

**Clinical trial results:****Immunogenicity and Safety Study of a Booster Dose of DTaP-IPV-Hep B-PRP-T Combined Vaccine at 15 to 18 Months of Age Following a Primary Series at 2, 3 and 4 Months of Age in Healthy Turkish Infants.****Summary**

EudraCT number	2011-004432-58
Trial protocol	Outside EU/EEA
Global end of trial date	07 July 2008

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	31 July 2014

Trial information**Trial identification**

Sponsor protocol code	A3L22
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00619502
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur, SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43 , emmanuel.feroldi@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43 , emmanuel.feroldi@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001201-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity

- To describe the antibody (Ab) persistence at 15 to 18 months of age for all valences following a three-dose primary series vaccination of either DTaP-IPV-Hep B-PRP-T or Pentaxim™ + Engerix™ B at 2, 3, and 4 months of age
- To describe the immunogenicity of a booster dose of DTaP-IPV-Hep B-PRP-T given at 15 to 18 months of age

Safety

- To describe the safety profile after a booster dose of DTaP-IPV-Hep B-PRP-T given at 15 to 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.

Background therapy:

This is a booster vaccination study in toddlers who completed a three dose primary series of DTaP-IPV-Hep B-PRP-T combined vaccine or of Pentaxim™ + Engerix™ B in Study A3L10. All subjects were to receive the DTaP-IPV-Hep B-PRP-T vaccine as a booster dose.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	14 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 254
Worldwide total number of subjects	254
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	254
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:

Participants were enrolled from 14 December 2007 to 07 January 2008 at 1 clinical center in Turkey.

Pre-assignment

Screening details:

Only subjects who met all inclusion, but none of the exclusion criteria were enrolled and vaccinated

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not Applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	DTaP-IPV-HepB-PRP~T

Arm description:

All participants received a primary series of 3 vaccinations with DTaP-IPV-HepB-PRP~T, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-HepB-PRP~T at 15 to 18 months of age in the present study.

Arm type	Experimental
Investigational medicinal product name	Hexaxim
Investigational medicinal product code	DTaP-IPV-HepB-PRP-T vaccine
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, Intramuscular injection into the right deltoid muscle.

Arm title	Pentaxim™ + Engerix B™
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Arm description:

All participants received a primary series of 3 vaccinations with Pentaxim™ and Engerix B™ vaccines, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-Hep B-PRP~T at 15 to 18 months of age in the present study.

Arm type	Active comparator
Investigational medicinal product name	Hexaxim
Investigational medicinal product code	DTaP-IPV-HepB-PRP-T vaccine
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, Intramuscular injection into the right deltoid muscle.

Number of subjects in period 1	DTaP-IPV-HepB- PRP~T	Pentaxim™ + Engerix B™
Started	130	124
Completed	122	114
Not completed	8	10
Lost to follow-up	8	10

Baseline characteristics

Reporting groups

Reporting group title	DTaP-IPV-HepB-PRP~T
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Reporting group description:

All participants received a primary series of 3 vaccinations with DTaP-IPV-HepB-PRP~T, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-HepB-PRP~T at 15 to 18 months of age in the present study.

Reporting group title	Pentaxim™ + Engerix B™
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Reporting group description:

All participants received a primary series of 3 vaccinations with Pentaxim™ and Engerix B™ vaccines, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-Hep B-PRP~T at 15 to 18 months of age in the present study.

Reporting group values	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Engerix B™	Total
Number of subjects	130	124	254
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)	130	124	254
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	17.6	17.6	-
standard deviation	± 0.198	± 0.279	-
Gender categorical			
Units: Subjects			
Female	56	54	110
Male	74	70	144

End points

End points reporting groups

Reporting group title	DTaP-IPV-HepB-PRP~T
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Reporting group description:

All participants received a primary series of 3 vaccinations with DTaP-IPV-HepB-PRP~T, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-HepB-PRP~T at 15 to 18 months of age in the present study.

Reporting group title	Pentaxim™ + Engerix B™
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Reporting group description:

All participants received a primary series of 3 vaccinations with Pentaxim™ and Engerix B™ vaccines, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-Hep B-PRP~T at 15 to 18 months of age in the present study.

Primary: Percentage of Participants With Pre-booster Antibody Persistence and Booster Response to DTaP-IPV-Hep B-PRP~T After Primary Vaccination With Either DTaP-IPV-Hep B-PRP~T or Pentaxim™ + Engerix B Vaccine™

End point title	Percentage of Participants With Pre-booster Antibody Persistence and Booster Response to DTaP-IPV-Hep B-PRP~T After Primary Vaccination With Either DTaP-IPV-Hep B-PRP~T or Pentaxim™ + Engerix B Vaccine™ ^[1]
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End point description:

Antibody titers measured by chemiluminescence detection for Hepatitis B (Hep B); Farr type radioimmunoassay for Haemophilus influenza type b (PRP); toxin neutralization for Diphtheria (D); indirect enzyme-linked immunosorbent assay (ELISA) for Tetanus (T); neutralization assay for Poliovirus types 1, 2, and 3; and ELISA for Pertussis toxoid (PT) and Filamentous hemagglutinin (FHA). Persistence and response: ≥ 10 mIU/mL for anti-Hep B, ≥ 0.15 μ g/mL for anti-PRP, ≥ 0.01 IU/mL for anti-D and anti-T, ≥ 8 (1/dil) for anti-Poliovirus; and ≥ 4 -fold increase from Day 0 for anti-PT and anti-FHA.

End point type	Primary
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End point timeframe:

Day 0 before and Day 30 Post-booster vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed, based on the vaccine groups from the primary series for the follow-up booster vaccination in this study.

End point values	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Engerix B™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	103		
Units: Percentage				
Anti-FHA Post-booster	92	97		
Anti-PT Post-booster	97	96		
Anti-Polio 3 Post-booster	100	100		
Anti-Polio 3 Pre-booster	85	97		
Anti-Polio 2 Post-booster	100	100		
Anti-Polio 2 Pre-booster	100	98		
Anti-Polio 1 Post-booster	100	100		
Anti-Polio 1 Pre-booster	99	99		
Anti-Tetanus Post-booster	100	100		
Anti-Tetanus Pre-booster	100	100		
Anti-Diphtheria Post-booster	100	100		

Anti-Diphtheria Pre-booster	90	88		
Anti-PRP Post-booster	100	100		
Anti-PRP Pre-booster	85	83		
Anti-Hep B Post-booster	97	100		
Anti-Hep B Pre-booster	81	99		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) Before and After Booster Vaccination With DTaP-IPV-Hep B-PRP~T

End point title	Geometric Mean Titers (GMTs) Before and After Booster Vaccination With DTaP-IPV-Hep B-PRP~T ^[2]
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End point description:

Antibody titers were measured by chemiluminescence detection for Hepatitis B (Hep B); Farr type radioimmunoassay for Haemophilus influenzae type b (PRP); toxin neutralization test for Diphtheria (D); indirect enzyme-linked immunosorbent assay (ELISA) for Tetanus (T); neutralization assay for Poliovirus types 1, 2, and 3; and ELISA for Pertussis toxoid (PT) and Filamentous hemagglutinin (FHA).

End point type	Primary
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End point timeframe:

Day 0 before and Day 30 post-booster vaccine

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed, based on the vaccine groups from the primary series for the follow-up booster vaccination in this study.

End point values	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Enderix B™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	103		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-FHA Post-booster	222 (194 to 254)	234 (201 to 272)		
Anti-FHA Pre-booster	12.5 (9.59 to 16.4)	8.18 (6.49 to 10.3)		
Anti-PT Post-booster	160 (137 to 187)	237 (202 to 278)		
Anti-PT Pre-booster	6.08 (4.74 to 7.79)	7.49 (5.97 to 9.41)		
Anti-Polio 3 Post-booster	5542 (4156 to 7392)	10152 (7806 to 13205)		
Anti-Polio 3 Pre-booster	47.1 (33.1 to 67.1)	101 (73 to 141)		
Anti-Polio 2 Post-booster	6099 (4916 to 7566)	9170 (7170 to 11727)		
Anti-Polio 2 Pre-booster	114 (84.9 to 153)	131 (95.3 to 179)		
Anti-Polio 1 Post-booster	5477 (4401 to 5814)	9050 (7134 to 11480)		
Anti-Polio 1 Pre-booster	110 (81.6 to 148)	114 (82.4 to 157)		

Anti-Tetanus Post-booster	8.98 (7.52 to 10.7)	13.1 (10.8 to 15.8)		
Anti-Tetanus Pre-booster	0.244 (0.204 to 0.292)	0.194 (0.158 to 0.238)		
Anti-Diphtheria Post-booster	5.09 (3.89 to 6.66)	10.2 (7.59 to 13.8)		
Anti-Diphtheria Pre-booster	0.028 (0.022 to 0.035)	0.032 (0.024 to 0.041)		
Anti-PRP Post-booster	72.5 (55.8 to 94.3)	86.9 (69.8 to 108)		
Anti-PRP Pre-booster	0.724 (0.541 to 0.968)	0.612 (0.443 to 0.844)		
Anti-Hep B Post-booster	1379 (916 to 2078)	26189 (19133 to 35846)		
Anti-Hep B Pre-booster	44.2 (32.3 to 60.7)	223 (176 to 282)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Solicited Injection Site and Systemic Reactions After Booster Vaccination With DTaP-IPV-Hep B-PRP~T

End point title	Number of Participants With Solicited Injection Site and Systemic Reactions After Booster Vaccination With DTaP-IPV-Hep B-PRP~T ^[3]
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End point description:

Solicited Injection Site Reactions: Pain, Erythema, Swelling, and Extensive Swelling of Vaccinated Limb. Solicited Systemic Reactions: Pyrexia (Temperature), Vomiting, Crying, Somnolence, Anorexia, and Irritability.

Grade 3 defined as: Pain, cries when injected limb is moved or movement of limb reduced; Erythema and Swelling, ≥ 5 cm; Extensive Swelling of Vaccinated Limb, All; Pyrexia, $\geq 39^{\circ}\text{C}$; Vomiting, ≥ 6 episodes/24 hours or requiring parenteral hydration; Crying > 3 hours; Somnolence, sleeping most of time or difficult to wake up; Anorexia, refuses ≥ 3 feeds or most feeds; Irritability, inconsolable.

End point type	Primary
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End point timeframe:

Day 0 up to Day 7 post-booster vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed, based on the vaccine groups from the primary series for the follow-up booster vaccination in this study.

End point values	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Engerix B™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	111		
Units: Participants				
Injection site Pain	56	67		
Grade 3 injection site Pain	4	2		
Injection site Erythema	34	50		
Grade 3 Injection site Erythema	3	4		
Injection site Swelling	26	36		
Grade 3 Injection site Swelling	2	3		
Extensive Swelling of vaccinated limb	0	0		

Pyrexia	29	36		
Grade 3 Pyrexia	1	0		
Vomiting	13	11		
Grade 3 Vomiting	2	2		
Crying	29	35		
Grade 3 Crying	3	4		
Somnolence	24	25		
Grade 3 Somnolence	2	3		
Anorexia	40	43		
Grade 3 Anorexia	9	8		
Irritability	51	61		
Grade 3 Irritability	5	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events data were collected from Day 0 after booster vaccination to up to 6 months after vaccination.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.0
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Reporting groups

Reporting group title	DTaP-IPV-HepB-PRP~T
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Reporting group description:

All participants received a primary series of 3 vaccinations with DTaP-IPV-HepB-PRP~T, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-HepB-PRP~T at 15 to 18 months of age in the present study.

Reporting group title	Pentaxim™ + Engerix B™
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Reporting group description:

All participants received a primary series of 3 vaccinations with Pentaxim™ and Engerix B™ vaccines, with 1 dose each at 2, 3, and 4 months of age, in Study A3L10; they received a booster dose of DTaP-IPV-Hep B-PRP~T at 15 to 18 months of age in the present study.

Serious adverse events	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Engerix B™	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 130 (3.08%)	2 / 122 (1.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Poisoning			
subjects affected / exposed	1 / 130 (0.77%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 122 (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			
Bronchitis			

subjects affected / exposed	1 / 130 (0.77%)	0 / 122 (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	1 / 130 (0.77%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis rotavirus		
subjects affected / exposed	0 / 130 (0.00%)	1 / 122 (0.82%)
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	DTaP-IPV-HepB-PRP~T	Pentaxim™ + Engerix B™	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 130 (43.08%)	67 / 122 (54.92%)	
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed ^[1]	24 / 121 (19.83%)	25 / 111 (22.52%)	
occurrences (all)	24	25	
General disorders and administration site conditions			
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed ^[2]	35 / 121 (28.93%)	50 / 111 (45.05%)	
occurrences (all)	35	50	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed ^[3]	56 / 121 (46.28%)	67 / 111 (60.36%)	
occurrences (all)	56	67	
Injection site swelling			
alternative assessment type: Systematic			

subjects affected / exposed ^[4] occurrences (all)	26 / 121 (21.49%) 26	36 / 111 (32.43%) 36	
Irritability alternative assessment type: Systematic subjects affected / exposed ^[5] occurrences (all)	51 / 121 (42.15%) 51	61 / 111 (54.95%) 61	
Pyrexia alternative assessment type: Systematic subjects affected / exposed ^[6] occurrences (all)	29 / 121 (23.97%) 29	36 / 111 (32.43%) 36	
Gastrointestinal disorders Vomiting alternative assessment type: Systematic subjects affected / exposed ^[7] occurrences (all)	13 / 121 (10.74%) 13	11 / 111 (9.91%) 11	
Psychiatric disorders Crying alternative assessment type: Systematic subjects affected / exposed ^[8] occurrences (all)	29 / 121 (23.97%) 29	35 / 111 (31.53%) 35	
Metabolism and nutrition disorders Anorexia alternative assessment type: Systematic subjects affected / exposed ^[9] occurrences (all)	40 / 121 (33.06%) 40	43 / 111 (38.74%) 43	

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.

[7] - 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.

[8] - 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.

[9] - 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
07 July 2008	The protocol amendment of 04 August 2008 was due to changes in the Sanofi Pasteur Global Clinical Immunology (GCI) laboratory methodology. Originally it had been planned to subcontract from GCI the analysis of the PRP valence, using the Enzyme linked immunosorbent assay (ELISA). However, due to capacity problems at the subcontracted laboratory and in order to speed up the availability of these data, the decision was made to perform this assay at GCI (using radioimmunoassay). The updated protocol documented this change and provided further details of CGI test methodology. Other administrative changes were also made to reflect changes to the nomenclature of the investigational product since the last protocol update, and changes to study personnel.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported