' Titers Before and After Dose 3 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Summary of Vaccine Antibodies' Titers Before and After Dose 3 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a diphtheria micrometabolic inhibition test (MIT); Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay (ELISA); Anti-hepatitis B (Hep B) Ab were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System; and Anti-polyribosyl ribitol phosphate (PRP) Ab were measured using a Farr-type radioimmunoassay. The following Ab criteria were applied: Pre-Dose 3 for Anti-Diphtheria and Anti-Tetanus (≥0.01 IU/mL), Anti-PT and Anti-FHA (≥4 EU/mL), Anti-Hep B (≥100 mIU/mL), and Anti-PRP (≥0.15 µg/mL) and Post-Dose 3 for Anti-Diphtheria and Anti-Tetanus (≥0.01 IU/mL), Anti-PT and Anti-FHA (≥4 EU/mL), Anti-Hep B (≥100 mIU/mL), and Anti-PRP (≥0.15 µg/mL).

End point type	Secondary

End point timeframe:

Pre- and Post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria; Pre-Dose 3	98.3	97.5		
Anti-Diphtheria; Post-Dose 3	100	99.6		
Anti-Tetanus; Pre-Dose 3	100	100		
Anti-Tetanus; Post-Dose 3	100	100		
Anti-PT; Pre-Dose 3	99.6	99.2		
Anti-PT; Post-Dose 3	100	100		
Anti-FHA; Pre-Dose 3	100	100		
Anti-FHA; Post-Dose 3	100	100		
Anti-Hep B; Pre-Dose 3	45.2	80.5		
Anti-Hep B; Post-Dose 3	91.2	98		
Anti-PRP; Pre-Dose 3	50.6	40.8		
Anti-PRP; Post-Dose 3	99.6	98.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Seroconversion or Booster Response to Pertussis Toxoid and Filamentous Hemagglutinin Antibodies After Vaccinations with DTaP-IPV-Hep B-PRP-T Vaccine or Infanrix hexa™ Administered With 13-Valent Pneumococcal Conjugate Vaccine

End point title	Percentage of Subjects with Seroconversion or Booster Response to Pertussis Toxoid and Filamentous Hemagglutinin Antibodies After Vaccinations with DTaP-IPV-Hep B-PRP-T Vaccine or Infanrix hexa™ Administered With 13-Valent Pneumococcal Conjugate Vaccine

End point description:

Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay (ELISA). Seroconversion for PT and FHA was defined as follows: ≥ 4-fold Ab concentrations increase from pre-Dose 1 (V01) to post-Dose 3 (V05). Booster response for PT and FHA was defined as Post-Dose 3 Ab concentrations ≥ 4-fold rise if pre-Dose 3 Ab concentrations < 4x LLOQ; Post-Dose 3 Ab concentrations ≥ 2-fold rise if pre-Dose 3 Ab concentrations ≥ 4x LLOQ.

End point type	Secondary

End point timeframe:

Post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Percentage of subjects				
number (not applicable)				
Anti-PT; Seroconversion	94.3	95.5		
Anti-PT; Booster response	94	99.2		
Anti-FHA; Seroconversion	97.6	94.2		
Anti-FHA; Booster response	96.6	95.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies Against Vaccine Antigens Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Vaccine

	Antigens Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a diphtheria micrometabolic inhibition test (MIT); Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay (ELISA); Anti-Polio types 1, 2, and 3 were measured by neutralization assay; Anti-hepatitis B (Hep B) Ab were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System; and Anti- polyribosyl ribitol phosphate (PRP) Ab were measured using a Farr-type radioimmunoassay.

End point type	Secondary

End point timeframe:

Pre- and Post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria; Pre-Dose 3	0.08 (0.069 to 0.092)	0.053 (0.046 to 0.06)		
Anti-Diphtheria; Post-Dose 3	1.7 (1.54 to 1.87)	1.2 (1.07 to 1.34)		
Anti-Tetanus; Pre-Dose 3	0.129 (0.114 to 0.146)	0.167 (0.149 to 0.188)		
Anti-Tetanus; Post-Dose 3	2.23 (2.01 to 2.47)	2.37 (2.16 to 2.6)		
Anti-PT; Pre-Dose 3	20.5 (18.8 to 22.5)	23.7 (21.5 to 26)		
Anti-PT; Post-Dose 3	90.9 (84.9 to 97.4)	129 (119 to 139)		
Anti-FHA; Pre-Dose 3	30.6 (28.3 to 33.1)	28.7 (26.3 to 31.4)		
Anti-FHA; Post-Dose 3	148 (138 to 158)	167 (155 to 179)		
Anti-Polio 1; Pre-Dose 3	15.8 (12.8 to 19.4)	27.3 (22.4 to 33.3)		
Anti-Polio 1; Post-Dose 3	1749 (1494 to 2047)	3279 (2869 to 3746)		
Anti-Polio 2; Pre-Dose 3	14.1 (11.5 to 17.2)	22.4 (18 to 27.8)		
Anti-Polio 2; Post-Dose 3	1729 (1454 to 2058)	2954 (2520 to 3462)		
Anti-Polio 3; Pre-Dose 3	15.7 (12.8 to 19.1)	20.9 (17.4 to 25)		
Anti-Polio 3; Post-Dose 3	1213 (1005 to 1463)	1906 (1594 to 2279)		
Anti-Hep B; Pre-Dose 3	76.5 (62 to 94.4)	260 (218 to 311)		
Anti-Hep B; Post-Dose 3	1370 (1069 to 1757)	5015 (4178 to 6020)		
Anti-PRP; Pre-Dose 3	0.168 (0.137 to 0.205)	0.115 (0.096 to 0.137)		

Anti-PRP; Post-Dose 3	9.73 (8.12 to 11.7)	5.64 (4.66 to 6.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Immune Responses to Prevenar 13 antigens Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects with Immune Responses to Prevenar 13 antigens Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F were measured by enzyme-linked immunosorbent assay (ELISA). Immune response was defined as subjects with antibody concentrations ≥ 0.35 µg/mL 1 month after a 2+1-dose schedule.

End point type	Secondary

End point timeframe:

Post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1	99.4	100		
Serotype 3	86.3	88		
Serotype 4	99.4	98.8		
Serotype 5	95.1	98.1		
Serotype 6A	100	98.8		
Serotype 6B	100	100		
Serotype 7F	100	100		
Serotype 9V	99.4	99.4		
Serotype 14	100	100		
Serotype 18C	98.2	100		
Serotype 19A	100	100		
Serotype 19F	100	100		
Serotype 23F	100	99.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Prevenar Vaccine Antibodies Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Geometric Mean Titers (GMTs) of Prevenar Vaccine Antibodies Following Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F were measured by enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	248		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1	2.15 (1.95 to 2.36)	2.47 (2.21 to 2.75)		
Serotype 3	0.669 (0.605 to 0.74)	0.824 (0.735 to 0.924)		
Serotype 4	1.5 (1.36 to 1.66)	1.95 (1.74 to 2.18)		
Serotype 5	1.07 (0.973 to 1.19)	1.32 (1.2 to 1.45)		
Serotype 6A	4.01 (3.63 to 4.44)	4.92 (4.34 to 5.58)		
Serotype 6B	2.82 (2.51 to 3.17)	4.29 (3.8 to 4.84)		
Serotype 7F	3.04 (2.79 to 3.31)	3.97 (3.6 to 4.38)		
Serotype 9V	1.36 (1.24 to 1.5)	1.7 (1.53 to 1.88)		
Serotype 14	6.79 (6 to 7.69)	7.77 (6.98 to 8.65)		
Serotype 18C	1.27 (1.14 to 1.41)	1.79 (1.61 to 1.99)		
Serotype 19A	4.43 (3.88 to 5.06)	5.78 (5.1 to 6.55)		
Serotype 19F	4.75 (4.27 to 5.3)	6 (5.31 to 6.78)		
Serotype 23F	2.89 (2.6 to 3.22)	4.24 (3.74 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Seroprotection or Vaccine Response One Month Post-dose 2 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects with Seroprotection or Vaccine Response One Month Post-dose 2 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a diphtheria micrometabolic inhibition test (MIT); Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay (ELISA); Anti-poliovirus 1, 2, and 3 were measured by neutralization assay; Anti-hepatitis B (Hep B) Ab were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System; and Anti-polyribosyl ribitol phosphate (PRP) Ab were measured using a Farr-type radioimmunoassay. The following Ab criteria were applied 1 month Post-Dose 3: Anti-Diphtheria and Anti-Tetanus (≥0.01 IU/mL), Anti-Polio 1, 2, and 3 (≥8 1[dil]), Anti-Hep B (≥10 mIU/mL), and Anti-PRP (≥0.15 µg/mL). Vaccine response for Anti-PT and Anti-FHA was defined as Post-Dose 2 Ab concentrations ≥ 4 × Lower Level Of Quantitation (LLOQ), if pre-Dose 1 Ab concentrations < 4 × LLOQ; Post-Dose 2 Ab concentrations ≥ pre-Dose 1 Ab concentrations, if pre-Dose 1 Ab concentrations ≥ 4 × LLOQ.

End point type	Other pre-specified

End point timeframe:

1 month Post-Dose 2

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	246		
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria	99.6	99.6		
Anti-Tetanus	100	100		
Anti-PT	98.4	99.2		
Anti-FHA	99.6	98.3		
Anti-Polio 1	90.8	95.4		
Anti-Polio 2	95	96.6		
Anti-Polio 3	96.7	98.3		
Anti-Hep B	97.2	98.4		
Anti-PRP	71.5	57.9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Antibodies Against Vaccine Antigens One Month Post-dose 2 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Geometric Mean Titers (GMTs) of Antibodies Against Vaccine Antigens One Month Post-dose 2 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a diphtheria micrometabolic inhibition test (MIT); Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti- Filamentous Hemaglutinin (FHA) Ab were measured by enzyme-linked immunosorbent assay (ELISA); Anti-poliovirus 1, 2, and 3 Ab were measured by neutralization assay; Anti-hepatitis B (Hep B) Ab were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System; and Anti-polyribosyl ribitol phosphate (PRP) Ab were measured using a Farr-type radioimmunoassay.

End point type	Other pre-specified

End point timeframe:

1 month Post-Dose 2

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	246		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria	0.13 (0.112 to 0.152)	0.118 (0.103 to 0.134)		
Anti-Tetanus	0.491 (0.439 to 0.549)	0.594 (0.54 to 0.652)		
Anti-PT	105 (97.8 to 113)	106 (97.7 to 115)		
Anti-FHA	94.9 (88.5 to 102)	97.7 (90.5 to 105)		
Anti-Polio 1	60 (47.6 to 75.5)	105 (84.5 to 129)		
Anti-Polio 2	62.1 (49.1 to 78.5)	89.5 (70.9 to 113)		
Anti-Polio 3	122 (97.7 to 152)	142 (115 to 175)		
Anti-Hep B	401 (330 to 488)	699 (577 to 847)		

Anti-PRP	0.507 (0.398 to 0.647)	0.226 (0.184 to 0.277)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Each Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Each Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Solicited injection site: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Anorexia, and Irritability.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 7 post-each vaccination

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	275		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; Post-Injection 1	43.9	32.1		
Injection site Pain; Post-Injection 2	40.1	29.9		
Injection site Pain; Post-Injection 3	65	56.8		
Injection site Erythema; Post-Injection 1	32.8	26.6		
Injection site Erythema; Post-Injection 2	46.5	40.6		
Injection site Erythema; Post-Injection 3	53.4	51.9		
Injection site Swelling; Post-Injection 1	24.7	18.2		
Injection site Swelling; Post-Injection 2	27.5	29.5		
Injection site Swelling; Post-Injection 3	28.2	38.7		
Pyrexia; Post-Injection 1	46.3	26.3		
Pyrexia; Post-Injection 2	61.7	49.8		
Pyrexia; Post-Injection 3	52.1	48.1		
Vomiting; Post-Injection 1	15.5	21.9		
Vomiting; Post-Injection 2	20.4	22.5		
Vomiting; Post-Injection 3	13.2	11.7		
Crying; Post-Injection 1	72	65.3		
Crying; Post-Injection 2	62.8	64.2		
Crying; Post-Injection 3	63.9	64.5		

Somnolence; Post-Injection 1	60.5	58.8		
Somnolence; Post-Injection 2	49.8	49.4		
Somnolence; Post-Injection 3	53	52.1		
Anorexia; Post-Injection 1	35.4	28.5		
Anorexia; Post-Injection 2	32	28		
Anorexia; Post-Injection 3	44.4	48.9		
Irritability; Post-Injection 1	81.9	76.6		
Irritability; Post-Injection 2	76.6	74.2		
Irritability; Post-Injection 3	75.6	74.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 1 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 1 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Solicited injection site: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Anorexia, and Irritability. Grade 3 Solicited injection site reactions: Pain – Cries when injected limb is moved, or the movement of the injected limb is reduced; Erythema and Swelling – ≥50 mm. Grade 3 Systemic reactions: Pyrexia – >39°C; Vomiting – ≥6 episodes per 24 hours or requiring parenteral hydration; Crying – >3 hours; Somnolence – Sleeping most of the time or difficult to wake up; Anorexia – Refuses ≥3 feeds/meals or refuses most meals; Irritability – Inconsolable.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 7 post-Dose 1

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	275		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	43.9	32.1		
Grade 3 Injection site Pain	3.3	2.9		
Injection site Erythema	32.8	26.6		
Grade 3 Injection site Erythema	3.3	1.8		
Injection site Swelling	24.7	18.2		
Grade 3 Injection site Swelling	2.6	1.1		
Pyrexia	46.3	26.3		
Grade 3 Pyrexia	0	0		
Vomiting	15.5	21.9		

Grade 3 Vomiting	0.4	0.7		
Crying	72	65.3		
Grade 3 Crying	3.3	0.4		
Somnolence	60.5	58.8		
Grade 3 Somnolence	1.8	0.7		
Anorexia	35.4	28.5		
Grade 3 Anorexia	0.7	0.7		
Irritability	81.9	76.6		
Grade 3 Irritability	4.8	6.2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 2 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 2 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Solicited injection site: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Anorexia, and Irritability. Grade 3 Solicited injection site reactions: Pain – Cries when injected limb is moved, or the movement of the injected limb is reduced; Erythema and Swelling – ≥50 mm. Grade 3 Systemic reactions: Pyrexia – >39°C; Vomiting – ≥6 episodes per 24 hours or requiring parenteral hydration; Crying – >3 hours; Somnolence – Sleeping most of the time or difficult to wake up; Anorexia – Refuses ≥3 feeds/meals or refuses most meals; Irritability – Inconsolable.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 7 post-Dose 2

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	272		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	40.1	29.9		
Grade 3 Injection site Pain	0.4	1.8		
Injection site Erythema	46.5	40.6		
Grade 3 Injection site Erythema	1.1	0.4		
Injection site Swelling	27.5	29.5		
Grade 3 Injection site Swelling	1.5	0		
Pyrexia	61.7	49.8		
Grade 3 Pyrexia	0.7	1.5		
Vomiting	20.4	22.5		

Grade 3 Vomiting	1.5	0.4		
Crying	62.8	64.2		
Grade 3 Crying	3.3	1.8		
Somnolence	49.8	49.4		
Grade 3 Somnolence	0.7	2.2		
Anorexia	32	28		
Grade 3 Anorexia	1.5	0		
Irritability	76.6	74.2		
Grade 3 Irritability	4.1	2.2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 3 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 3 with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point description:

Solicited injection site: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Anorexia, and Irritability. Grade 3 Solicited injection site reactions: Pain – Cries when injected limb is moved, or the movement of the injected limb is reduced; Erythema and Swelling – ≥50 mm. Grade 3 Systemic reactions: Pyrexia – >39°C; Vomiting – ≥6 episodes per 24 hours or requiring parenteral hydration; Crying – >3 hours; Somnolence – Sleeping most of the time or difficult to wake up; Anorexia – Refuses ≥3 feeds/meals or refuses most meals; Irritability – Inconsolable.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 7 post-Dose 3

End point values	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	268		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	65	56.8		
Grade 3 Injection site Pain	6.8	4.1		
Injection site Erythema	53.4	51.9		
Grade 3 Injection site Erythema	2.6	4.1		
Injection site Swelling	28.2	38.7		
Grade 3 Injection site Swelling	1.5	2.3		
Pyrexia	52.1	48.1		
Grade 3 Pyrexia	2.3	1.5		
Vomiting	13.2	11.7		

Grade 3 Vomiting	0	0		
Crying	63.9	64.5		
Grade 3 Crying	5.3	2.6		
Somnolence	53	52.1		
Grade 3 Somnolence	1.1	1.5		
Anorexia	44.4	48.9		
Grade 3 Anorexia	2.6	0.8		
Irritability	75.6	74.7		
Grade 3 Irritability	3.4	1.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event data were collected from Day 0 (post-vaccination) up to Day 30 post-final vaccination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	DTaP-IPV-HB-Hib+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of DTaP-IPV-HB-Hib vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	
Reporting group title	Infanrix hexa+Prevenar 13
Reporting group description:	
Subjects who received 3 doses of Infanrix hexa vaccine co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age.	

Serious adverse events	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 271 (5.54%)	15 / 275 (5.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			

subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Breath holding			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Inguinal mass			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	3 / 271 (1.11%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	2 / 271 (0.74%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	3 / 271 (1.11%)	3 / 275 (1.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 271 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 271 (0.37%)	2 / 275 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 271 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DTaP-IPV-HB-Hib+Prevenar 13	Infanrix hexa+Prevenar 13	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 271 (81.92%)	210 / 275 (76.36%)	
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed[1]	164 / 271 (60.52%)	161 / 274 (58.76%)	
occurrences (all)	164	161	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed[2]	166 / 271 (61.25%)	135 / 274 (49.27%)	
occurrences (all)	166	135	
Injection site induration			
subjects affected / exposed	12 / 271 (4.43%)	17 / 275 (6.18%)	
occurrences (all)	16	32	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed[3]	173 / 271 (63.84%)	151 / 274 (55.11%)	
occurrences (all)	173	151	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed[4]	142 / 271 (52.40%)	138 / 274 (50.36%)	
occurrences (all)	142	138	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed[5]	75 / 271 (27.68%)	103 / 274 (37.59%)	
occurrences (all)	75	103	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	23 / 271 (8.49%)	22 / 275 (8.00%)	
occurrences (all)	23	27	
Teething			
subjects affected / exposed	13 / 271 (4.80%)	23 / 275 (8.36%)	
occurrences (all)	18	31	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[6]	55 / 271 (20.30%)	61 / 274 (22.26%)	
occurrences (all)	55	61	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 271 (11.44%)	26 / 275 (9.45%)	
occurrences (all)	35	28	
Psychiatric disorders			
Crying			
alternative assessment type: Systematic			
subjects affected / exposed[7]	195 / 271 (71.96%)	179 / 274 (65.33%)	
occurrences (all)	195	179	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[8]	222 / 271 (81.92%)	210 / 274 (76.64%)	
occurrences (all)	222	210	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	62 / 271 (22.88%)	71 / 275 (25.82%)	
occurrences (all)	77	96	
Rhinitis			
subjects affected / exposed	45 / 271 (16.61%)	45 / 275 (16.36%)	
occurrences (all)	52	53	
Otitis media			
subjects affected / exposed	27 / 271 (9.96%)	26 / 275 (9.45%)	
occurrences (all)	32	31	
Nasopharyngitis			
subjects affected / exposed	24 / 271 (8.86%)	29 / 275 (10.55%)	
occurrences (all)	35	33	

Metabolism and nutrition disorders Anorexia alternative assessment type: Systematic subjects affected / exposed[9] occurrences (all)	 118 / 271 (43.54%) 118	 130 / 274 (47.45%) 130	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after each vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2012	The scale for assessment of Extensive Limb Swelling was added and the protocol was corrrected with the new Sponsor's Responsible Medical Officer information.
14 June 2013	The Global Clinical Immunology (GCI) re-implemented the micrometabolic inhibition test using pH indicator for development (MIT-pH) assay for the DTaP-IPV-HB-Hib studies and discontinued the micrometabolic inhibition test using cell survival assessed by crystal violet staining (MIT-CV) method.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported