



## Clinical trial results:

### Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-Hep B-PRP-T Combined Vaccine at 2, 4, and 6 Months of Age versus Sanofi Pasteur's DTaP-IPV//PRP-T Combined Vaccine at 2, 4, and 6 Months of Age + Hep B Vaccine at 1 and 6 Months of Age, in South Korean Infants Primed with Hep B at Birth

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002873-36 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 20 April 2016  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 14 October 2017 |
| First version publication date | 14 October 2017 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | A3L31 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02094833     |
| WHO universal trial number (UTN)   | U1111-1127-6896 |

Notes:

#### Sponsors

|                              |                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------|
| Sponsor organisation name    | Sanofi Pasteur SA                                                                      |
| Sponsor organisation address | 2, avenue Pont Pasteur, Lyon cedex 07, France, F-69367                                 |
| Public contact               | Medical Product Leader, Sanofi Pasteur SA, 33 4 37 65 67 99, Emmanuel.Vidor@sanofi.com |
| Scientific contact           | Medical Product Leader, Sanofi Pasteur SA, 33 4 37 65 67 99, Emmanuel.Vidor@sanofi.com |

Notes:

#### Paediatric regulatory details

|                                                                      |     |
|----------------------------------------------------------------------|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 28 October 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 20 April 2016   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority in terms of seroprotection (Diphtheria, Tetanus, poliovirus types 1, 2, and 3, PRP-T, Hepatitis B) and vaccine response for pertussis antigens (pertussis toxoid [PT] and filamentous haemagglutinin [FHA]) of Group A (DTaP-IPV-Hep B-PRP-T combined vaccine) versus Group B (DTaP-IPV//PRP~T vaccine [Pentaxim]), one month after the third dose of combined vaccines.

Protection of trial subjects:

Only subjects that met all the study inclusion and no exclusion criteria were randomized and vaccinated in the study. In addition, 9 subjects who did not meet the eligibility criteria were also vaccinated in the study but were not included in the Per Protocol Analysis Set. 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:

All subjects enrolled in this study received a dose of recombinant hepatitis B vaccine at birth according to the National Immunization Program in Republic of Korea.

Evidence for comparator:

Not applicable

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 19 March 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 | Korea, Republic of: 310 |
| Worldwide total number of subjects   | 310                     |
| EEA total number of subjects         | 0                       |

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)  | 310 |

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

## Subject disposition

### Recruitment

Recruitment details:

Study subjects were enrolled from 19 March 2014 to 01 October 2015 at 18 clinic centers in Republic of Korea.

### Pre-assignment

Screening details:

A total of 310 subjects were included in the study. Of those subjects, 301 subjects who met all inclusion and no exclusion criteria were randomized and vaccinated; 9 subjects were vaccinated but excluded from the Per Protocol Analysis Set.

### Period 1

|                                  |                                |
|----------------------------------|--------------------------------|
| Period 1 title                   | Overall trial (overall period) |
| Is this the baseline period?     | Yes                            |
| Allocation method                | Randomised - controlled        |
| Blinding used                    | Not blinded                    |
| Blinding implementation details: |                                |
| Not applicable                   |                                |

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | DTaP-IPV-Hep B-PRP~T |

Arm description:

Infants received 3 injections of DTaP-IPV-Hep B-PRP~T at 2, 4, and 6 months of age.

|                                        |                                                |
|----------------------------------------|------------------------------------------------|
| Arm type                               | Experimental                                   |
| Investigational medicinal product name | DTaP-IPV-Hep B-PRP~T (Hexaxim™)                |
| 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 right thigh, 1 injection at 2, 4, and 6 months of age

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | DTaP-IPV//PRP~T and Hepatitis B |
|------------------|---------------------------------|

Arm description:

Infants received Hep B Vaccine (Euvax B®) at 1 and 6 months of age and DTaP-IPV/PRP~T combined vaccine (Pentaxim™) at 2, 4, and 6 months of age.

|                                        |                                                    |
|----------------------------------------|----------------------------------------------------|
| Arm type                               | Active comparator                                  |
| Investigational medicinal product name | DTaP-IPV//PRP~T (Pentaxim™)                        |
| 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 aspect of the right thigh, 1 injection each at 2, 4, and 6 months of age

|                                        |                                                       |
|----------------------------------------|-------------------------------------------------------|
| Investigational medicinal product name | Recombinant hepatitis B monovalent vaccine (Euvax B®) |
| Investigational medicinal product code |                                                       |
| Other name                             |                                                       |
| Pharmaceutical forms                   | Suspension for injection                              |
| Routes of administration               | Intramuscular use                                     |

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**Dosage and administration details:**

0.5 mL, intramuscular into the anterolateral aspect of the left thigh, 1 injection each at 1 and 6 months of age

| <b>Number of subjects in period 1</b> | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |
|---------------------------------------|----------------------|---------------------------------|
| Started                               | 153                  | 157                             |
| Completed                             | 148                  | 153                             |
| Not completed                         | 5                    | 4                               |
| Consent withdrawn by subject          | 4                    | 2                               |
| Lost to follow-up                     | -                    | 1                               |
| Protocol deviation                    | 1                    | 1                               |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                  |                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                            | DTaP-IPV-Hep B-PRP~T            |
| Reporting group description:<br>Infants received 3 injections of DTap-IPV-Hep B-PRP~T at 2, 4, and 6 months of age.                                                              |                                 |
| Reporting group title                                                                                                                                                            | DTaP-IPV//PRP~T and Hepatitis B |
| Reporting group description:<br>Infants received Hep B Vaccine (Euvax B®) at 1 and 6 months of age and DTap-IPV/PRP~T combined vaccine (Pentaxim™) at 2, 4, and 6 months of age. |                                 |

| Reporting group values                             | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B | Total |
|----------------------------------------------------|----------------------|---------------------------------|-------|
| Number of subjects                                 | 153                  | 157                             | 310   |
| 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)           | 153                  | 157                             | 310   |
| 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                                    | 33.9                 | 33.8                            |       |
| standard deviation                                 | ± 2.8                | ± 2.8                           | -     |
| Gender categorical                                 |                      |                                 |       |
| Units: Subjects                                    |                      |                                 |       |
| Female                                             | 63                   | 75                              | 138   |
| Male                                               | 90                   | 82                              | 172   |

## End points

### End points reporting groups

|                                                                                                                                                   |                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                             | DTaP-IPV-Hep B-PRP~T            |
| Reporting group description:                                                                                                                      |                                 |
| Infants received 3 injections of DTaP-IPV-Hep B-PRP~T at 2, 4, and 6 months of age.                                                               |                                 |
| Reporting group title                                                                                                                             | DTaP-IPV//PRP~T and Hepatitis B |
| Reporting group description:                                                                                                                      |                                 |
| Infants received Hep B Vaccine (Euvax B®) at 1 and 6 months of age and DTaP-IPV//PRP~T combined vaccine (Pentaxim™) at 2, 4, and 6 months of age. |                                 |

### Primary: Percentage of Subjects with Seroconversion or Seroconversion Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Percentage of Subjects with Seroconversion or Seroconversion Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                            |
| Anti-Diphtheria antibodies were assessed by a toxin neutralization test. Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti-Filamentous hemagglutinin (FHA) antibodies were assessed using an enzyme-linked immunosorbent assay. Anti-PRP antibodies were assessed by a Farr-type radioimmunoassay. Anti-Hepatitis B antibodies were measured by the VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. Anti-Poliovirus (Polio) types 1, 2, and 3 antibodies were assessed by a neutralization assay, the poliovirus Micrometabolic Inhibition Test. Seroconversion was defined as the following: Anti-Diphtheria ≥0.01 International Units (IU)/mL, Anti-Tetanus ≥0.1 IU/mL, Anti-PRP ≥0.15 µg/mL, Anti Poliovirus types 1, 2, and 3 ≥8 (1/dilution), and Anti-Hepatitis B ≥10 mIU/mL. Seroconversion for Anti-PT and Anti-FHA was defined as a ≥4-fold increase from 1 month pre-dose 1 to 1 month post-dose 3 in Anti-PT and Anti-FHA antibody concentrations (EU/mL). |                                                                                                                                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Primary                                                                                                                                                                                    |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                            |
| 1 month post-dose 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                            |

| End point values              | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|-------------------------------|----------------------|---------------------------------|--|--|
| Subject group type            | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed   | 132                  | 131                             |  |  |
| Units: Percentage of subjects |                      |                                 |  |  |
| number (not applicable)       |                      |                                 |  |  |
| Anti-Diphtheria               | 100                  | 100                             |  |  |
| Anti-Tetanus                  | 99.2                 | 100                             |  |  |
| Anti-Polio 1                  | 100                  | 100                             |  |  |
| Anti-Polio 2                  | 100                  | 100                             |  |  |
| Anti-Polio 3                  | 100                  | 100                             |  |  |
| Anti-PRP                      | 100                  | 100                             |  |  |
| Anti-Hepatitis B              | 97.7                 | 96.9                            |  |  |
| Anti-PT                       | 94.6                 | 93                              |  |  |
| Anti-FHA                      | 91.7                 | 89.3                            |  |  |

## Statistical analyses

|                                                                                                                                                                 |                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                               | Non-inferiority: Diphtheria                            |
| Statistical analysis description:                                                                                                                               |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Diphtheria. |                                                        |
| Comparison groups                                                                                                                                               | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis                                                                                                                         | 263                                                    |
| Analysis specification                                                                                                                                          | Pre-specified                                          |
| Analysis type                                                                                                                                                   | non-inferiority <sup>[1]</sup>                         |
| Parameter estimate                                                                                                                                              | Percent observed (Group A-Group B)                     |
| Point estimate                                                                                                                                                  | 0                                                      |
| Confidence interval                                                                                                                                             |                                                        |
| level                                                                                                                                                           | 95 %                                                   |
| sides                                                                                                                                                           | 2-sided                                                |
| lower limit                                                                                                                                                     | -2.87                                                  |
| upper limit                                                                                                                                                     | 2.98                                                   |

Notes:

[1] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Diphtheria, non-inferiority was met.

|                                                                                                                                                              |                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                            | Non-inferiority: Tetanus                               |
| Statistical analysis description:                                                                                                                            |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Tetanus. |                                                        |
| Comparison groups                                                                                                                                            | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis                                                                                                                      | 263                                                    |
| Analysis specification                                                                                                                                       | Pre-specified                                          |
| Analysis type                                                                                                                                                | non-inferiority <sup>[2]</sup>                         |
| Parameter estimate                                                                                                                                           | Percent observed (Group A-Group B)                     |
| Point estimate                                                                                                                                               | -0.8                                                   |
| Confidence interval                                                                                                                                          |                                                        |
| level                                                                                                                                                        | 95 %                                                   |
| sides                                                                                                                                                        | 2-sided                                                |
| lower limit                                                                                                                                                  | -4.29                                                  |
| upper limit                                                                                                                                                  | 2.29                                                   |

Notes:

[2] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Tetanus, non-inferiority was met.

|                                                                                                                                                              |                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                            | Non-inferiority: Polio 1                               |
| Statistical analysis description:                                                                                                                            |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Polio 1. |                                                        |
| Comparison groups                                                                                                                                            | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Number of subjects included in analysis | 263                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[3]</sup>     |
| Parameter estimate                      | Percent observed (Group A-Group B) |
| Point estimate                          | 0                                  |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -2.87                              |
| upper limit                             | 2.85                               |

Notes:

[3] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Polio 1, non-inferiority was met.

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | Non-inferiority: Polio 2 |
|-----------------------------------|--------------------------|

Statistical analysis description:

This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Polio 2.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis | 263                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           | non-inferiority <sup>[4]</sup>                         |
| Parameter estimate                      | Percent observed (Group A-Group B)                     |
| Point estimate                          | 0                                                      |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -2.87                                                  |
| upper limit                             | 2.91                                                   |

Notes:

[4] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Polio 2, non-inferiority was met.

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | Non-inferiority: Polio 3 |
|-----------------------------------|--------------------------|

Statistical analysis description:

This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Polio 3.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis | 263                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           | non-inferiority <sup>[5]</sup>                         |
| Parameter estimate                      | Percent observed (Group A-Group B)                     |
| Point estimate                          | 0                                                      |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -2.87                                                  |
| upper limit                             | 2.89                                                   |

Notes:

[5] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Polio 3, non-inferiority was met.

|                                                                                                                                                          |                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                        | Non-inferiority: PRP                                   |
| Statistical analysis description:                                                                                                                        |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for PRP. |                                                        |
| Comparison groups                                                                                                                                        | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis                                                                                                                  | 263                                                    |
| Analysis specification                                                                                                                                   | Pre-specified                                          |
| Analysis type                                                                                                                                            | non-inferiority <sup>[6]</sup>                         |
| Parameter estimate                                                                                                                                       | Percent observed (Group A-Group B)                     |
| Point estimate                                                                                                                                           | 0                                                      |
| Confidence interval                                                                                                                                      |                                                        |
| level                                                                                                                                                    | 95 %                                                   |
| sides                                                                                                                                                    | 2-sided                                                |
| lower limit                                                                                                                                              | -2.83                                                  |
| upper limit                                                                                                                                              | 2.85                                                   |

Notes:

[6] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For PRP, non-inferiority was met.

|                                                                                                                                                                                   |                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                 | Non-inferiority: Hepatitis B                           |
| Statistical analysis description:                                                                                                                                                 |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T combined vaccine (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for Hepatitis B. |                                                        |
| Comparison groups                                                                                                                                                                 | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis                                                                                                                                           | 263                                                    |
| Analysis specification                                                                                                                                                            | Pre-specified                                          |
| Analysis type                                                                                                                                                                     | non-inferiority <sup>[7]</sup>                         |
| Parameter estimate                                                                                                                                                                | Percent observed (Group A-Group B)                     |
| Point estimate                                                                                                                                                                    | 0.8                                                    |
| Confidence interval                                                                                                                                                               |                                                        |
| level                                                                                                                                                                             | 95 %                                                   |
| sides                                                                                                                                                                             | 2-sided                                                |
| lower limit                                                                                                                                                                       | -3.81                                                  |
| upper limit                                                                                                                                                                       | 5.56                                                   |

Notes:

[7] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T combined vaccine (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For Hepatitis B, non-inferiority was met.

|                                                                                                                                                         |                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                       | Non-inferiority: PT                                    |
| Statistical analysis description:                                                                                                                       |                                                        |
| This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for PT. |                                                        |
| Comparison groups                                                                                                                                       | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis                                                                                                                 | 263                                                    |
| Analysis specification                                                                                                                                  | Pre-specified                                          |
| Analysis type                                                                                                                                           | non-inferiority <sup>[8]</sup>                         |
| Parameter estimate                                                                                                                                      | Percent observed (Group A-Group B)                     |
| Point estimate                                                                                                                                          | 1.6                                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4.68   |
| upper limit         | 8.03    |

Notes:

[8] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For PT, non-inferiority was met.

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | Non-inferiority: FHA |
|-----------------------------------|----------------------|

Statistical analysis description:

This analysis was performed to determine the non-inferiority of the DTaP-IPV-Hep B-PRP~T (Group A) vs DTaP-IPV//PRP~T and Hepatitis B (Group B) for FHA.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | DTaP-IPV-Hep B-PRP~T v DTaP-IPV//PRP~T and Hepatitis B |
| Number of subjects included in analysis | 263                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           | non-inferiority <sup>[9]</sup>                         |
| Parameter estimate                      | Percent observed (Group A-Group B)                     |
| Point estimate                          | 2.4                                                    |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -4.96                                                  |
| upper limit                             | 9.75                                                   |

Notes:

[9] - Non-inferiority was assessed by DTaP-IPV-Hep B-PRP~T (Group A) minus DTaP-IPV//PRP~T and Hepatitis B (Group B). If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and non-inferiority was met. For FHA, non-inferiority was met.

### **Secondary: Summary of Vaccine Antibodies' Titers Before First Dose and After Third Dose Vaccination with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)**

|                 |                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Summary of Vaccine Antibodies' Titers Before First Dose and After Third Dose Vaccination with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-Diphtheria antibodies were assessed by a toxin neutralization test. Anti-Tetanus, Anti-PT, and Anti-FHA antibodies were assessed using an enzyme-linked immunosorbent assay. Anti-PRP antibodies were assessed by a Farr-type radioimmunoassay. Anti-Hepatitis B was measured by the VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence. Anti-Polio types 1, 2, and 3 antibodies were assessed by a neutralization assay, the poliovirus Micrometabolic Inhibition Test. Seroprotection was defined as: Anti-Diphtheria  $\geq 0.01$  IU/mL (pre- and post-doses), Anti-Tetanus  $\geq 0.1$  IU/mL (post dose), Anti-PRP  $\geq 0.15$  µg/mL (post dose), Anti Poliovirus types 1, 2, and 3  $\geq 8$  (1/dilution; post doses), Anti-Hepatitis B  $\geq 10$  mIU/mL (pre- and post doses). Vaccine response was defined as Anti-PT or Anti-FHA antibody concentrations in ELISA units (EU)/mL  $\geq 4\times$  lower limit of quantitation (LLOQ) if pre-vaccination concentration  $< 4\times$  LLOQ or  $\geq$  pre-vaccination concentration if pre-vaccination concentration  $\geq 4\times$  LLOQ.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose 1 and post-dose 3

| End point values                                  | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|---------------------------------------------------|----------------------|---------------------------------|--|--|
| Subject group type                                | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed                       | 132                  | 131                             |  |  |
| Units: Percentage of subjects                     |                      |                                 |  |  |
| number (not applicable)                           |                      |                                 |  |  |
| Anti-Diphtheria; Pre-dose 1 ( $\geq 0.01$ IU/mL)  | 54.7                 | 48.1                            |  |  |
| Anti-Diphtheria; Pre-dose 1 ( $\geq 0.1$ IU/mL)   | 5.5                  | 4.6                             |  |  |
| Anti-Diphtheria; Post-dose 3 ( $\geq 0.01$ IU/mL) | 100                  | 100                             |  |  |
| Anti-Diphtheria; Post-dose 3 ( $\geq 0.1$ IU/mL)  | 98.5                 | 97.6                            |  |  |
| Anti-Tetanus; Post-dose 3 ( $\geq 0.01$ IU/mL)    | 100                  | 100                             |  |  |
| Anti-Tetanus; Post-dose 3 ( $\geq 0.1$ IU/mL)     | 99.2                 | 100                             |  |  |
| Anti-Polio 1; Post-dose 3 ( $\geq 8$ [1/dil])     | 100                  | 100                             |  |  |
| Anti-Polio 2; Post-dose 3 ( $\geq 8$ [1/dil])     | 100                  | 100                             |  |  |
| Anti-Polio 3; Post-dose 3 ( $\geq 8$ [1/dil])     | 100                  | 100                             |  |  |
| Anti-PRP; Post-dose 3 ( $\geq 0.15$ µg/ml)        | 100                  | 100                             |  |  |
| Anti-PRP; Post-dose 3 ( $\geq 1$ µg/ml)           | 87.1                 | 96.9                            |  |  |
| Anti-Hepatitis B; Pre-dose 1 ( $\geq 10$ mIU/mL)  | 74                   | 68.7                            |  |  |
| Anti-Hepatitis B; Post-dose 3 ( $\geq 10$ mIU/mL) | 97.7                 | 96.9                            |  |  |
| Anti-PT; Vaccine response                         | 98.4                 | 98.4                            |  |  |
| Anti-PT; 4-fold increase                          | 94.6                 | 93                              |  |  |
| Anti-FHA; Vaccine response                        | 97.7                 | 96.2                            |  |  |
| Anti-FHA; 4-fold increase                         | 91.7                 | 89.3                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Concentrations (GMCs) of Antibodies Against Vaccine Antigens Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Geometric Mean Concentrations (GMCs) of Antibodies Against Vaccine Antigens Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-Diphtheria antibodies were assessed by a toxin neutralization test. Anti-Tetanus, Anti-Pertussis toxoid (PT), and Anti-Filamentous hemagglutinin (FHA) antibodies were assessed using an enzyme-linked immunosorbent assay. Anti-Hib capsular polyribosyl ribitol phosphate conjugated to tetanus protein (PRP) antibodies were assessed by a Farr-type radioimmunoassay. Anti-Hepatitis B was measured by the VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. Anti-Poliovirus (Polio) types 1, 2, and 3 antibodies were assessed by a neutralization assay, the poliovirus Micrometabolic Inhibition Test.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose 1 and post-dose 3

| End point values                         | DTaP-IPV-Hep B-PRP~T  | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|------------------------------------------|-----------------------|---------------------------------|--|--|
| Subject group type                       | Reporting group       | Reporting group                 |  |  |
| Number of subjects analysed              | 132                   | 131                             |  |  |
| Units: Concentrations/titers             |                       |                                 |  |  |
| geometric mean (confidence interval 95%) |                       |                                 |  |  |
| Anti-Diphtheria; Pre-Dose 1              | 0.01 (0.008 to 0.013) | 0.009 (0.007 to 0.012)          |  |  |
| Anti-Diphtheria; Post-Dose 3             | 1.01 (0.874 to 1.16)  | 0.676 (0.582 to 0.786)          |  |  |
| Anti-Tetanus; Post-Dose 3                | 3.05 (2.67 to 3.48)   | 2.53 (2.3 to 2.78)              |  |  |
| Anti-Polio 1; Post-Dose 3                | 823 (695 to 975)      | 1210 (1003 to 1459)             |  |  |
| Anti-Polio 2; Post-Dose 3                | 1380 (1126 to 1692)   | 1588 (1255 to 2009)             |  |  |
| Anti-Polio 3; Post-Dose 3                | 899 (721 to 1120)     | 1280 (1000 to 1639)             |  |  |
| Anti-PRP; Post-Dose 3                    | 5.44 (4.37 to 6.77)   | 9.35 (7.67 to 11.4)             |  |  |
| Anti-Hepatitis B; Pre-Dose 1             | 37.3 (26 to 53.4)     | 41.8 (29 to 60.2)               |  |  |
| Anti-Hepatitis B; Post-Dose 3            | 1068 (805 to 1416)    | 827 (601 to 1138)               |  |  |
| Anti-PT; Pre-Dose 1                      | 2.84 (2.35 to 3.43)   | 2.98 (2.4 to 3.69)              |  |  |
| Anti-PT; Post-Dose 3                     | 99 (90.6 to 108)      | 143 (129 to 157)                |  |  |
| Anti-FHA; Pre-Dose 1                     | 6.3 (5.2 to 7.64)     | 6.84 (5.5 to 8.51)              |  |  |
| Anti-FHA; Post-Dose 3                    | 153 (141 to 166)      | 163 (148 to 180)                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Concentration (GMC) Ratios of Antibodies Against Vaccine Antigens Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                        |                                                                                                                                                                                                                                                                                               |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Geometric Mean Concentration (GMC) Ratios of Antibodies Against Vaccine Antigens Following Vaccinations with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)                                                                                |
| End point description: | Anti-Diphtheria antibodies were assessed by a toxin neutralization test. Anti-Hepatitis B was measured by the VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. Anti-PT and Anti-FHA antibodies were assessed using an enzyme-linked immunosorbent assay. |
| End point type         | Secondary                                                                                                                                                                                                                                                                                     |

End point timeframe:

Pre-dose 1 and post-dose 3

| End point values                         | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|------------------------------------------|----------------------|---------------------------------|--|--|
| Subject group type                       | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed              | 132                  | 131                             |  |  |
| Units: Concentration ratio               |                      |                                 |  |  |
| geometric mean (confidence interval 95%) |                      |                                 |  |  |
| Anti-Diphtheria                          | 99.4 (71.3 to 139)   | 80.3 (58.2 to 111)              |  |  |
| Anti-Hepatitis B                         | 28.7 (17.9 to 46.1)  | 19.8 (12 to 32.7)               |  |  |
| Anti-PT                                  | 34.4 (27.4 to 43.2)  | 48 (37.3 to 61.9)               |  |  |
| Anti-FHA                                 | 24.2 (19.4 to 30.2)  | 23.9 (18.3 to 31)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Any Vaccination with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                 |                                                                                                                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Any Vaccination with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying abnormal, Somnolence, Decreased appetite, Irritability. Grade 3 Injection site reactions: Pain, Cries when injected limb is moved, or the movement of the limb is reduced; Erythema and Swelling,  $\geq 50$  mm. Grade 3 Systemic reactions: Pyrexia,  $>39.5^{\circ}\text{C}$ ; Vomiting,  $\geq 6$  episodes per 24 hours or requiring parenteral hydration; Crying abnormal,  $>3$  hours; Somnolence, Sleeping most of the time or difficult to wake up; Decreased appetite, Refuses  $\geq 3$  feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

|                                        |           |
|----------------------------------------|-----------|
| End point type                         | Secondary |
| End point timeframe:                   |           |
| Day 0 up to Day 7 post-any vaccination |           |

| End point values                | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|---------------------------------|----------------------|---------------------------------|--|--|
| Subject group type              | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed     | 149                  | 155                             |  |  |
| Units: Percentage of subjects   |                      |                                 |  |  |
| number (not applicable)         |                      |                                 |  |  |
| Any Injection site Pain         | 61.7                 | 58.1                            |  |  |
| Grade 3 Injection site Pain     | 2                    | 1.3                             |  |  |
| Any Injection site Erythema     | 53.7                 | 44.5                            |  |  |
| Grade 3 Injection site Erythema | 2.7                  | 2.6                             |  |  |
| Any Injection site Swelling     | 47.7                 | 43.2                            |  |  |
| Grade 3 Injection site Swelling | 1.3                  | 0.6                             |  |  |
| Any Pyrexia                     | 20.1                 | 7.7                             |  |  |
| Grade 3 Pyrexia                 | 0                    | 0                               |  |  |
| Any Vomiting                    | 26.8                 | 24.5                            |  |  |
| Grade 3 Vomiting                | 0.7                  | 1.3                             |  |  |
| Any Crying abnormal             | 48.3                 | 33.5                            |  |  |
| Grade 3 Crying abnormal         | 4                    | 2.6                             |  |  |
| Any Somnolence                  | 51                   | 45.2                            |  |  |
| Grade 3 Somnolence              | 2                    | 1.9                             |  |  |
| Any Decreased appetite          | 34.9                 | 35.5                            |  |  |
| Grade 3 Decreased appetite      | 0.7                  | 0.6                             |  |  |
| Any Irritability                | 53.7                 | 49                              |  |  |
| Grade 3 Irritability            | 3.4                  | 1.9                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 1 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 1 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying abnormal, Somnolence, Decreased appetite, Irritability. Grade 3 Injection site reactions: Pain, Cries when injected limb is moved, or the movement of the limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Systemic reactions: Pyrexia, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Somnolence, Sleeping most of the time or difficult to wake up; Decreased appetite, 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-vaccination 1

| End point values                | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|---------------------------------|----------------------|---------------------------------|--|--|
| Subject group type              | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed     | 149                  | 155                             |  |  |
| Units: Percentage of subjects   |                      |                                 |  |  |
| number (not applicable)         |                      |                                 |  |  |
| Any Injection site Pain         | 47.7                 | 41.9                            |  |  |
| Grade 3 Injection site Pain     | 1.3                  | 1.3                             |  |  |
| Any Injection site Erythema     | 33.6                 | 20.6                            |  |  |
| Grade 3 Injection site Erythema | 1.3                  | 1.3                             |  |  |
| Any Injection site Swelling     | 26.8                 | 22.6                            |  |  |
| Grade 3 Injection site Swelling | 0.7                  | 0.6                             |  |  |
| Any Pyrexia                     | 8.1                  | 1.3                             |  |  |
| Grade 3 Pyrexia                 | 0                    | 0                               |  |  |
| Any Vomiting                    | 18.1                 | 15.5                            |  |  |
| Grade 3 Vomiting                | 0                    | 0.6                             |  |  |
| Any Crying abnormal             | 36.9                 | 25.2                            |  |  |
| Grade 3 Crying abnormal         | 2                    | 1.9                             |  |  |
| Any Somnolence                  | 41.6                 | 35.5                            |  |  |
| Grade 3 Somnolence              | 0.7                  | 1.9                             |  |  |
| Any Decreased appetite          | 27.5                 | 27.1                            |  |  |
| Grade 3 Decreased appetite      | 0.7                  | 0.6                             |  |  |
| Any Irritability                | 42.3                 | 38.1                            |  |  |
| Grade 3 Irritability            | 2                    | 1.3                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 2 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 2 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Decreased appetite, Irritability. Grade 3 Injection site reactions: Pain, Cries when injected limb is moved, or the movement of the limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Systemic reactions: Pyrexia, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Somnolence, Sleeping most of the time or difficult to wake up; Decreased appetite, 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-vaccination 2

| End point values                | DTaP-IPV-Hep B-PRP~T | DTaP-IPV//PRP~T and Hepatitis B |  |  |
|---------------------------------|----------------------|---------------------------------|--|--|
| Subject group type              | Reporting group      | Reporting group                 |  |  |
| Number of subjects analysed     | 149                  | 154                             |  |  |
| Units: Percentage of subjects   |                      |                                 |  |  |
| number (not applicable)         |                      |                                 |  |  |
| Any Injection site Pain         | 41.6                 | 26.6                            |  |  |
| Grade 3 Injection site Pain     | 1.3                  | 0                               |  |  |
| Any Injection site Erythema     | 38.9                 | 22.7                            |  |  |
| Grade 3 Injection site Erythema | 0                    | 0                               |  |  |
| Any Injection site Swelling     | 28.9                 | 22.1                            |  |  |
| Grade 3 Injection site Swelling | 0                    | 0                               |  |  |
| Any Pyrexia                     | 9.4                  | 2.6                             |  |  |
| Grade 3 Pyrexia                 | 0                    | 0                               |  |  |
| Any Vomiting                    | 13.4                 | 10.4                            |  |  |
| Grade 3 Vomiting                | 0                    | 0.6                             |  |  |
| Any Crying abnormal             | 23.5                 | 15.6                            |  |  |
| Grade 3 Crying abnormal         | 1.3                  | 0                               |  |  |
| Any Somnolence                  | 20.8                 | 20.1                            |  |  |
| Grade 3 Somnolence              | 1.3                  | 0                               |  |  |
| Any Decreased appetite          | 16.1                 | 12.3                            |  |  |
| Grade 3 Decreased appetite      | 0                    | 0                               |  |  |
| Any Irritability                | 28.9                 | 20.8                            |  |  |
| Grade 3 Irritability            | 1.3                  | 0                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 3 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®)

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination 3 with DTaP-IPV-Hep B-PRP~T (Hexaxim™) or DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying, Somnolence, Decreased appetite, Irritability. Grade 3 Injection site reactions: Pain, Cries when injected limb is moved, or the movement of the limb is reduced; Erythema and Swelling, ≥50 mm. Grade 3 Systemic reactions: Pyrexia, >39.5°C; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Somnolence, Sleeping most of the time or difficult to wake up; Decreased appetite, Refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

Solicited injection site reactions are reported at the Hexaxim and Pentaxim injection sites for each group, respectively, and solicited systemic reactions are reported at the Hexaxim and Pentaxim+Euvax injection sites for each group, respectively.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 0 up to Day 7 post-vaccination 3

| <b>End point values</b>         | DTaP-IPV-Hep<br>B-PRP~T | DTaP-<br>IPV//PRP~T<br>and Hepatitis B |  |  |
|---------------------------------|-------------------------|----------------------------------------|--|--|
| Subject group type              | Reporting group         | Reporting group                        |  |  |
| Number of subjects analysed     | 148                     | 154                                    |  |  |
| Units: Percentage of subjects   |                         |                                        |  |  |
| number (not applicable)         |                         |                                        |  |  |
| Any Injection site Pain         | 31.8                    | 37.3                                   |  |  |
| Grade 3 Injection site Pain     | 0                       | 0                                      |  |  |
| Any Injection site Erythema     | 33.1                    | 30.7                                   |  |  |
| Grade 3 Injection site Erythema | 1.4                     | 0.7                                    |  |  |
| Any Injection site Swelling     | 29.7                    | 26.8                                   |  |  |
| Grade 3 Injection site Swelling | 0.7                     | 0                                      |  |  |
| Any Pyrexia                     | 4.1                     | 3.9                                    |  |  |
| Grade 3 Pyrexia                 | 0                       | 0                                      |  |  |
| Any Vomiting                    | 4.7                     | 7.8                                    |  |  |
| Grade 3 Vomiting                | 0.7                     | 0                                      |  |  |
| Any Crying abnormal             | 14.2                    | 12.4                                   |  |  |
| Grade 3 Crying abnormal         | 1.4                     | 0.7                                    |  |  |
| Any Somnolence                  | 16.2                    | 17                                     |  |  |
| Grade 3 Somnolence              | 0                       | 0                                      |  |  |
| Any Decreased appetite          | 8.8                     | 14.4                                   |  |  |
| Grade 3 Decreased appetite      | 0                       | 0                                      |  |  |
| Any Irritability                | 20.3                    | 22.9                                   |  |  |
| Grade 3 Irritability            | 0.7                     | 0.7                                    |  |  |

## 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-vaccination 3 and SAEs were collected throughout the study.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | DTaP-IPV-Hep B-PRP-T (Hexaxim™) |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |
|-----------------------|----------------------------------------------------------------|

Reporting group description: -

| <b>Serious adverse events</b>                        | DTaP-IPV-Hep B-PRP-T (Hexaxim™) | DTAP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |  |
|------------------------------------------------------|---------------------------------|----------------------------------------------------------------|--|
| Total subjects affected by serious adverse events    |                                 |                                                                |  |
| subjects affected / exposed                          | 19 / 149 (12.75%)               | 19 / 155 (12.26%)                                              |  |
| number of deaths (all causes)                        | 0                               | 0                                                              |  |
| number of deaths resulting from adverse events       | 0                               | 0                                                              |  |
| Injury, poisoning and procedural complications       |                                 |                                                                |  |
| Humerus fracture                                     |                                 |                                                                |  |
| subjects affected / exposed                          | 1 / 149 (0.67%)                 | 0 / 155 (0.00%)                                                |  |
| occurrences causally related to treatment / all      | 0 / 1                           | 0 / 0                                                          |  |
| deaths causally related to treatment / all           | 0 / 0                           | 0 / 0                                                          |  |
| Vascular disorders                                   |                                 |                                                                |  |
| Kawasaki's disease                                   |                                 |                                                                |  |
| subjects affected / exposed                          | 0 / 149 (0.00%)                 | 1 / 155 (0.65%)                                                |  |
| occurrences causally related to treatment / all      | 0 / 0                           | 0 / 1                                                          |  |
| deaths causally related to treatment / all           | 0 / 0                           | 0 / 0                                                          |  |
| General disorders and administration site conditions |                                 |                                                                |  |
| Pyrexia                                              |                                 |                                                                |  |
| subjects affected / exposed                          | 1 / 149 (0.67%)                 | 0 / 155 (0.00%)                                                |  |
| occurrences causally related to treatment / all      | 0 / 1                           | 0 / 0                                                          |  |
| deaths causally related to treatment / all           | 0 / 0                           | 0 / 0                                                          |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Intussusception                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 7 / 149 (4.70%) | 4 / 155 (2.58%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Croup infectious                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpangina                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis enteroviral                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 155 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media acute                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Peritonsillar abscess                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 155 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 155 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 2 / 155 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 5 / 155 (3.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory syncytial virus bronchiolitis       |                 |                 |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 1 / 155 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 149 (2.68%) | 4 / 155 (2.58%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | DTaP-IPV-Hep B-PRP-T (Hexaxim™) | DTaP-IPV//PRP~T (Pentaxim™) and Hepatitis B Vaccine (Euvax B®) |  |
|-------------------------------------------------------|---------------------------------|----------------------------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                 |                                                                |  |
| subjects affected / exposed                           | 92 / 149 (61.74%)               | 90 / 155 (58.06%)                                              |  |
| Nervous system disorders                              |                                 |                                                                |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                      |                                                                                                                     |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--|
| Somnolence<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 76 / 149 (51.01%)<br>76                                                                                              | 70 / 155 (45.16%)<br>70                                                                                             |  |
| General disorders and administration site conditions<br>Injection site Pain<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site Erythema<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site Swelling<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 92 / 149 (61.74%)<br>92<br><br>80 / 149 (53.69%)<br>80<br><br>71 / 149 (47.65%)<br>71<br><br>30 / 149 (20.13%)<br>30 | 90 / 155 (58.06%)<br>90<br><br>69 / 155 (44.52%)<br>69<br><br>67 / 155 (43.23%)<br>67<br><br>12 / 155 (7.74%)<br>12 |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                    | 5 / 149 (3.36%)<br>5<br><br>40 / 149 (26.85%)<br>40                                                                  | 10 / 155 (6.45%)<br>12<br><br>38 / 155 (24.52%)<br>38                                                               |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinorrhoea                                                                                                                                                                                                                                                                                                                                                                                                                                  | 11 / 149 (7.38%)<br>12                                                                                               | 8 / 155 (5.16%)<br>9                                                                                                |  |

|                                                                                                                                                            |                         |                         |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                           | 16 / 149 (10.74%)<br>18 | 19 / 155 (12.26%)<br>25 |  |
| Psychiatric disorders<br>Crying abnormal<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                 | 72 / 149 (48.32%)<br>72 | 52 / 155 (33.55%)<br>52 |  |
| Irritability<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                             | 80 / 149 (53.69%)<br>80 | 76 / 155 (49.03%)<br>76 |  |
| Infections and infestations<br>Bronchiolitis<br>subjects affected / exposed<br>occurrences (all)                                                           | 9 / 149 (6.04%)<br>10   | 11 / 155 (7.10%)<br>16  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                                                                             | 8 / 149 (5.37%)<br>9    | 11 / 155 (7.10%)<br>21  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                                                                        | 32 / 149 (21.48%)<br>43 | 35 / 155 (22.58%)<br>50 |  |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)                                                                                           | 8 / 149 (5.37%)<br>8    | 7 / 155 (4.52%)<br>11   |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                                                               | 9 / 149 (6.04%)<br>10   | 6 / 155 (3.87%)<br>7    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                                                      | 12 / 149 (8.05%)<br>22  | 15 / 155 (9.68%)<br>22  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 52 / 149 (34.90%)<br>52 | 55 / 155 (35.48%)<br>55 |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 December 2013 | Secondary endpoints (4-fold elevation of pre-vaccination titers after vaccination for PT and FHA) were moved to primary endpoints while vaccine response (identified as $\geq 4$ -fold increase of the LLOQ) was moved to the secondary endpoints; sample size section was updated; specifications to the administration of the vaccine were added; correspondence details of the laboratory for serology tests were added; and the planned trial calendar was updated. |
| 31 July 2014     | Inclusion criteria regarding hepatitis B surface antigen (HBsAg) negative status was updated to include documented HBsAg negative status during the last trimester of pregnancy (or post-birth) or documented HBsAg negative and HBsAb positive status before last trimester of pregnancy                                                                                                                                                                               |
| 12 December 2014 | Sample size was increased and the number of centers involved in the study was increased to facilitate the achievement of the enrollment in an acceptable timing; the planned trial calendar was also updated.                                                                                                                                                                                                                                                           |
| 19 May 2015      | Clarified the parameters used to calculate the minimal acceptable power for the primary analysis.                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported