Clinical trial results:
Safety and Immunogenicity of Booster Vaccination with PEDIACEL®, a Combined Diphtheria, Tetanus, Five Component Acellular Pertussis, Inactivated Poliomyelitis and Haemophilus Influenzae Type b Conjugate Vaccine (Adsorbed), Compared to Booster Vaccination with Infanrix® hexa when Both Vaccines Are Co-Administered with Prevenar® to Toddlers 11-18 Months of Age

Summary

EudraCT number	2006-000898-30
Trial protocol	DE
Global end of trial date	17 September 2007

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	30 January 2015

Trial information

Trial identification

Sponsor protocol code	A5I19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00355654
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Associate Vice President, Clinical Development, Sanofi Pasteur Inc, +1 (570) 957-3570, emilia.jordanov@sanofipasteur.com
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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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of PEDIACEL® booster dose by comparing the fever rates between PEDIACEL® and Infanrix® hexa vaccines when both are co-administered with Prevenar® to toddlers at 11-18 months of age.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment were also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

The control, Infanrix® hexa, is a licensed combination vaccine.

Actual start date of recruitment	29 September 2006
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	Germany: 847
Worldwide total number of subjects	847
EEA total number of subjects	847

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)	847
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 29 September 2006 to 29 June 2007 at 53 clinical centers in Germany.

Pre-assignment

Screening details:

A total of 847 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled; 845 were vaccinated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Subjects and assessors were blinded to the vaccine. Each site had 1 designated person who was unblinded to the randomisation/vaccine administered and was responsible for the preparation and administration of the vaccine. All others remained blinded to the vaccine group until after the safety assessment. Before the assessment, the code was broken if it was necessary to determine/influence treatment of serious AEs. It was also broken afterwards for Pediacel subjects to receive ENGERIX-B Kinder.

Arms

Are arms mutually exclusive?	Yes
Arm title	PEDIACEL

Arm description:

Subjects who received PEDIACEL (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months followed by ENGERIX-B Kinder (0.5 mL) 1 month later, at 12 to 19 months.

Arm type	Experimental
Investigational medicinal product name	PEDIACEL
Investigational medicinal product code	HCPDT-IPV-PRP-T
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid muscle, one dose at 11-18 months of age.

Investigational medicinal product name	Prevenar
Investigational medicinal product code	Pneumococcal saccharide conjugated vaccine, adsorb
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the deltoid muscle, one dose at 11-18 months of age.

Investigational medicinal product name	ENGERIX-B Kinder
Investigational medicinal product code	Hepatitis B recombinant vaccine, adsorbed
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid muscle, one dose at 12-19 months of age.

Arm title	Infanrix hexa

Arm description:

Subjects who received Infanrix hexa as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months.

Arm type	Active comparator
Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	DTPa-HBV-IPV+Hib
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid muscle, one dose at 11-18 months of age.

Investigational medicinal product name	Prevenar
Investigational medicinal product code	Pneumococcal saccharide conjugated vaccine, adsorb
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the deltoid muscle, one dose at 11-18 months of age.

Number of subjects in period 1	PEDIACEL	Infanrix hexa
Started	423	424
Completed	420	417
Not completed	3	7
Consent withdrawn by subject	1	2
Lost to follow-up	1	3
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	PEDIACEL
Reporting group description:	
Subjects who received PEDIACEL (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months followed by ENGERIX-B Kinder (0.5 mL) 1 month later, at 12 to 19 months.	
Reporting group title	Infanrix hexa
Reporting group description:	
Subjects who received Infanrix hexa as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months.	

Reporting group values	PEDIACEL	Infanrix hexa	Total
Number of subjects	423	424	847
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)	423	424	847
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
arithmetic mean	14	14.1	
standard deviation	± 1.9	± 1.91	-
Gender categorical			
Units: Subjects			
Female	176	207	383
Male	247	217	464

End points

End points reporting groups

Reporting group title	PEDIACEL
Reporting group description:	
Subjects who received PEDIACEL (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months followed by ENGERIX-B Kinder (0.5 mL) 1 month later, at 12 to 19 months.	
Reporting group title	Infanrix hexa
Reporting group description:	
Subjects who received Infanrix hexa as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months.	

Primary: Number of Subjects Reporting Fever Within Four Days of Booster Vaccination With Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Number of Subjects Reporting Fever Within Four Days of Booster Vaccination With Either PEDIACEL or Infanrix Hexa Vaccine
End point description:	
Fever was defined as a temperature ≥ 38.0°C.	
End point type	Primary
End point timeframe:	
Day 0 up to Day 4 post-vaccination	

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Subjects				
number (not applicable)				
Fever (≥ 38.0°C)	250	262		

Statistical analyses

Statistical analysis title	Non-Inferiority of PEDIACEL to Infanrix Hexa
Statistical analysis description:	
Non-Inferiority of PEDIACEL to Infanrix Hexa with respect to Fever rates (≥ 38.0°C) within 4 Days post-booster vaccination when both were co-administered with Prevenar.	
Comparison groups	PEDIACEL v Infanrix hexa
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-3.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	3.4

Notes:

[1] - Non-inferiority is achieved if the upper limit of the two-sided 95% CI of PEDIACEL - Infanrix hexa is < 10% (primary objective).
Difference= PEDIACEL fever rate - Infanrix hexa fever rate. The CIs were computed using the normal approximation to the binomial distribution without continuity correction.

Secondary: Number of Subjects Reporting Severe Fever Within Four Days Following Booster Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Number of Subjects Reporting Severe Fever Within Four Days Following Booster Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Severe fever was defined as a temperature of ≥ 39.6°C.

End point type	Secondary

End point timeframe:

Day 0 up to Day 4 post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Subjects				
number (not applicable)				
Visit 1 (11 to 18 months)	28	17		
Visit 2 (12 to 19 months)	10	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection Against Vaccine Antigens Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects With Seroprotection Against Vaccine Antigens Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Antibodies were measured by radioimmunoassay for polyribosylribitol phosphate (PRP); serum neutralization assay for diphtheria toxoid and poliovirus types 1, 2, and 3; and enzyme-linked immunosorbent assay for tetanus toxoid and all pneumococcal serotypes. Seroprotection was defined as titers of ≥1.0 µg/mL for PRP, ≥0.1 µg/mL for diphtheria toxoid and tetanus toxoid, ≥1:8 [1/dil] for poliovirus 1, 2, and 3, and ≥0.15 µg/mL for all pneumococcal serotypes.

End point type	Secondary

End point timeframe:

1 month post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Percentage of subjects				
number (not applicable)				
PRP (≥1.00 µg/mL)	100	100		
Diphteria toxoid (≥ 0.1 IU/mL)	100	100		
Tetanus toxoid (≥ 0.1 IU/mL)	100	100		
Polio 1 (≥ 1:8 1/dil)	100	100		
Polio 2 (≥ 1:8 1/dil)	100	100		
Polio 3 (≥ 1:8 1/dil)	100	100		
Pneumo 4 (≥ 0.15 µg/mL)	100	100		
Pneumo 6B (≥ 0.15µg/mL)	81.9	82.4		
Pneumo 9V (≥ 0.15 µg/mL)	97.4	98.7		
Pneumo 14 (≥ 0.15 µg/mL)	100	100		
Pneumo 18C (≥ 0.15 µg/mL)	98.7	100		
Pneumo 19F (≥ 0.15 µg/mL)	100	100		
Pneumo 23F (≥ 0.15 µg/mL)	75.7	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies to Vaccine Antigens Before and Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies to Vaccine Antigens Before and Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Antibodies were measured by radioimmunoassay for polyribosylribitol phosphate (PRP); serum neutralization assay for diphtheria toxoid and poliovirus types 1, 2, and 3; enzyme-linked immunosorbent assay for tetanus toxoid, all pneumococcal (Pneumo 4, 6B, 9V, 14, 18C, 19F, 23F) serotypes, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM).

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and 1 month post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Titers				
geometric mean (confidence interval 95%)				
PRP (Pre-Booster)	0.44 (0.31 to 0.63)	0.56 (0.4 to 0.78)		
PRP (Post-Booster)	37.16 (27.8 to 49.67)	30.27 (24.23 to 37.82)		
Diphtheria toxoid (Pre-Booster)	0.06 (0.04 to 0.09)	0.06 (0.04 to 0.08)		
Diphtheria toxoid (Post-Booster)	2.72 (2.04 to 3.64)	2.23 (1.71 to 2.9)		
Tetanus toxoid (Pre-Booster)	0.39 (0.31 to 0.49)	0.41 (0.33 to 0.5)		
Tetanus toxoid (Post-Booster)	6.47 (5.25 to 7.97)	4.67 (3.99 to 5.47)		
Polio 1 (Pre-Booster)	230.86 (148.41 to 359.1)	311.93 (209.67 to 464.05)		
Polio 1 (Post-Booster)	5281.24 (3722.08 to 7493.52)	6873.53 (5302.4 to 8910.19)		
Polio 2 (Pre-Booster)	156.07 (98.8 to 246.55)	235.26 (160.52 to 344.79)		
Polio 2 (Post-Booster)	7791.2 (5634.91 to 10772.63)	6596.57 (5110.91 to 8514.09)		
Polio 3 (Pre-Booster)	339.96 (216.74 to 533.25)	464.31 (326.34 to 660.61)		
Polio 3 (Post-Booster)	8076.24 (5380.26 to 12123.16)	10770.02 (8274.75 to 14017.75)		
PT (Pre-Booster)	19.5 (15.7 to 24.22)	17.99 (14.85 to 21.8)		
PT (Post-Booster)	128.94 (105.7 to 157.28)	126.8 (109.89 to 146.31)		
FHA (Pre-Booster)	23.13 (18.31 to 29.23)	24.65 (19.73 to 30.8)		
FHA (Post-Booster)	125.53 (105.21 to 149.79)	190.58 (166.15 to 218.59)		
PRN (Pre-Booster)	20.02 (15.38 to 26.07)	18.3 (13.79 to 24.28)		
PRN (Post-Booster)	257.46 (205.63 to 322.35)	324.3 (253.96 to 414.1)		
FIM (Pre-Booster)	2.11 (1.98 to 2.26)	2.18 (2.01 to 2.35)		
FIM (Post-Booster)	6.61 (4.79 to 9.12)	2.64 (2.22 to 3.13)		
Pneumo 4 (Pre-Booster)	0.03 (0.02 to 0.04)	0.04 (0.03 to 0.06)		
Pneumo 4 (Post-Booster)	5.04 (4.01 to 6.34)	4.41 (3.51 to 5.55)		
Pneumo 6B (Pre-Booster)	0.1 (0.08 to 0.13)	0.11 (0.08 to 0.14)		
Pneumo 6B (Post-Booster)	0.66 (0.46 to 0.95)	0.56 (0.41 to 0.77)		

Pneumo 9V (Pre-Booster)	0.04 (0.03 to 0.05)	0.04 (0.03 to 0.05)		
Pneumo 9V (Post-Booster)	3.48 (2.62 to 4.62)	3.27 (2.65 to 4.03)		
Pneumo 14 (Pre-Booster)	0.08 (0.06 to 0.12)	0.1 (0.07 to 0.15)		
Pneumo 14 (Post-Booster)	4.35 (3.5 to 5.4)	4.85 (3.87 to 6.07)		
Pneumo 18C (Pre-Booster)	0.02 (0.01 to 0.03)	0.02 (0.01 to 0.03)		
Pneumo 18C (Post-Booster)	3.57 (2.92 to 4.37)	3.89 (3.26 to 4.63)		
Pneumo 19F (Pre-Booster)	0.52 (0.41 to 0.65)	0.63 (0.49 to 0.81)		
Pneumo 19F (Post-Booster)	1.72 (1.4 to 2.11)	1.86 (1.54 to 2.25)		
Pneumo 23F (Pre-Booster)	0.04 (0.03 to 0.06)	0.04 (0.03 to 0.06)		
Pneumo 23F (Post-Booster)	0.51 (0.36 to 0.73)	0.46 (0.33 to 0.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Booster Response for Pertussis Antigens Post- Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects with Booster Response for Pertussis Antigens Post- Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Antibodies were measured using an enzyme-linked immunosorbent assay for pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM). Booster response was defined as ≥ 4-fold rise from baseline if baseline antibody response was < 4x lower limit of quantification (LLOQ) or ≥ 2-fold rise from baseline if baseline antibody response was ≥ 4xLLOQ.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) to 1 month post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Percentage of subjects				
number (not applicable)				
PT	90.4	92.1		
FHA	86.7	94.7		
PRN	95.9	96.1		
FIM	26.4	5.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Seroprotection Against Hepatitis B Antigens Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects with Seroprotection Against Hepatitis B Antigens Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Anti-Hepatitis B antibodies were measured using enhanced chemiluminescence [ECi]). Seroprotection was defined as titers at the level of ≥ 10 mIU/mL for Hepatitis B.

End point type	Secondary

End point timeframe:

1 month post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	80		
Units: Percentage of subjects				
number (not applicable)				
Pre-Booster	0	93.7		
Post-Booster and Pre-ENGERIX-B Kinder	93.2	98.7		
Post-ENGERIX-B Kinder	100	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies to Hepatitis B Antigens Before and Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Geometric Mean Titers (GMTs) of Antibodies to Hepatitis B Antigens Before and Following Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Anti-Hepatitis B antibodies were measured using enhanced chemiluminescence [ECi]).

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) to 1 month post-vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	80		
Units: Titers				
geometric mean (confidence interval 95%)				
Pre-Booster	0 (0 to 0)	196 (131.91 to 291.25)		
Post-Booster and Pre-ENGERIX-B Kinder	194.48 (132.62 to 285.21)	2866.13 (1872.12 to 4387.91)		
Post-ENGERIX-B Kinder	9066.36 (6029.63 to 13632.49)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting a Solicited Injection Site or Systemic Reactions Following Any Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects Reporting a Solicited Injection Site or Systemic Reactions Following Any Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Solicited injection site: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite loss, and Irritability.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-each vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Percentage of subjects				
number (not applicable)				
Tenderness	69	63.7		
Erythema	68	68.4		
Swelling	38.4	35.9		
Fever	71.8	70.5		
Vomiting	15.6	14.8		
Crying abnormal	45.5	44.5		
Drowsiness	50.5	44		
Appetite loss	49.5	51		
Irritability	57.3	58.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting a Solicited Injection Site or Systemic Reactions Following Each Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects Reporting a Solicited Injection Site or Systemic Reactions Following Each Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Solicited injection site: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite loss, and Irritability. Grade 3 injection site: Tenderness – Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling – ≥5 cm. Grade 3 systemic reactions: Fever – ≥39.6°C; Vomiting – ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal – >3 hours; Drowsiness – Sleeping most of the time or difficulty to wake up; Appetite loss – refuses ≥ 3 feeds or refuses most feeds; and Irritability– Inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-each vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Percentage of subjects				
number (not applicable)				
Tenderness (Visit 1)	63	63.7		
Grade 3 Tenderness (Visit 1)	3.3	3.3		
Tenderness (Visit 2)	33.7	0		
Grade 3 Tenderness (Visit 2)	0	0		
Erythema (Visit 1)	62.8	68.4		
Grade 3 Erythema (Visit 1)	13.7	13.3		
Erythema (Visit 2)	24.4	0		
Grade 3 Erythema (Visit 2)	0	0		
Swelling (Visit 1)	35	35.9		
Grade 3 Swelling (Visit 1)	8.8	7.4		
Swelling (Visit 2)	9.8	0		
Grade 3 Swelling (Visit 2)	0.2	0		
Fever (Visit 1)	63.7	65		
Grade 3 Fever (Visit 1)	7.8	6		
Fever (Visit 2)	28.9	19.4		
Grade 3 Fever (Visit 2)	5	3.7		
Vomiting (Visit 1)	9.2	11.2		
Grade 3 Vomiting (Visit 1)	0.2	0.7		

Vomiting (Visit 2)	7.9	4.3		
Grade 3 Vomiting (Visit 2)	1	0		
Crying abnormal (Visit 1)	39.1	41.2		
Grade 3 Crying abnormal (Visit 1)	1.9	3.3		
Crying abnormal (Visit 2)	19.6	13.7		
Grade 3 Crying abnormal (Visit 2)	1.4	1.2		
Drowsiness (Visit 1)	39.8	40		
Grade 3 Drowsiness (Visit 1)	1.2	2.1		
Drowsiness (Visit 2)	25.1	10.6		
Grade 3 Drowsiness (Visit 2)	0.5	0.7		
Appetite loss (Visit 1)	41.5	45.5		
Grade 3 Appetite loss (Visit 1)	3.3	3.8		
Appetite loss (Visit 2)	24.2	18.3		
Grade 3 Appetite loss (Visit 2)	2.6	2.4		
Irritability (Visit 1)	51.4	55.2		
Grade 3 Irritability (Visit 1)	3.8	1.7		
Irritability (Visit 2)	29.7	18.8		
Grade 3 Irritability (Visit 2)	1.2	1.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Extensive Limb Swelling Following Booster Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point title	Percentage of Subjects Reporting Extensive Limb Swelling Following Booster Vaccination with Either PEDIACEL or Infanrix Hexa Vaccine

End point description:

Extensive limb swelling is defined as swelling extending from the injection site beyond 1 or both adjacent joints (i.e., elbow and/or shoulder).

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-each vaccination

End point values	PEDIACEL	Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Percentage of subjects				
number (not applicable)				
Extensive limb swelling	0.5	1.2		

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 (post-vaccination) up to 1 month post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	PEDIACEL

Reporting group description:

Subjects who received PEDIACEL (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months followed by ENGERIX-B Kinder (0.5 mL) 1 month later, at 12 to 19 months.

Reporting group title	Infanrix hexa

Reporting group description:

Subjects who received Infanrix hexa as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar (0.5 mL) at 11 to 18 months.

Serious adverse events	PEDIACEL	Infanrix hexa	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 422 (2.84%)	14 / 421 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental exposure			
subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	2 / 422 (0.47%)	2 / 421 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electric shock			
subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 422 (0.24%)	2 / 421 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 422 (0.24%)	0 / 421 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 422 (0.47%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 422 (0.24%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	1 / 422 (0.24%)	0 / 421 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 422 (0.71%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 422 (0.24%)	3 / 421 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 422 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PEDIACEL	Infanrix hexa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 422 (71.80%)	296 / 421 (70.31%)	
Nervous system disorders			
Solicited injection site Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[1]	213 / 422 (50.47%)	185 / 420 (44.05%)	
occurrences (all)	213	185	
General disorders and administration site conditions			
Solicited injection site Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed	291 / 422 (68.96%)	268 / 421 (63.66%)	
occurrences (all)	291	268	
Solicited injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed	287 / 422 (68.01%)	288 / 421 (68.41%)	
occurrences (all)	287	288	
Solicited injection site Swelling			
alternative assessment type: Systematic			

subjects affected / exposed	162 / 422 (38.39%)	151 / 421 (35.87%)	
occurrences (all)	162	151	
Solicited injection site Fever			
alternative assessment type: Systematic			
subjects affected / exposed[2]	303 / 422 (71.80%)	296 / 420 (70.48%)	
occurrences (all)	303	296	
Gastrointestinal disorders			
Solicited injection site Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[3]	66 / 422 (15.64%)	62 / 420 (14.76%)	
occurrences (all)	66	62	
Psychiatric disorders			
Solicited injection site Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed[4]	192 / 422 (45.50%)	187 / 420 (44.52%)	
occurrences (all)	192	187	
Solicited injection site Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[5]	242 / 422 (57.35%)	245 / 420 (58.33%)	
occurrences (all)	242	245	
Metabolism and nutrition disorders			
Solicited injection site Appetite loss			
alternative assessment type: Systematic			
subjects affected / exposed[6]	209 / 422 (49.53%)	214 / 420 (50.95%)	
occurrences (all)	209	214	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2006	Infant inclusion criteria were revised to meet the current practices of infant immunizations in Germany, visit procedures were revised to standardize a definition of "whole limb swelling", List of Investigators were updated, and the consent form was further revised to clarify compliance with immunization requirements and possible benefits.
15 September 2006	Batch numbers of the vaccines were added, List of Investigators were updated, and the consent form was further revised to clarify compliance with immunization requirements.
21 March 2007	Retrospective power calculations were added, assay methodology was updated, and List of Investigators were updated.
12 September 2007	PRP testing and the List of Investigators were updated.
14 September 2007	Polio testing and the definition of fever were updated, two per protocol analysis sets were defined to reflect different testing schedules, the temperature condition for the sera storage was removed, and the CTL was updated in the List of Participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported