Clinical trial results:
Booster Effect and Safety of a DTaP-IPV-Hib Combined Vaccine, with or without Hep B, in Healthy Subjects 11 to 18 Months of Age Who Received a Hexavalent or Hexavalent/Pentavalent Combined Vaccine during the Primary Series

Summary

EudraCT number	2012-001042-18
Trial protocol	DE CZ ES
Global end of trial date	27 October 2015

Results information

Result version number	v1 (current)
This version publication date	19 July 2017
First version publication date	19 July 2017

Trial information

Trial identification

Sponsor protocol code	A3L40

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1122-2362

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@sanofi.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43, emmanuel.feroldi@sanofi.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	20 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity
Groups 1 and 2
• Assess the antibody persistence of DTaP-IPV-HB-Hib or Infanrix hexa following a 3-dose primary series at 2, 3, and 4 months of age (MoA) before the administration of a booster dose of either vaccine
• Describe the immunogenicity and booster effect of the DTaP-IPV-HBHib or Infanrix hexa vaccine given as a booster dose at 11 to 15 MoA concomitantly with PCV13 (after a primary series with the same vaccine)
• To describe the immunogenicity of a booster dose of PCV13 given from 11 to 15 MoA
Group 3
• Assess the antibody persistence of all valences contained in the vaccines administered in a mixed schedule following a 3-dose primary series at 2, 4, and 6 MoA before the administration of a booster dose of Pentavac
• Describe the immunogenicity and booster effect of Pentavac given at 18 MoA after the administration of a mixed schedule primary series combining a hexavalent and a pentavalent vaccine

To describe the safety profile for group 1, 2 and 3

Protection of trial subjects:

Only subjects that met all the study inclusion and no exclusion criteria were 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:

Subjects in this trial previously completed a 3-dose primary series of either DTaP-IPV-HB-Hib vaccine + PCV13, Infanrix hexa + PCV13, or DTaP-IPV-HB-Hib/Pentavac/DTaP-IPV-HB-Hib/PCV13 in Study A3L39.

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 November 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	Spain: 198
Country: Number of subjects enrolled	Czech Republic: 262
Country: Number of subjects enrolled	Germany: 203
Worldwide total number of subjects	663
EEA total number of subjects	663

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	663
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 11 November 2014 to September 23, 2015 at 25 clinic centers in Czech Republic, 14 centers in Germany, and 12 centers in Spain.

Pre-assignment

Screening details:

A total of 663 subjects who met all inclusion and no exclusion criteria were enrolled; 662 subjects were vaccinated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Arm type	Experimental
Investigational medicinal product name	DTaP-IPV-HB-Hib combined vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the anterolateral area of the right thigh, booster dose co-adminstered with PCV13 at 11 to 15 months

Investigational medicinal product name	PCV13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the anterolateral area of the left thigh, booster dose co-adminstered with DTaP-IPV-HB-Hib vaccine at 11 to 15 months

Arm title	Group 2

Arm description:

Subjects previously received Infanrix hexa (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of Infanrix hexa concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Arm type	Active comparator

Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the anterolateral area of the right thigh, booster dose co-administered with PCV13 at 11 to 15 months

Investigational medicinal product name	PCV13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the anterolateral area of the left thigh, booster dose co-adminstered with Infanrix hexa vaccine at 11 to 15 months

Arm title	Group 3

Arm description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (open-label) in a 2-dose series at 2 and 6 months and a dose of Pentavac (DTaP-IPV/Hib) vaccine in Study A3L39 and received a booster dose of Pentavac (open label) concomitantly with a booster dose of PCV13 at 18 months of age in the current study.

Arm type	Experimental
Investigational medicinal product name	Pentavac (DTap-IPV/Hib) combined vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the anterolateral area of the right thigh, booster dose co-administered with a booster dose of PCV13 at 18 months

Investigational medicinal product name	PCV13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the anterolateral area of the left thigh, booster dose co-adminstered with Pentavac at 18 months

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	234	231	198
Completed	234	230	196
Not completed	0	1	2
Consent withdrawn by subject	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects previously received DTaP-IPV-HB-Hib vaccine (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.	
Reporting group title	Group 2
Reporting group description:	
Subjects previously received Infanrix hexa (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of Infanrix hexa concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.	
Reporting group title	Group 3
Reporting group description:	
Subjects previously received DTaP-IPV-HB-Hib vaccine (open-label) in a 2-dose series at 2 and 6 months and a dose of Pentavac (DTaP-IPV/Hib) vaccine in Study A3L39 and received a booster dose of Pentavac (open label) concomitantly with a booster dose of PCV13 at 18 months of age in the current study.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	234	231	198
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)	234	231	198
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: months			
arithmetic mean	12.4	12.5	18.1
standard deviation	± 0.5	± 0.6	± 0.3
Gender categorical Units: Subjects			
Female	110	119	102
Male	124	112	96

Reporting group values	Total		
Number of subjects	663		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	663		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	331		
Male	332		

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Reporting group title	Group 2

Reporting group description:

Subjects previously received Infanrix hexa (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of Infanrix hexa concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Reporting group title	Group 3

Reporting group description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (open-label) in a 2-dose series at 2 and 6 months and a dose of Pentavac (DTaP-IPV/Hib) vaccine in Study A3L39 and received a booster dose of Pentavac (open label) concomitantly with a booster dose of PCV13 at 18 months of age in the current study.

Primary: Antibody Persistence of DTaP-IPV-HB-Hib or Infanrix hexa™ Following a 3-dose Primary Series, Before a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac and the Immunogenicity and Booster Effect After a Booster Dose of Any Vaccine

End point title	Antibody Persistence of DTaP-IPV-HB-Hib or Infanrix hexa™ Following a 3-dose Primary Series, Before a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac and the Immunogenicity and Booster Effect After a Booster Dose of Any Vaccine[1]

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a neutralization test. Anti-Tetanus, Anti-Pertussis Toxoid (PT), Anti-Filamentous Hemagglutinin (FHA) antibodies were measured by ELISA. Anti-Polio types 1, 2, and 3 were measured by neutralization assay. Anti-Hepatitis B (Hep B) were assessed by VITROS ECi/ECiQ. Anti-Haemophilus influenza type b polysaccharide covalently bound to the tetanus protein (PRP) Abs were measured by a radioimmunoassay. Anti-Diphtheria and Tetanus titers were assessed at ≥0.01 and 0.1 IU/mL. Anti-PT and FHA titers were assessed at ≥lower limit of quantitation (LLOQ) where LLOQ=2 EU/mL. Anti-Polio types 1, 2, and 3 were assessed at ≥8 (1/dil). Anti-Hep B titers were assessed at ≥10 mIU/mL and ≥100 mIU/mL (except post-booster in Group 3) and Anti-PRP titers at ≥0.15 and 1.0 µg/mL. For PT and FHA booster response, post-booster Ab concentrations ≥4-fold rise if pre-booster <4x LLOQ and post-booster Ab concentrations ≥2-fold rise if pre-booster ≥4x LLOQ.

End point type	Primary

End point timeframe:

Post-dose 3 primary series, pre- and post-booster

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 study vaccine administered for this outcome.

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	218	189	
Units: Percentage of subjects				
number (not applicable)				
Anti-Diptheria; ≥0.01 IU/mL; Post-dose 3	100	100	100	
Anti-Diptheria; ≥0.1 IU/mL; Post-dose 3	62.6	59.6	97.1	
Anti-Diptheria; ≥0.01 IU/mL; Pre-booster	98.5	99.5	98.8	
Anti-Diptheria; ≥0.1 IU/mL; Pre-booster	64.3	47.8	47.5	
Anti-Diptheria; ≥0.01 IU/mL; Post-booster	100	100	100	
Anti-Diptheria; ≥0.1 IU/mL; Post-booster	100	100	100	
Anti-Tetanus; ≥0.01 IU/mL; Post-dose 3	100	100	100	
Anti-Tetanus; ≥0.1 IU/mL; Post-dose 3	99.5	100	100	
Anti-Tetanus; ≥0.01 IU/mL; Pre-booster	100	100	100	
Anti-Tetanus; ≥0.1 IU/mL; Pre-booster	85.6	85.6	98.8	
Anti-Tetanus; ≥0.01 IU/mL; Post-booster	100	100	100	
Anti-Tetanus; ≥0.1 IU/mL; Post-booster	100	100	100	
Anti-PT; ≥LLOQ; Post-dose 3	100	100	100	
Anti-PT; ≥LLOQ; Pre-booster	99.5	100	85.9	
Anti-FHA; ≥LLOQ; Post-dose 3	100	100	100	
Anti-FHA; ≥LLOQ; Pre-booster	100	100	100	
Anti-Polio 1; ≥8 (1/dil); Post-dose 3	100	100	100	
Anti-Polio 1; ≥8 (1/dil); Pre-booster	83.7	93.6	99.4	
Anti-Polio 1; ≥8 (1/dil); Post-booster	99.5	100	100	
Anti-Polio 2; ≥8 (1/dil); Post-dose 3	100	100	99.4	
Anti-Polio 2; ≥8 (1/dil); Pre-booster	88.3	90.7	94.7	
Anti-Polio 2; ≥8 (1/dil); Post-booster	100	100	100	
Anti-Polio 3; ≥8 (1/dil); Post-dose 3	100	100	100	
Anti-Polio 3; ≥8 (1/dil); Pre-booster	91.3	93.5	97.1	
Anti-Polio 3; ≥8 (1/dil); Post-booster	100	100	100	
Anti-Hep B; ≥10 mIU/mL; Post-dose 3	97.2	98.6	98.9	
Anti-Hep B; ≥100 mIU/mL; Post-dose 3	73.7	86.7	96.1	
Anti-Hep B; ≥10 mIU/mL; Pre-booster	86	97.2	92.4	
Anti-Hep B; ≥100 mIU/mL; Pre-booster	44.8	67.1	71.9	
Anti-Hep B; ≥10 mIU/mL; Post-booster	99.6	100	0	
Anti-Hep B; ≥100 mIU/mL; Post-booster	94.2	98.1	0	
Anti-PRP; ≥0.15 µg/mL; Post-dose 3	90.6	85.5	100	
Anti-PRP; ≥1.0 µg/mL; Post-dose 3	61.8	37.2	96.1	
Anti-PRP; ≥0.15 µg/mL; Pre-booster	72	57.7	87.6	
Anti-PRP; ≥1.0 µg/mL; Pre-booster	27.1	9.1	36	
Anti-PRP; ≥0.15 µg/mL; Post-booster	100	99.5	95.2	
Anti-PRP; ≥1.0 µg/mL; Post-booster	96.6	95.3	84.4	

Statistical analyses

No statistical analyses for this end point

Primary: Booster Vaccine Response Against Pertussis Toxoid and Filamentous Hemagglutinin Following Administration of DTaP-IPV-HB-Hib or Infanrix hexa™ in a 3-dose Primary Series and a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac

End point title	Booster Vaccine Response Against Pertussis Toxoid and Filamentous Hemagglutinin Following Administration of DTaP-IPV-HB-Hib or Infanrix hexa™ in a 3-dose Primary Series and a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac[2]

End point description:

Anti-Pertussis Toxoid (PT) and Anti-Filamentous Hemagglutinin (FHA) antibodies were measured by enzyme-linked immunosorbent assay. Booster vaccine response for PT and FHA antigens were defined as post-booster antibody concentrations ≥4-fold rise if pre-booster antibody concentrations <4X LLOQ or post-booster antibody concentration ≥2-fold rise if pre-booster antibody concentrations ≥4X LLOQ.

End point type	Primary

End point timeframe:

Post-dose 3 primary series, pre- and post-booster

Notes:

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

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	218	189	
Units: Percentage of subjects				
number (not applicable)				
Anti-PT	97	98	99.4	
Anti-FHA	94.8	94.1	94.2	

Statistical analyses

No statistical analyses for this end point

Primary: Seroconversion Against Pertussis Toxoid and Filamentous Hemagglutinin Following Administration of DTaP-IPV-HB-Hib or Infanrix hexa™ in a 3-dose Primary Series and a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac

End point title	Seroconversion Against Pertussis Toxoid and Filamentous Hemagglutinin Following Administration of DTaP-IPV-HB-Hib or Infanrix hexa™ in a 3-dose Primary Series and a Booster Dose of DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac[3]

End point description:

Anti-Pertussis Toxoid (PT) and Anti-Filamentous Hemagglutinin (FHA) antibodies were measured by enzyme-linked immunosorbent assay. Seroconversion for PT and FHA antigens was defined as Anti-PT and Anti-FHA ≥4-fold antibody titers increase from Day 0 to Day 30.

End point type	Primary

End point timeframe:

Post-booster

Notes:

[3] - 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 study vaccine administered for this outcome.

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	218	189	
Units: Percentage of subjects				
number (not applicable)				
Anti-PT	78.8	79.6	95.8	
Anti-FHA	60.4	80.7	83	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers of Antibodies Against Vaccine Antigens After a 3-Dose Primary Series with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Before Administration of a Booster Dose and the Immunogenicity and Booster Effect After Booster of Either Vaccine

End point title	Geometric Mean Titers of Antibodies Against Vaccine Antigens After a 3-Dose Primary Series with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Before Administration of a Booster Dose and the Immunogenicity and Booster Effect After Booster of Either Vaccine[4]

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a toxin neutralization test. Anti-Tetanus, Anti-Pertussis Toxoid (PT), Anti-Filamentous Hemagglutinin (FHA) antibodies were measured by enzyme-linked immunosorbent assay. Anti-Poliovirus types 1, 2, and 3 were measured by neutralization assay. Anti-Hepatitis B (Hep B) were measured by VITROS ECi/ECiQ Immunodiagnostic System. Anti-Haemophilus influenza type b polysaccharide covalently bound to the tetanus protein (PRP) Abs were measured using a Farr-type radioimmunoassay.

End point type	Primary

End point timeframe:

Post-dose 3 primary series, pre- and post-booster

Notes:

[4] - 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 study vaccine administered for this outcome.

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	218	189	
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphteria; Post-dose 3	0.174 (0.151 to 0.201)	0.155 (0.135 to 0.177)	0.735 (0.633 to 0.853)	
Anti-Diphteria; Pre-booster	0.172 (0.141 to 0.208)	0.107 (0.091 to 0.126)	0.098 (0.082 to 0.118)	
Anti-Diphteria; Post-booster	6.08 (5.08 to 7.27)	4.1 (3.52 to 4.78)	3.43 (3.05 to 3.85)	

Anti-Tetanus; Post-dose 3	0.77 (0.693 to 0.856)	0.872 (0.784 to 0.971)	2.27 (2.04 to 2.53)	
Anti-Tetanus; Pre-booster	0.272 (0.238 to 0.312)	0.253 (0.222 to 0.287)	1.16 (1.04 to 1.3)	
Anti-Tetanus; Post-booster	4.32 (3.82 to 4.88)	3.78 (3.39 to 4.21)	6.85 (6.26 to 7.49)	
Anti-PT; Post-dose 3	114 (106 to 123)	133 (123 to 144)	99.9 (91.7 to 109)	
Anti-PT; Pre-booster	16.1 (14.5 to 17.9)	21.4 (19.2 to 23.8)	5.44 (4.66 to 6.35)	
Anti-PT; Post-booster	112 (102 to 122)	158 (144 to 173)	113 (101 to 125)	
Anti-FHA; Post-dose 3	139 (129 to 149)	85.2 (78.6 to 92.3)	167 (154 to 181)	
Anti-FHA; Pre-booster	34.2 (30.9 to 37.9)	24.9 (22.1 to 27.9)	20.9 (17.6 to 24.7)	
Anti-FHA; Post-booster	172 (158 to 187)	173 (158 to 189)	210 (189 to 232)	
Anti-Polio 1; Post-dose 3	110 (93.6 to 130)	269 (224 to 322)	866 (725 to 1034)	
Anti-Polio 1; Pre-booster	38.8 (30.8 to 48.8)	80.6 (65.7 to 99)	294 (239 to 363)	
Anti-Polio 1; Post-booster	1070 (880 to 1302)	2696 (2283 to 3184)	1882 (1632 to 2170)	
Anti-Polio 2; Post-dose 3	192 (162 to 227)	358 (295 to 435)	2119 (1707 to 2631)	
Anti-Polio 2; Pre-booster	51 (41 to 63.5)	75.6 (60.7 to 94.1)	306 (241 to 390)	
Anti-Polio 2; Post-booster	1858 (1576 to 2192)	2887 (2449 to 3403)	3085 (2622 to 3630)	
Anti-Polio 3; Post-dose 3	300 (256 to 352)	702 (584 to 845)	1448 (1180 to 1777)	
Anti-Polio 3; Pre-booster	68.7 (56.6 to 83.4)	135 (109 to 166)	258 (199 to 335)	
Anti-Polio 3; Post-booster	2301 (1924 to 2752)	3902 (3265 to 4662)	3501 (3039 to 4033)	
Anti-Hep B; Post-dose 3	230 (188 to 281)	376 (316 to 448)	2613 (2104 to 3245)	
Anti-Hep B; Pre-booster	74.6 (59.7 to 93.2)	169 (140 to 203)	189 (144 to 248)	
Anti-Hep B; Post-booster	2140 (1707 to 2683)	4642 (3837 to 5616)	0 (0 to 0)	
Anti-PRP; Post-dose 3	1.32 (1.07 to 1.62)	0.596 (0.497 to 0.714)	8.85 (7.5 to 10.4)	
Anti-PRP; Pre-booster	0.383 (0.308 to 0.476)	0.173 (0.144 to 0.209)	0.712 (0.569 to 0.891)	
Anti-PRP; Post-booster	28.8 (23.6 to 35.1)	16.5 (13.6 to 19.8)	15.8 (11.6 to 21.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios of Antibodies Against Vaccine Antigens After a 3-Dose Primary Series with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Before a Booster Dose and the Immunogenicity and Booster Effect After Booster of Either Vaccine

End point title	Geometric Mean Titer Ratios of Antibodies Against Vaccine

	Antigens After a 3-Dose Primary Series with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Before a Booster Dose and the Immunogenicity and Booster Effect After Booster of Either Vaccine[5]

End point description:

Anti-Diphtheria antibodies (Ab) were measured by a toxin neutralization test. Anti-Tetanus, Anti-Pertussis Toxoid (PT), Anti-Filamentous Hemagglutinin (FHA) antibodies were measured by enzyme-linked immunosorbent assay. Anti-Poliovirus types 1, 2, and 3 were measured by neutralization assay. Anti-Hepatitis B (Hep B) were measured by VITROS ECi/ECiQ Immunodiagnostic System. Anti-Haemophilus influenza type b polysaccharide covalently bound to the tetanus protein (PRP) Abs were measured using a Farr-type radioimmunoassay.

End point type	Primary

End point timeframe:

Post-booster

Notes:

[5] - 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 study vaccine administered for this outcome.

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	218	189	
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Anti-Diphtheria	32.8 (26.6 to 40.4)	38.4 (31.6 to 46.6)	35.8 (30.6 to 41.8)	
Anti-Tetanus	16.2 (14.3 to 18.3)	15 (13.4 to 16.8)	5.77 (5.13 to 6.49)	
Anti-PT	7.28 (6.54 to 8.1)	7.38 (6.69 to 8.14)	21 (18.2 to 24.2)	
Anti-FHA	5.07 (4.63 to 5.54)	6.96 (6.26 to 7.74)	10 (8.72 to 11.5)	
Anti-Polio 1	26.8 (21.6 to 33.3)	33.6 (27.1 to 41.7)	6.26 (5.05 to 7.75)	
Anti-Polio 2	36.8 (29.7 to 45.7)	37.6 (31 to 45.7)	9.15 (7.26 to 11.5)	
Anti-Polio 3	33.7 (27.8 to 40.8)	29.8 (24.4 to 36.3)	12.2 (9.63 to 15.4)	
Anti-Hep B	29.2 (25 to 33.9)	27.9 (24.3 to 31.9)	0 (0 to 0)	
Anti-PRP	72.3 (59.3 to 88.2)	91.8 (76.1 to 111)	20 (14.4 to 27.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Immune Responses to Prevenar 13 Antigens Following Co-administration with DTaP-IPV-HB-Hib or Infanrix hexa™

End point title	Percentage of Subjects with Immune Responses to Prevenar 13 Antigens Following Co-administration with DTaP-IPV-HB-Hib or Infanrix hexa™[6][7]

End point description:

The pneumococcal capsular polysaccharide (PS) immunoglobulin G ELISA was used to quantitate the

amount of anti-streptococcus pneumoniae PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) antibodies in human serum. The percentage of subjects reported represent subjects with anti-pneumococcal serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) antibody concentrations at ≥0.35 µg/mL.

End point type	Primary

End point timeframe:

1 month post-booster

Notes:

[6] - 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 study vaccine administered for this outcome.
[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were only assessed in Groups 1 and 2.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	218		
Units: Percentage of subjects				
number (not applicable)				
Serotype 1	100	99.5		
Serotype 3	82.7	90.2		
Serotype 4	99	99.5		
Serotype 5	98.1	99		
Serotype 6A	100	100		
Serotype 6B	99	100		
Serotype 7F	100	100		
Serotype 9V	99	99.5		
Serotype 14	100	100		
Serotype 18C	97.1	98.6		
Serotype 19A	100	100		
Serotype 19F	100	100		
Serotype 23F	99.5	99		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Concentrations (GMCs) of Prevenar Antibodies Following Co-administration with DTaP-IPV-HB-Hib or Infanrix hexa™

End point title	Geometric Mean Concentrations (GMCs) of Prevenar Antibodies Following Co-administration with DTaP-IPV-HB-Hib or Infanrix hexa™[8][9]

End point description:

The pneumococcal capsular polysaccharide (PS) immunoglobulin G ELISA was used to quantitate the amount of anti-streptococcus pneumoniae PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) antibodies in human serum. Anti-pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F antibody concentrations were assessed at ≥0.35 µg/mL.

End point type	Primary

End point timeframe:

1 month post-booster

Notes:

[8] - 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 study vaccine administered for this outcome.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were only assessed in Groups 1 and 2.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	218		
Units: Concentrations (1/dil)				
geometric mean (confidence interval 95%)				
Serotype 1	2.44 (2.23 to 2.67)	3.4 (3.09 to 3.75)		
Serotype 3	0.708 (0.633 to 0.791)	0.933 (0.828 to 1.05)		
Serotype 4	2.11 (1.88 to 2.37)	2.95 (2.63 to 3.3)		
Serotype 5	1.36 (1.24 to 1.49)	1.8 (1.63 to 1.97)		
Serotype 6A	6.37 (5.78 to 7.03)	7.45 (6.75 to 8.23)		
Serotype 6B	5.43 (4.83 to 6.11)	7.48 (6.79 to 8.24)		
Serotype 7F	4.24 (3.86 to 4.65)	5.27 (4.8 to 5.79)		
Serotype 9V	1.51 (1.39 to 1.65)	1.88 (1.72 to 2.05)		
Serotype 14	9.7 (8.81 to 10.7)	10.8 (9.86 to 11.9)		
Serotype 18C	1.27 (1.14 to 1.42)	2 (1.78 to 2.24)		
Serotype 19A	8.91 (8.02 to 9.89)	11.1 (9.96 to 12.3)		
Serotype 19F	7.16 (6.47 to 7.92)	9.4 (8.52 to 10.4)		
Serotype 23F	2.95 (2.61 to 3.33)	4.18 (3.7 to 4.74)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Booster Vaccinations with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Booster Vaccinations with DTaP-IPV-HB-Hib, Infanrix hexa™, or Pentavac Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13)[10]

End point description:

Solicited injection site reactions: Tenderness/Pain, Erythema, Swelling, and Extensive swelling of vaccinated limb. Solicited systemic reactions: Fever (Temperature)/Pyrexia, Vomiting, Crying abnormal, Drowsiness/Somnolence, Appetite lost/Anorexia, and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved, or the movement of the injected limb is reduced; Erythema and Swelling, ≥50 mm; Extensive swelling of the arm, Not applicable. Grade 3 Solicited systemic reactions: Fever, >39.5°C or >103.1°F; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥3 feeds/meals or refuses most meals; Irritability, Inconsolable.

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-booster

Notes:

[10] - 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 study vaccine administered for this outcome.

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	234[11]	228	198	
Units: Percentage of subjects				
number (not applicable)				
Any Inj. site Pain; DTaP-IPV-HB-Hib	51.1	0	0	
Grade 3 Inj. site Pain; DTaP-IPV-HB-Hib	6.8	0	0	
Any Inj. site Pain; Infanrix hexa	0	53.7	0	
Grade 3 Inj. site Pain; Infanrix hexa	0	4.8	0	
Any Inj. site Pain; Pentavac	0	0	50.3	
Grade 3 Inj. site Pain; Pentavac	0	0	5.1	
Any Inj. site Pain; Prevenar	51.9	52.9	42.7	
Grade 3 Inj. site Pain; Prevenar	6	4.8	4.9	
Any Inj. site Erythema; DTaP-IPV-HB-Hib	41.3	0	0	
Grade 3 Inj. site Erythema; DTaP-IPV-HB-Hib	0.9	0	0	
Any Inj. site Erythema; Infanrix hexa	0	44.9	0	
Grade 3 Inj. site Erythema; Infanrix hexa	0	2.6	0	
Any Inj. site Erythema; Pentavac	0	0	12.2	
Grade 3 Inj. site Erythema; Pentavac	0	0	0.5	
Any Inj. site Erythema; Prevenar	37.4	40.1	6.7	
Grade 3 Inj. site Erythema; Prevenar	0	1.8	0	
Any Inj. site Swelling; DTaP-IPV-HB-Hib	23.1	0	0	
Grade 3 Inj. site Swelling; DTaP-IPV-HB-Hib	1.3	0	0	
Any Inj. site Swelling; Infanrix hexa	0	27.8	0	
Grade 3 Inj. site Swelling; Infanrix hexa	0	2.2	0	
Any Inj. site Swelling; Pentavac	0	0	13.7	
Grade 3 Inj. site Swelling; Pentavac	0	0	0	
Any Inj. site Swelling; Prevenar	19.6	25.1	6.1	
Grade 3 Inj. site Swelling; Prevenar	0.4	2.2	0.6	
Any Extensive Swelling of Limb; DTaP-IPV-HB-Hib	0	0	0	
Grade 3 Extensive Swelling of Limb;DTaP-IPV-HB-Hib	0	0	0	

Any Extensive Swelling of Limb; Infanrix hexa	0	0.4	0	
Grade 3 Extensive Swelling of Limb; Infanrix hexa	0	0.4	0	
Any Extensive Swelling of Limb; Pentavac	0	0	0	
Grade 3 Extensive Swelling of Limb; Pentavac	0	0	0	
Any Extensive Swelling of Limb; Prevenar	0	0	0	
Grade 3 Extensive Swelling of Limb; Prevenar	0	0	0	
Any Pyrexia	50.2	43.6	24.5	
Grade 3 Pyrexia	5.1	4	1	
Any Vomiting	8.5	7	4.6	
Grade 3 Vomiting	0.9	0.4	0	
Any Crying abnormal	45.5	41.4	41.1	
Grade 3 Crying abnormal	3.8	1.3	1	
Any Somnolence	48.5	44.5	38.6	
Grade 3 Somnolence	0.9	0	0	
Any Anorexia	38.7	32.6	39.6	
Grade 3 Anorexia	2.6	0.9	1	
Any Irritability	60.4	56.8	56.9	
Grade 3 Irritability	2.1	1.3	0.5	

Notes:

[11] - For safety analyses, 236 subjects were included in Group 1 post-booster.

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 up to Day 7 post-booster vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Reporting group title	Group 2

Reporting group description:

Subjects previously received Infanrix hexa (blind-observer) in a 3-dose series at 2, 3, and 4 months in Study A3L39 and received a booster dose of Infanrix hexa concomitantly with a booster dose of PCV13 at 11 to 15 months of age in the current study.

Reporting group title	Group 3

Reporting group description:

Subjects previously received DTaP-IPV-HB-Hib vaccine (open-label) in a 2-dose series at 2 and 6 months and a dose of Pentavac (DTaP-IPV/Hib) vaccine in Study A3L39 and received a booster dose of Pentavac (open label) concomitantly with a booster dose of PCV13 at 18 months of age in the current study.

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 236 (0.42%)	3 / 228 (1.32%)	0 / 198 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 236 (0.00%)	2 / 228 (0.88%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute pyelonephritis			
subjects affected / exposed	0 / 236 (0.00%)	1 / 228 (0.44%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bronchopneumonia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 228 (0.00%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 236 (60.17%)	129 / 228 (56.58%)	112 / 198 (56.57%)
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	114 / 236 (48.31%)	101 / 228 (44.30%)	76 / 198 (38.38%)
occurrences (all)	114	101	76
General disorders and administration site conditions			
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed	122 / 236 (51.69%)	122 / 228 (53.51%)	99 / 198 (50.00%)
occurrences (all)	122	122	99
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed	97 / 236 (41.10%)	102 / 228 (44.74%)	24 / 198 (12.12%)
occurrences (all)	97	102	24
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	54 / 236 (22.88%)	63 / 228 (27.63%)	27 / 198 (13.64%)
occurrences (all)	54	63	27
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	118 / 236 (50.00%)	99 / 228 (43.42%)	48 / 198 (24.24%)
occurrences (all)	118	99	48
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			

subjects affected / exposed	20 / 236 (8.47%)	16 / 228 (7.02%)	9 / 198 (4.55%)
occurrences (all)	20	16	9
Psychiatric disorders			
Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	107 / 236 (45.34%)	94 / 228 (41.23%)	81 / 198 (40.91%)
occurrences (all)	107	94	81
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	142 / 236 (60.17%)	129 / 228 (56.58%)	112 / 198 (56.57%)
occurrences (all)	142	129	112
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 236 (0.85%)	3 / 228 (1.32%)	10 / 198 (5.05%)
occurrences (all)	2	3	10
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed	91 / 236 (38.56%)	74 / 228 (32.46%)	78 / 198 (39.39%)
occurrences (all)	91	74	78

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2014	Details regarding technical issues with vaccine administration and country-specific information were further clarified.
26 February 2015	Definition of booster response was reworded to ensure consistency and information on assays used in the study were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported