Clinical trial results:
Immunogenicity and Safety Study of a Hexavalent DTaP-IPV-HB-Hib Combined Vaccine in a 3-dose Primary Series in Healthy Infants in Europe

Summary

EudraCT number	2012-001055-39
Trial protocol	DE CZ ES
Global end of trial date	27 November 2014

Results information

Result version number	v1 (current)
This version publication date	21 April 2016
First version publication date	21 April 2016

Trial information

Trial identification

Sponsor protocol code	A3L39

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1122-2329

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-000120-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	10 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Groups 1 and 2 only
To demonstrate the non-inferiority of the DTaP-IPV-HB-Hib vaccine to the control Infanrix hexa vaccine, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates to PT, FHA, Hep B, and PRP antigens, 1 month after a 3-dose primary series.

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:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 January 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: 265
Country: Number of subjects enrolled	Czech Republic: 276
Country: Number of subjects enrolled	Germany: 253
Worldwide total number of subjects	794
EEA total number of subjects	794

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)	794

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:

The study subjects were enrolled from 21 January 2014 to 18 August 2014 at 25 clinic centers in Czech Republic, 12 in Spain, and 15 in Germany.

Pre-assignment

Screening details:

A total of 794 subjects who met all of the inclusion and none of the exclusion criteria were randomized and vaccinated in this study.

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	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

This was an observer-blind study. The Investigator, subjects and parents, and Sponsor were blinded to vaccine treatment. To maintain the blind, the product preparation and administration, and the assessment of safety were performed by 2 different individuals in separate rooms. In the event of an emergency (i.e., serious adverse event) the code could be broken by the Investigator as explained in the code-breaking procedures outlined in the Operating Guidelines.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects received 3 doses of DTaP-IPV-HB-Hib vaccine coadministered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.

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, 1 injection each at 2, 3, 4 months of age co-administered with Prevenar 13 and RotaTeq.

Investigational medicinal product name	Prevenar 13
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 into anterolateral area of the left thigh, 1 injection each at 2, 3, and 4 months co-administered with DTaP-IPV-HB-Hib and RotaTeq.

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

0.2 mL, oral route, 1 injection each at 2, 3, and 4 months co-administered with DTaP-IPV-HB-Hib and

Arm title	Group 2
Arm description:	
Subjects received 3 doses of Infanrix hexa co-administered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.	
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, 1 injection each at 2, 3, and 4 months co-administered with Prevenar 13 and RotaTeq.	
Investigational medicinal product name	Prevenar 13
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 into anterolateral area of the left thigh, 1 injection each at 2, 3, and 4 months co-administered with Infanrix hexa and RotaTeq.	
Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
0.2 mL, oral route, 1 injection each at 2, 3, and 4 months co-administered with Infanrix hexa and Prevenar 13.	
Arm title	Group 3
Arm description:	
Subjects from the sites in Spain, they received 2 doses of DTaP-IPV-HB-Hib vaccine 1 injection each at 2 and 6 months of age and 1 dose of Pentavac at 4 months. DTaP-IPV-HB-Hib vaccine and Pentavac were co-administered with Prevenar 13 at 2 and 4 months of age and at 6 months (depending on local use and at the Investigator’s discretion), NeisVac-C at 2 months, and RotaTeq at 2, 4, and 6 months of age + Hep B vaccine at birth.	
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, 1 injection each at 2 and 6 months of age co-administered with Prevenar 13 and Pentavac.	
Investigational medicinal product name	Prevenar 13
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 into anterolateral area of the left thigh, 1 injection each at 2 and 4 months co-administered with DTaP-IPV-HB-Hib and Pentavac.

Investigational medicinal product name	DTaP-IPV//PRP-T combined vaccine (Pentavac)
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, 1 injection each at 2 and 4 months co-administered with DTaP-IPV-HB-Hib vaccine and Prevenar 13.

Investigational medicinal product name	NeisVac-C
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 into the anterolateral area of the left thigh, 1 injection at 2 months of age.

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

0.2 mL, oral route, 1 administration each at 2, 4, and 6 months of age.

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	266	263	265
Completed	265	262	263
Not completed	1	1	2
Consent withdrawn by subject	-	1	-
Lost to follow-up	-	-	1
Protocol deviation	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects received 3 doses of DTaP-IPV-HB-Hib vaccine coadministered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.	
Reporting group title	Group 2
Reporting group description:	
Subjects received 3 doses of Infanrix hexa co-administered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.	
Reporting group title	Group 3
Reporting group description:	
Subjects from the sites in Spain, they received 2 doses of DTaP-IPV-HB-Hib vaccine 1 injection each at 2 and 6 months of age and 1 dose of Pentavac at 4 months. DTaP-IPV-HB-Hib vaccine and Pentavac were co-administered with Prevenar 13 at 2 and 4 months of age and at 6 months (depending on local use and at the Investigator's discretion), NeisVac-C at 2 months, and RotaTeq at 2, 4, and 6 months of age + Hep B vaccine at birth.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	266	263	265
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)	266	263	265
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	63	62.7	62
standard deviation	± 5.6	± 5.4	± 4.7
Gender categorical Units: Subjects			
Female	127	137	125
Male	139	126	140

Reporting group values	Total		
Number of subjects	794		
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)	794		
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: days			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	389		
Male	405		

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description:	
Subjects received 3 doses of DTaP-IPV-HB-Hib vaccine coadministered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.	
Reporting group title	Group 2
Reporting group description:	
Subjects received 3 doses of Infanrix hexa co-administered with Prevenar 13 and RotaTeq, 1 injection each at 2, 3, and 4 months of age at the study sites in Germany and Czech Republic.	
Reporting group title	Group 3
Reporting group description:	
Subjects from the sites in Spain, they received 2 doses of DTaP-IPV-HB-Hib vaccine 1 injection each at 2 and 6 months of age and 1 dose of Pentavac at 4 months. DTaP-IPV-HB-Hib vaccine and Pentavac were co-administered with Prevenar 13 at 2 and 4 months of age and at 6 months (depending on local use and at the Investigator's discretion), NeisVac-C at 2 months, and RotaTeq at 2, 4, and 6 months of age + Hep B vaccine at birth.	

Primary: Seroprotection or Response to Pertussis toxoid, Filamentous hemagglutinin, Hepatitis B and Hib Polysaccharide Antigens After Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13

End point title	Seroprotection or Response to Pertussis toxoid, Filamentous hemagglutinin, Hepatitis B and Hib Polysaccharide Antigens After Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13[1]
End point description:	
End point was assessed in Groups 1 and 2. Anti-Pertussis toxoid (PT) and anti-Filamentous hemagglutinin (FHA) antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Anti-Hepatitis B (Hep B) antibodies were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. Anti-Hib polysaccharide (PRP) concentrations were measured using a Farr-type radioimmunoassay (RIA). Seroprotection was defined as anti-Hep B antibody concentrations ≥ 10 mIU/mL and anti-PRP antibody concentrations ≥ 0.15 µg/mL. Vaccine response for PT and FHA were defined as follows: Post-dose 3 antibody concentrations ≥ 4X lower limit of quantitation (LLOQ), if Pre-dose 1 antibody concentrations < 4X LLOQ; Post-dose 3 antibody concentrations ≥ Pre-dose 1 antibody concentrations, if Pre-dose 1 antibody concentrations ≥ 4X LLOQ.	
End point type	Primary
End point timeframe:	
1 month post-dose 3	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	239		
Units: Percentage of subjects				
number (not applicable)				
Anti-PT	98.3	97.8		
Anti-FHA	99.1	94.8		

Anti-Hep B	95.7	98.7		
Anti-PRP	91.1	86.3		

Statistical analyses

Statistical analysis title	Non-inferiority (Group 1 - Group 2); Anti-PT
Statistical analysis description:	
Non-inferiority analysis of seroprotection, vaccine response rates of DTaP-IPV-HB-Hib vs Infanrix hexa.	
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Vaccine response (Group 1 - Group 2)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	3.44

Notes:

[2] - The 95% confidence interval (CI) was calculated based on the Wilson score method without continuity correction. If the lower bound of the 95% CI was greater than - δ then the null hypothesis H0 was rejected and non-inferiority would be concluded. In this analysis, DTaP-IPV-HB-Hib vaccine was non-inferior to Infanrix hexa vaccine.

Statistical analysis title	Non-inferiority (Group 1 - Group 2); Anti-FHA
Statistical analysis description:	
Non-inferiority analysis of seroprotection, vaccine response rates of DTaP-IPV-HB-Hib vs Infanrix hexa.	
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Vaccine response (Group 1 - Group 2)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	8.12

Notes:

[3] - The 95% confidence interval (CI) was calculated based on the Wilson score method without continuity correction. If the lower bound of the 95% CI was greater than - δ then the null hypothesis H0 was rejected and non-inferiority would be concluded. In this analysis, DTaP-IPV-HB-Hib vaccine was non-inferior to Infanrix hexa vaccine.

Statistical analysis title	Non-inferiority (Group 1 - Group 2); Anti-Hep B
Statistical analysis description:	
Non-inferiority analysis of seroprotection, vaccine response rates of DTaP-IPV-HB-Hib vs Infanrix hexa.	
Comparison groups	Group 1 v Group 2

Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Seroprotection (Group 1 - Group 2)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.59
upper limit	0.11

Notes:

[4] - The 95% confidence interval (CI) was calculated based on the Wilson score method without continuity correction. If the lower bound of the 95% CI was greater than - δ then the null hypothesis H0 was rejected and non-inferiority would be concluded. In this analysis, DTaP-IPV-HB-Hib vaccine was non-inferior to Infanrix hexa vaccine.

Statistical analysis title	Non-inferiority (Group 1 - Group 2); Anti-PRP

Statistical analysis description:

Non-inferiority analysis of seroprotection, vaccine response rates of DTaP-IPV-HB-Hib vs Infanrix hexa.

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Seroprotection (Group 1 - Group 2)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	10.74

Notes:

[5] - The 95% confidence interval (CI) was calculated based on the Wilson score method without continuity correction. If the lower bound of the 95% CI was greater than - δ then the null hypothesis H0 was rejected and non-inferiority would be concluded. In this analysis, DTaP-IPV-HB-Hib vaccine was non-inferior to Infanrix hexa vaccine.

Secondary: Summary of Vaccine Antibody Titers Before and After Dose 3 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13

End point title	Summary of Vaccine Antibody Titers Before and After Dose 3 Vaccinations with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13

End point description:

Anti-Tetanus antibodies were measured by enzyme-linked immunosorbent assay. Anti-Diphtheria antibodies were measured by a toxin neutralization test. Anti-Hepatitis B (Hep B) antibodies were measured by VITROS ECi/ECiQ Immunodiagnostic System. Anti-Poliovirus types 1, 2, and 3 were measured by neutralization assay. Anti-Hib polysaccharide (PRP) concentrations were measured using a Farr-type radioimmunoassay. Anti-Diphtheria and anti-Tetanus titers were assessed ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL. Vaccine response was anti-PT or anti-FHA concentrations in EU/mL ≥4x LLOQ if pre-vaccination concentration < 4x LLOQ or ≥ pre-vaccination concentration if pre-vaccination concentrations ≥ 4x LLOQ. Anti-Polio 1, 2, and 3 titers were assessed ≥ 8 (1/dil). Anti-Hep B titers were assessed ≥ 10 mIU/mL. Anti-PRP titers were assessed ≥ 0.15 µg/mL. Pre-dose 1 values were not available for Anti-Diphtheria, Anti-Tetanus, Anti-Polio 1, 2, 3, Anti-Hep B, and Anti-PRP for Groups 1 and 2.

End point type	Secondary

End point timeframe:

Pre- and Post-dose 3

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	231	231	
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria; ≥ 0.01 IU/mL; Pre-dose 1	0	0	60.8	
Anti-Diphtheria; ≥ 0.01 IU/mL; Post-dose 3	100	100	100	
Anti-Diphtheria; ≥ 0.1 IU/mL; Pre-dose 1	0	0	11.1	
Anti-Diphtheria; ≥ 0.1 IU/mL; Post-dose 3	61.8	58	97.6	
Anti-Tetanus; ≥ 0.01 IU/mL; Pre-dose 1	0	0	96.4	
Anti-Tetanus; ≥ 0.01 IU/mL; Post-dose 3	100	100	100	
Anti-Tetanus; ≥ 0.1 IU/mL; Pre-dose 1	0	0	85.5	
Anti-Tetanus; ≥ 0.1 IU/mL; Post-dose 3	100	100	100	
Anti-PT; ≥LLOQ; Pre-dose 1	63.1	66.1	63.1	
Anti-PT; ≥4 EU/mL; Post-dose 3	100	100	100	
Anti-FHA; ≥LLOQ; Pre-dose 1	91.9	89.8	89.2	
Anti-FHA; ≥4 EU/mL; Post-dose 3	100	100	100	
Anti-Polio 1; ≥ 8 (1/dil); Pre-dose 1	0	0	46.8	
Anti-Polio 1; ≥ 8 (1/dil); Post-dose 3	100	100	100	
Anti-Polio 2; ≥ 8 (1/dil); Pre-dose 1	0	0	56.7	
Anti-Polio 2; ≥ 8 (1/dil); Post-dose 3	100	100	99.5	
Anti-Polio 3; ≥ 8 (1/dil); Pre-dose 1	0	0	21.2	
Anti-Polio 3; ≥ 8 (1/dil); Post-dose 3	100	100	100	
Anti-Hep B; ≥ 10 mIU/mL; Pre-dose 1	0	0	39	
Anti-Hep B; ≥ 10 mIU/mL; Post-dose 3	95.7	98.7	99.1	
Anti-PRP; ≥ 15 µg/mL; Pre-dose 1	0	0	32.2	
Anti-PRP; ≥ 15 µg/mL; Post-dose 3	91.1	86.3	100	

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 Prevenar®13

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 Prevenar®13

End point description:

Anti-Pertussis toxoid (PT), anti-Filamentous hemagglutinin (FHA), and anti-Tetanus antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Anti-Diphtheria antibodies were measured by a toxin neutralization test. Anti-Hepatitis B (Hep B) antibodies were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology.

Anti-Poliovirus types 1, 2, and 3 were measured by neutralization assay. Anti-Hib polysaccharide (PRP) concentrations were measured using a Farr-type radioimmunoassay (RIA).

End point type	Secondary

End point timeframe:

Post-dose 3

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	235	236	227	
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria	0.163 (0.142 to 0.187)	0.148 (0.13 to 0.169)	0.79 (0.694 to 0.898)	
Anti-Tetanus	0.759 (0.689 to 0.836)	0.874 (0.791 to 0.965)	2.21 (2 to 2.44)	
Anti-Pertussis toxoid	116 (108 to 124)	131 (121 to 141)	97.1 (89.9 to 105)	
Anti-Filamentous hemagglutinin	141 (131 to 151)	84.3 (78 to 91)	165 (153 to 178)	
Anti-Polio 1	113 (96.7 to 133)	268 (226 to 317)	891 (760 to 1044)	
Anti-Polio 2	191 (163 to 225)	365 (305 to 437)	2027 (1669 to 2462)	
Anti-Polio 3	302 (261 to 351)	662 (552 to 793)	1485 (1243 to 1775)	
Anti-Hepatitis B	207 (170 to 253)	382 (324 to 450)	2719 (2272 to 3255)	
Anti-PRP	1.19 (0.978 to 1.45)	0.6 (0.505 to 0.713)	7.91 (6.75 to 9.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Immune Responses to Prevenar 13 and RotaTeq Antigens Following Co-administration with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™

End point title	Percentage of Subjects with Immune Responses to Prevenar 13 and RotaTeq Antigens Following Co-administration with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™[6]

End point description:

Anti-rotavirus IgA antibodies in human serum was measured by enzyme-linked immunosorbent assay (ELISA). The pneumococcal capsular polysaccharide (PS) IgG ELISA was used to quantitate the amount of anti-streptococcus pneumonia PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) antibodies in human serum. Immune responses were defined as Anti-rotavirus IgA ≥ 20 U/mL and for all pneumococcal serotypes ≥ 0.35 µg/mL.

End point type	Secondary

End point timeframe:

Pre-dose 1 (Anti-RV IgA) and post-dose 3 (for Anti-RV IgA and all pneumococcal serotypes)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	237		
Units: Percentage of subjects				
number (not applicable)				
Anti-Rotavirus IgA; Pre-dose 1	0.9	2.5		
Anti-Rotavirus IgA; Post-dose 3	92.5	89.5		
Pneumococcal Serotype 1; Post-dose 3	99.1	99.1		
Pneumococcal Serotype 3; Post-dose 3	95.2	96.8		
Pneumococcal Serotype 4; Post-dose 3	98.6	99.1		
Pneumococcal Serotype 5; Post-dose 3	87	95.4		
Pneumococcal Serotype 6A; Post-dose 3	93.1	93.2		
Pneumococcal Serotype 6B; Post-dose 3	77	86.4		
Pneumococcal Serotype 7F; Post-dose 3	100	100		
Pneumococcal Serotype 9V; Post-dose 3	95.8	97.7		
Pneumococcal Serotype 14; Post-dose 3	99.5	100		
Pneumococcal Serotype 18C; Post-dose 3	98.6	97.7		
Pneumococcal Serotype 19A; Post-dose 3	99.1	99.5		
Pneumococcal Serotype 19F; Post-dose 3	100	100		
Pneumococcal Serotype 23F; Post-dose 3	92.6	95		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations (GMCs) of Prevenar and RotaTeq Vaccine Antibodies Following Co-administration with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™

End point title	Geometric Mean Concentrations (GMCs) of Prevenar and RotaTeq Vaccine Antibodies Following Co-administration with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™[7]

End point description:

Anti-rotavirus IgA antibodies in human serum was measured by enzyme-linked immunosorbent assay (ELISA). The pneumococcal capsular polysaccharide (PS) IgG ELISA was used to quantitate the amount of anti-streptococcus pneumonia PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) antibodies in human serum.

End point type	Secondary

End point timeframe:

Post-dose 3

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	220		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Rotavirus	455 (350 to 593)	322 (250 to 415)		
Pneumococcal Serotype 1	1.84 (1.67 to 2.03)	2.33 (2.12 to 2.57)		
Pneumococcal Serotype 3	1.09 (0.995 to 1.19)	1.33 (1.22 to 1.44)		
Pneumococcal Serotype 4	2.06 (1.9 to 2.25)	2.76 (2.52 to 3.03)		
Pneumococcal Serotype 5	0.777 (0.704 to 0.858)	0.996 (0.913 to 1.09)		
Pneumococcal Serotype 6A	1.4 (1.24 to 1.58)	1.67 (1.49 to 1.88)		
Pneumococcal Serotype 6B	0.762 (0.662 to 0.877)	1.09 (0.948 to 1.26)		
Pneumococcal Serotype 7F	2.46 (2.26 to 2.69)	2.89 (2.65 to 3.16)		
Pneumococcal Serotype 9V	1.16 (1.06 to 1.27)	1.46 (1.34 to 1.59)		
Pneumococcal Serotype 14	6.78 (5.91 to 7.77)	9.34 (8.36 to 10.4)		
Pneumococcal Serotype 18C	1.62 (1.47 to 1.78)	2.03 (1.84 to 2.24)		
Pneumococcal Serotype 19A	3.3 (2.99 to 3.64)	4.01 (3.63 to 4.43)		
Pneumococcal Serotype 19F	3.19 (2.95 to 3.45)	4.05 (3.74 to 4.39)		
Pneumococcal Serotype 23F	1.33 (1.18 to 1.52)	1.61 (1.42 to 1.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Any Vaccination with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Any Vaccination with Hexavalent DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa™ Concomitantly Administered With Prevenar®13

End point description:

Solicited injection site reactions: Pain (Tenderness), Erythema, and Swelling. Solicited systemic reactions: Pyrexia (Fever), Vomiting, Crying, Somnolence (Drowsiness), Anorexia (Appetite lost), 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 Solicited systemic

reactions: Pyrexia (Fever), > 39.5°C; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Somnolence (Drowsiness), Sleeping most of the time or difficult to wake up; Appetite lost (Anorexia), Refuses ≥ 3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-any injection

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	265	261	265	
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	67.5	67.8	65.7	
Grade 3 Injection site Pain	8.7	6.9	6	
Injection site Erythema	61.5	57.5	43	
Grade 3 Injection site Erythema	2.3	1.1	0.8	
Injection site Swelling	48.7	46	32.1	
Grade 3 Injection site Swelling	1.9	1.9	0.4	
Pyrexia	72.8	56.7	58.9	
Grade 3 Pyrexia	3	1.1	1.9	
Vomiting	35.5	27.6	35.5	
Grade 3 Vomiting	1.1	0.8	0.8	
Crying abnormal	76.6	74.3	76.6	
Grade 3 Crying abnormal	9.1	8	7.9	
Somnolence	73.6	70.1	72.8	
Grade 3 Somnolence	3.4	1.5	4.9	
Anorexia	55.8	48.7	64.5	
Grade 3 Anorexia	2.3	1.9	1.1	
Irritability	78.9	75.9	83.8	
Grade 3 Irritability	9.8	8	9.4	

Statistical analyses

No statistical analyses for this end point

Secondary: 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 Prevenar®13

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 Prevenar®13

End point description:

Solicited injection site reactions: Pain (Tenderness), Erythema, and Swelling. Solicited systemic reactions: Pyrexia (Fever), Vomiting, Crying, Somnolence (Drowsiness), Anorexia (Appetite lost), 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 Solicited systemic reactions: Pyrexia (Fever), > 39.5°C; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral

hydration; Crying abnormal, > 3 hours; Somnolence (Drowsiness), Sleeping most of the time or difficult to wake up; Appetite lost (Anorexia), Refuses ≥ 3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary
End point timeframe:	
Day 0 up to Day 7 post-each injection	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	265	261	265	
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; DTaP-IPV-HB-Hib site	63.8	0	0	
Injection site Pain; DTaP-IPV-HB-Hib/Pentavac	0	0	62.6	
Injection site Pain; Prevenar 13	61.5	60.5	56.6	
Injection site Pain; Infanrix hexa	0	62.1	0	
Inj. site Pain, Post-Inj. 1; DTaP-IPV-HB-Hib site	44.5	0	0	
Pain, Post-Inj. 1; DTaP-IPV-HB-Hib/Pentavac	0	0	49.8	
Pain, Post-Inj. 1; Prevenar 13	42.3	45.6	46.4	
Pain, Post-Inj. 1; Infanrix hexa	0	46.4	0	
Inj. site Pain, Post-Inj. 2; DTaP-IPV-HB-Hib site	45.7	0	0	
Pain, Post-Inj. 2; DTaP-IPV-HB-Hib/Pentavac	0	0	31.4	
Pain, Post-Inj. 2; Prevenar 13	43.4	39.1	27.3	
Pain, Post-Inj. 2; Infanrix hexa	0	39.8	0	
Inj. site Pain, Post-Inj. 3; DTaP-IPV-HB-Hib site	33.7	0	0	
Pain, Post-Inj. 3; DTaP-IPV-HB-Hib/Pentavac	0	0	35	
Pain, Post-Inj. 3; Prevenar 13	32.2	32.6	31.8	
Pain, Post-Inj. 3; Infanrix hexa	0	37.5	0	
Injection site Erythema; DTaP-IPV-HB-Hib site	55.1	0	0	
Injection site Erythema; DTaP-IPV-HB-Hib/Pentavac	0	0	37.4	
Injection site Erythema; Prevenar 13	50.2	46.7	26.4	
Injection site Erythema; Infanrix hexa	0	48.3	0	
Inj. site Erythema, Post-Inj. 1; DTaP-IPV-HB-Hib	28.3	0	0	
Erythema, Post-Inj. 1; DTaP-IPV-HB-Hib/Pentavac	0	0	14.7	
Erythema, Post-Inj. 1; Prevenar 13	27.5	23.8	9.8	
Erythema, Post-Inj. 1; Infanrix hexa	0	24.1	0	
Inj. site Erythema, Post-Inj. 2; DTaP-IPV-HB-Hib	39.6	0	0	
Erythema, Post-Inj. 2; DTaP-IPV-HB-Hib/Pentavac	0	0	16.3	
Erythema, Post-Inj. 2; Prevenar 13	30.2	29.5	12.1	
Erythema, Post-Inj. 2; Infanrix hexa	0	33.7	0	

Inj. site Erythema, Post-Inj. 3; DTaP-IPV-HB-Hib	38.3	0	0	
Erythema, Post-Inj. 3; DTaP-IPV-HB-Hib/Pentavac	0	0	20.9	
Erythema, Post-Inj. 3; Prevenar 13	31.1	28.4	13.7	
Erythema, Post-Inj. 3; Infanrix hexa	0	31	0	
Injection site Swelling; DTaP-IPV-HB-Hib site	42.6	0	0	
Injection site Swelling; DTaP-IPV-HB-Hib/Pentavac	0	0	26.8	
Injection site Swelling; Prevenar 13	38.9	36	21.5	
Injection site Swelling; Infanrix hexa	0	38.3	0	
Inj. site Swelling, Post-Inj. 1; DTaP-IPV-HB-Hib	21.5	0	0	
Swelling, Post-Inj. 1; DTaP-IPV-HB-Hib/Pentavac	0	0	15.1	
Swelling, Post-Inj. 1; Prevenar 13	22.3	18.4	11.7	
Swelling, Post-Inj. 1; Infanrix hexa	0	17.6	0	
Inj. site Swelling, Post-Inj. 2; DTaP-IPV-HB-Hib	25.7	0	0	
Swelling, Post-Inj. 2; DTaP-IPV-HB-Hib/Pentavac	0	0	11	
Swelling, Post-Inj. 2; Prevenar 13	21.9	21.5	9.8	
Swelling, Post-Inj. 2; Infanrix hexa	0	19.9	0	
Inj. site Swelling, Post-Inj. 3; DTaP-IPV-HB-Hib	25.8	0	0	
Swelling, Post-Inj. 3; DTaP-IPV-HB-Hib/Pentavac	0	0	13.3	
Swelling, Post-Inj. 3; Prevenar 13	20.1	23	9	
Swelling, Post-Inj. 3; Infanrix hexa	0	25.7	0	
Pyrexia	72.8	56.7	58.9	
Pyrexia; Post-Injection 1	54	29.6	34.1	
Pyrexia; Post-Injection 2	51.7	39.5	24.6	
Pyrexia; Post-Injection 3	30	26.4	40.1	
Vomiting	35.5	27.6	35.5	
Vomiting; Post-Injection 1	23	13.4	20	
Vomiting; Post-Injection 2	18.5	14.9	12.5	
Vomiting; Post-Injection 3	14.8	9.6	17.1	
Crying abnormal	76.6	74.3	76.6	
Crying abnormal; Post-Injection 1	59.6	52.5	57.4	
Crying abnormal; Post-Injection 2	60.4	52.9	51.1	
Crying abnormal; Post-Injection 3	39.8	38.3	49.8	
Somnolence	73.6	70.1	72.8	
Somnolence; Post-Injection 1	60.4	54.8	56.2	
Somnolence; Post-Injection 2	49.1	45.6	43.9	
Somnolence; Post-Injection 3	39.8	34.1	36.1	
Anorexia	55.8	48.7	64.5	
Anorexia; Post-Injection 1	39.6	32.2	49.1	
Anorexia; Post-Injection 2	33.6	25.3	35.6	
Anorexia; Post-Injection 3	23.9	18.4	36.9	
Irritability	78.9	75.9	83.8	
Irritability; Post-Injection 1	64.9	55.6	70.6	
Irritability; Post-Injection 2	59.6	51.3	62.9	
Irritability; Post-Injection 3	46.2	44.8	59.3	

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 30 post-each vaccination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects received 3 doses of DTaP-IPV-HB-Hib vaccine coadministered with Prevenar 13 and RotaTeq at 2, 3, and 4 months of age.	
Reporting group title	Group 2
Reporting group description:	
Subjects received 3 doses of Infanrix hexa co-administered with Prevenar 13 and RotaTeq at 2, 3, and 4 months of age.	
Reporting group title	Group 3
Reporting group description:	
Subjects received 2 doses of DTaP-IPV-HB-Hib vaccine at 2 and 6 months of age and 1 dose of Pentavac at 4 months. DTaP-IPV-HB-Hib vaccine and Pentavac were co-administered with Prevenar 13 at 2 and 4 months of age and at 6 months (depending on local use and at the Investigator's discretion), NeisVac-C at 2 months, and RotaTeq at 2, 4, and 6 months of age.	

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 265 (4.53%)	9 / 261 (3.45%)	11 / 265 (4.15%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Haemangioma			

subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Head injury			
subjects affected / exposed	2 / 265 (0.75%)	1 / 261 (0.38%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip dysplasia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			

subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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
Inguinal hernia strangulated			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Psychiatric disorders			
Restlessness			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 265 (0.75%)	1 / 261 (0.38%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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

Gastroenteritis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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
Pneumonia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 261 (0.00%)	0 / 265 (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
Pyelonephritis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diet refusal			
subjects affected / exposed	0 / 265 (0.00%)	1 / 261 (0.38%)	0 / 265 (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
Weight gain poor			
subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	209 / 265 (78.87%)	198 / 261 (75.86%)	222 / 265 (83.77%)
Nervous system disorders			
Any Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	195 / 265 (73.58%)	183 / 261 (70.11%)	193 / 265 (72.83%)
occurrences (all)	395	351	360
General disorders and administration site conditions			
Any Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed	179 / 265 (67.55%)	177 / 261 (67.82%)	174 / 265 (65.66%)
occurrences (all)	640	629	583
Any Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed	163 / 265 (61.51%)	150 / 261 (57.47%)	114 / 265 (43.02%)
occurrences (all)	516	445	230
Any Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	129 / 265 (48.68%)	120 / 261 (45.98%)	85 / 265 (32.08%)
occurrences (all)	363	329	184
Any Pyrexia			
alternative assessment type: Systematic			

subjects affected / exposed	193 / 265 (72.83%)	148 / 261 (56.70%)	156 / 265 (58.87%)
occurrences (all)	359	249	260
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 265 (1.13%)	12 / 261 (4.60%)	15 / 265 (5.66%)
occurrences (all)	4	14	16
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 265 (0.75%)	2 / 261 (0.77%)	17 / 265 (6.42%)
occurrences (all)	2	2	18
Any Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	94 / 265 (35.47%)	72 / 261 (27.59%)	94 / 265 (35.47%)
occurrences (all)	149	99	131
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 265 (12.83%)	22 / 261 (8.43%)	12 / 265 (4.53%)
occurrences (all)	45	24	13
Psychiatric disorders			
Any Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	203 / 265 (76.60%)	194 / 261 (74.33%)	203 / 265 (76.60%)
occurrences (all)	423	375	418
Any Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	209 / 265 (78.87%)	198 / 261 (75.86%)	222 / 265 (83.77%)
occurrences (all)	452	396	509
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 265 (3.02%)	15 / 261 (5.75%)	20 / 265 (7.55%)
occurrences (all)	10	16	24
Respiratory tract infection			
subjects affected / exposed	4 / 265 (1.51%)	4 / 261 (1.53%)	22 / 265 (8.30%)
occurrences (all)	4	4	24
Respiratory tract infection viral			

subjects affected / exposed	0 / 265 (0.00%)	0 / 261 (0.00%)	20 / 265 (7.55%)
occurrences (all)	0	0	22
Rhinitis			
subjects affected / exposed	24 / 265 (9.06%)	13 / 261 (4.98%)	1 / 265 (0.38%)
occurrences (all)	24	16	1
Metabolism and nutrition disorders			
Any Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed	148 / 265 (55.85%)	127 / 261 (48.66%)	171 / 265 (64.53%)
occurrences (all)	257	198	321

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2013	Administration of a third dose of pneumococcal conjugate vaccine (Prevenar 13) was added as optional based on local use and at the Investigator's discretion, immune response analysis was also to be assessed in Germany and Czech Republic, and the reference to the booster study was deleted (no diary cards were provided to subjects/parents at the end of the study in Spain).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported