



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) | EMA-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 $\geq 4X$ lower limit of quantitation (LLOQ), if Pre-dose 1 antibody concentrations $< 4X$ LLOQ; Post-dose 3 antibody concentrations \geq Pre-dose 1 antibody concentrations, if Pre-dose 1 antibody concentrations $\geq 4X$ 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 $\geq 4 \times$ LLOQ if pre-vaccination concentration $< 4 \times$ LLOQ or \geq pre-vaccination concentration if pre-vaccination concentrations $\geq 4 \times$ 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 μ g/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; \geq LLOQ; Pre-dose 1 | 63.1 | 66.1 | 63.1 | |
| Anti-PT; ≥ 4 EU/mL; Post-dose 3 | 100 | 100 | 100 | |
| Anti-FHA; \geq 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 μ g/mL; Pre-dose 1 | 0 | 0 | 32.2 | |
| Anti-PRP; ≥ 15 μ g/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 RotaTeg 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 RotaTeg 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 RotaTeg 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 occurrences (all) | 193 / 265 (72.83%) 359 | 148 / 261 (56.70%) 249 | 156 / 265 (58.87%) 260 |
| Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 265 (1.13%) 4 | 12 / 261 (4.60%) 14 | 15 / 265 (5.66%) 16 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Any Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 2 / 265 (0.75%) 2 94 / 265 (35.47%) 149 | 2 / 261 (0.77%) 2 72 / 261 (27.59%) 99 | 17 / 265 (6.42%) 18 94 / 265 (35.47%) 131 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 34 / 265 (12.83%) 45 | 22 / 261 (8.43%) 24 | 12 / 265 (4.53%) 13 |
| Psychiatric disorders Any Crying abnormal alternative assessment type: Systematic subjects affected / exposed occurrences (all) Any Irritability alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 203 / 265 (76.60%) 423 209 / 265 (78.87%) 452 | 194 / 261 (74.33%) 375 198 / 261 (75.86%) 396 | 203 / 265 (76.60%) 418 222 / 265 (83.77%) 509 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Respiratory tract infection viral | 8 / 265 (3.02%) 10 4 / 265 (1.51%) 4 | 15 / 261 (5.75%) 16 4 / 261 (1.53%) 4 | 20 / 265 (7.55%) 24 22 / 265 (8.30%) 24 |

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