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
Arm title	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

Arm title	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

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

Number of subjects in period 1	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:	
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.	

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 Seroprotection 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 Seroprotection 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 chemiluminesce detection technology. Anti-Poliovirus (Polio) types 1, 2, and 3 antibodies were assessed by a neutralization assay, the poliovirus Micrometabolic Inhibition Test. Seroprotection 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

Statistical analysis title	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[1]
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.

Statistical analysis title	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[2]
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.

Statistical analysis title	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[3]
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.

Statistical analysis title	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[4]
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.

Statistical analysis title	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[5]
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.

Statistical analysis title	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[6]
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.

Statistical analysis title	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[7]
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.

Statistical analysis title	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[8]
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.

Statistical analysis title	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[9]
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 chemiluminesce. 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 ≥0.01 IU/mL (pre- and post-doses), Anti-Tetanus ≥0.1 IU/mL (post dose), Anti-PRP ≥0.15 µg/mL (post dose), Anti Poliovirus types 1, 2, and 3 ≥8 (1/dilution; post doses), Anti-Hepatitis B ≥10 mIU/mL (pre- and post doses). Vaccine response was defined as Anti-PT or Anti-FHA antibody concentrations in ELISA units (EU)/mL ≥4X lower limit of quantitation (LLOQ) if pre-vaccination concentration <4X LLOQ or ≥pre-vaccination concentration if pre-vaccination concentration ≥4X 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 (≥0.01 IU/mL)	54.7	48.1		
Anti-Diphtheria; Pre-dose 1 (≥0.1 IU/mL)	5.5	4.6		
Anti-Diphtheria; Post-dose 3 (≥0.01 IU/mL)	100	100		
Anti-Diphtheria; Post-dose 3 (≥0.1 IU/mL)	98.5	97.6		
Anti-Tetanus; Post-dose 3 (≥0.01 IU/mL)	100	100		
Anti-Tetanus; Post-dose 3 (≥0.1 IU/mL)	99.2	100		
Anti-Polio 1; Post-dose 3 (≥8 [1/dil])	100	100		
Anti-Polio 2; Post-dose 3 (≥8 [1/dil])	100	100		
Anti-Polio 3; Post-dose 3 (≥8 [1/dil])	100	100		
Anti-PRP; Post-dose 3 (≥0.15 µg/ml)	100	100		
Anti-PRP; Post-dose 3 (≥1 µg/ml)	87.1	96.9		
Anti-Hepatitis B; Pre-dose 1 (≥10 mIU/mL)	74	68.7		
Anti-Hepatitis B; Post-dose 3 (≥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 chemiluminesce 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 chemiluminesce 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, ≥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-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 Pentxim+Euvax injection sites for each group, respectively.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-vaccination 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	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: -

Serious adverse events	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 %

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported