Clinical trial results:
Immunogenicity Study of DTaP-IPV-Hep B-PRP~T Combined Vaccine in Comparison to Infanrix®Hexa, at 2-4-6 Months of Age in Healthy Peruvian Infants

Summary

EudraCT number	2011-004434-33
Trial protocol	Outside EU/EEA
Global end of trial date	19 May 2009

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	20 August 2014

Trial information

Trial identification

Sponsor protocol code	A3L17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00831753
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 54 83 , emmanuel.feroldi@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 54 83 , 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	27 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the hexavalent DTaP-IPV-Hep B-PRP-T combined vaccine induces an immune response that is at least as good as the response following Infanrix hexa™ in terms of seroprotection rates to Hep B, 1 month after a three-dose primary series (2, 4, and 6 months).

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:

N/A

Evidence for comparator:

Infanrix hexa™ (DTAP-HB-IPV/HB) is a licensed vaccine being studied to compare immunological and safety profiles to the investigational DTaP-IPV- Hep B-PRP~T vaccine when administered to Peruvian infants at 2, 4, and 6 months of age.

Actual start date of recruitment	23 May 2008
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	Peru: 263
Worldwide total number of subjects	263
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)	263
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 participants were enrolled from 23 May 2008 to 18 July 2008 at 1 clinical center in Peru.

Pre-assignment

Screening details:

A total of 263 participants who met the inclusion and and none of the exclusion criteria were enrolled and vaccinated.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

The investigator (blind observer or assessor) and subject's parents or guardians did not know the vaccine administered. The assessor was in charge of the assessment of safety held in a separate room and away from where the vaccines were prepared. A nurse/vaccinator was in charge of the preparation and administration of the vaccine(s) in another room away from the assessor. When necessary the scratch off emergency decoding procedure described in the study protocol were to be followed.

Arms

Are arms mutually exclusive?	Yes
Arm title	DTaP-IPV-Hep B-PRP~T Group

Arm description:

All participants received a 3-dose primary series of diphtheria, tetanus, pertussis (2-component acellular), recombinant hepatitis B (Hep B) Hansenula polymorpha and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T) combined vaccine. A dose at 2, 4, and 6 months of age, respectively.

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

Dosage and administration details:

0.5 mL dose, a dose each at age 2, 4, and 6 months, respectively.

Arm title	Infanrix Hexa™ Group

Arm description:

All study participants received a 3-dose primary series of Infanrix hexa™ vaccine, with 1 dose each at 2, 4, and 6 months of age, respectively.

Arm type	Active comparator
Investigational medicinal product name	Infanrix hexa™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, a dose each at age 2, 4, and 6 months, respectively.

Notes:
[1] - The roles blinded appear inconsistent with a simple blinded trial.
Justification: The roles blinded in the study is as described.

Number of subjects in period 1	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group
Started	132	131
Completed	132	131

Baseline characteristics

Reporting groups	
Reporting group title	DTaP-IPV-Hep B-PRP~T Group
Reporting group description:	
All participants received a 3-dose primary series of diphtheria, tetanus, pertussis (2-component acellular), recombinant hepatitis B (Hep B) Hansenula polymorpha and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T) combined vaccine. A dose at 2, 4, and 6 months of age, respectively.	
Reporting group title	Infanrix Hexa™ Group
Reporting group description:	
All study participants received a 3-dose primary series of Infanrix hexa™ vaccine, with 1 dose each at 2, 4, and 6 months of age, respectively.	

Reporting group values	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group	Total
Number of subjects	132	131	263
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)	132	131	263
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	1.75	1.72	
standard deviation	± 0.132	± 0.123	-
Gender categorical			
Units: Subjects			
Female	58	74	132
Male	74	57	131

End points

End points reporting groups

Reporting group title	DTaP-IPV-Hep B-PRP~T Group

Reporting group description:

All participants received a 3-dose primary series of diphtheria, tetanus, pertussis (2-component acellular), recombinant hepatitis B (Hep B) Hansenula polymorpha and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T) combined vaccine. A dose at 2, 4, and 6 months of age, respectively.

Reporting group title	Infanrix Hexa™ Group

Reporting group description:

All study participants received a 3-dose primary series of Infanrix hexa™ vaccine, with 1 dose each at 2, 4, and 6 months of age, respectively.

Primary: Number of Participants Achieving Seroprotection for Anti Hep-B After a Primary Series of Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™

End point title	Number of Participants Achieving Seroprotection for Anti Hep-B After a Primary Series of Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™[1]

End point description:

Anti-hepatitis B (Hep B) antibodies were measured by chemiluminescence detection. Seroprotection was defined as a titer ≥ 10 mIU/mL.

End point type	Primary

End point timeframe:

Day 150 (1 month after dose 3)

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 / vaccine administered in the study.

End point values	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	130		
Units: Participants	131	130		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Achieving Seroprotection to Vaccine Antigens After a Primary Series Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine

End point title	Number of Participants Achieving Seroprotection to Vaccine Antigens After a Primary Series Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine[2]

End point description:

Seroprotection was assessed in all participants who did not have any protocol violation that might have

interfered with primary criteria evaluation (Per-Protocol Population). Antibody titers were measured by chemiluminescence detection for hepatitis B (Hep B), by Farr type radioimmunoassay for Haemophilus influenzae type b (PRP), and by toxin neutralization test for diphtheria. Seroprotection criteria were defined as:
Criteria 1: Anti-Hep B titer ≥ 10 mIU/mL; Anti-PRP titer ≥ 0.15 µg/mL; Anti-diphtheria titer ≥ 0.01 IU/mL.
Criteria 2: Anti-Hep B titer ≥ 100 mIU/mL; Anti-PRP titer ≥ 1 µg/mL; Anti-diphtheria titer or ≥ 0.1 IU/mL.

End point type	Primary

End point timeframe:

Day 150 (1 month after dose 3)

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 / vaccine administered in the study.

End point values	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	130		
Units: Participants				
Anti-Hep B (Criteria 1)	131	130		
Anti-Hep B (Criteria 2)	124	129		
Anti-PRP (Criteria 1)	132	129		
Anti-PRP (Criteria 2)	112	109		
Anti-Diphtheria (Criteria 1)	126	130		
Anti-Diphtheria (Criteria 2)	77	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies to Vaccine Antigens After a Primary Series of Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine.

End point title	Geometric Mean Titers (GMTs) of Antibodies to Vaccine Antigens After a Primary Series of Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine.

End point description:

Antibody GMTs were assessed in all participants who did not have any protocol violation that might have interfered with primary criteria evaluation (Per-Protocol Population).
Antibody titers were measured by chemiluminescence detection for hepatitis B (Hep B), by Farr type radioimmunoassay for Haemophilus influenzae type b (PRP), and by toxin neutralization test for diphtheria.

End point type	Secondary

End point timeframe:

Day 150 (1 month after dose 3)

End point values	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	130		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Hep B	986 (764 to 1270)	1139 (961 to 1350)		
Anti-PRP	5.22 (4.04 to 6.73)	3.93 (3.17 to 4.86)		
Anti-Diphtheria	0.156 (0.119 to 0.204)	0.192 (0.154 to 0.239)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Solicited Injection Site or Solicited Systemic Reactions After Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine.

End point title	Number of Participants Reporting Solicited Injection Site or Solicited Systemic Reactions After Vaccination With Either DTaP-IPV-Hep B-PRP~T or Infanrix Hexa™ Vaccine.

End point description:

Solicited reactions were assessed in all participants who received at least one dose of investigational or control vaccine, according to the vaccine actually received (Safety Analysis Population.
Solicited Injection Site Reactions: Pain, Erythema, Swelling. Solicited Systemic Reactions: Pyrexia (Temperature), Vomiting, Crying, Somnolence, Anorexia, Irritability.
Grade 3 reactions were defined as: Pain, cries when injected limb is moved or movement of injected limb is reduced; Erythema and Swelling ≥ 5 cm; Pyrexia > 39.5ºC; Vomiting ≥ 6 episodes per 24 hour or requiring parenteral hydration; Crying, > 3 hours; Somnolence, sleeping most of the time or difficult to wake up; Anorexia refuses ≥ 3 feeds/meals or refuses most feeds/meals; Irritability inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 after each injection .

End point values	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	131		
Units: Participants				
Pain Post-injection 1	82	71		
Pain Post-injection 2	68	68		
Pain Post-injection 3	53	55		
Grade 3 Pain Post-any injection	10	6		
Erythema Post-injection 1	32	16		
Erythema Post-injection 2	48	30		
Erythema Post-injection 3	45	46		
Grade 3 Erythema Post-any injection	3	5		

Swelling Post-injection 1	34	12		
Swelling Post-injection 2	26	24		
Swelling Post-injection 3	28	32		
Grade 3 Swelling Post-any injection	3	2		
Pyrexia Post-injection 1	11	11		
Pyrexia Post-injection 2	21	17		
Pyrexia Post-injection 3	18	18		
Gade 3 Pyrexia Post-any injection	0	3		
Vomiting Post-injection 1	20	24		
Vomiting Post-injection 2	8	6		
Vomiting Post-injection 3	6	10		
Grade 3 Vomiting Post-any injection	0	0		
Crying Post-injection 1	81	68		
Crying Post-injection 2	57	52		
Crying Post-injection 3	43	47		
Grade 3 Crying Post-any injection	1	1		
Somnolence Post-injection 1	55	65		
Somnolence Post-injection 2	41	37		
Somnolence Post-injection 3	23	28		
Grade 3 Somnolence Post-any injection	2	2		
Anorexia Post-injection 1	35	42		
Anorexia Post-injection 2	24	22		
Anorexia Post-injection 3	24	25		
Grade 3 Anorexia Post-any injection	0	1		
Irritability Post-injection 1	85	81		
Irritability Post-injection 2	63	65		
Irritability Post-injection 3	40	55		
Grade 3 Irritability Post-any injection	2	1		

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 the first injection to up to 30 days after each injection.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	DTaP-IPV-Hep B-PRP~T Group

Reporting group description:

All participants received a 3-dose primary series of diphtheria, tetanus, pertussis (2-component acellular), recombinant hepatitis B (Hep B) Hansenula polymorpha and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T) combined vaccine. A dose at 2, 4, and 6 months of age, respectively.

Reporting group title	Infanrix Hexa™ Group

Reporting group description:

All study participants received a 3-dose primary series of Infanrix hexa™ vaccine, with 1 dose each at 2, 4, and 6 months of age, respectively.

Serious adverse events	DTaP-IPV-Hep B-PRP~T Group	Infanrix Hexa™ Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 132 (2.27%)	2 / 131 (1.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 132 (0.76%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 Group	Infanrix Hexa™ Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 132 (77.27%)	106 / 131 (80.92%)	
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	73 / 132 (55.30%)	82 / 131 (62.60%)	
occurrences (all)	73	82	
General disorders and administration site conditions			
Injection site haemorrhage			
subjects affected / exposed	8 / 132 (6.06%)	4 / 131 (3.05%)	
occurrences (all)	9	4	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	102 / 132 (77.27%)	101 / 131 (77.10%)	
occurrences (all)	102	101	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	78 / 132 (59.09%)	66 / 131 (50.38%)	
occurrences (all)	78	66	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	54 / 132 (40.91%)	52 / 131 (39.69%)	
occurrences (all)	54	52	

Fever			
alternative assessment type: Systematic			
subjects affected / exposed	37 / 132 (28.03%)	36 / 131 (27.48%)	
occurrences (all)	37	36	
Pyrexia			
subjects affected / exposed	11 / 132 (8.33%)	7 / 131 (5.34%)	
occurrences (all)	13	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	38 / 132 (28.79%)	44 / 131 (33.59%)	
occurrences (all)	61	65	
Diarrhoea			
subjects affected / exposed	17 / 132 (12.88%)	18 / 131 (13.74%)	
occurrences (all)	19	21	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 132 (21.97%)	32 / 131 (24.43%)	
occurrences (all)	29	32	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	13 / 132 (9.85%)	12 / 131 (9.16%)	
occurrences (all)	14	14	
Cough			
subjects affected / exposed	14 / 132 (10.61%)	18 / 131 (13.74%)	
occurrences (all)	16	24	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	9 / 132 (6.82%)	6 / 131 (4.58%)	
occurrences (all)	9	6	
Dermatitis diaper			
subjects affected / exposed	14 / 132 (10.61%)	10 / 131 (7.63%)	
occurrences (all)	15	10	
Psychiatric disorders			
Irritability			
alternative assessment type: Systematic			

subjects affected / exposed	100 / 132 (75.76%)	98 / 131 (74.81%)	
occurrences (all)	100	98	
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	100 / 132 (75.76%)	93 / 131 (70.99%)	
occurrences (all)	100	93	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	62 / 132 (46.97%)	80 / 131 (61.07%)	
occurrences (all)	78	118	
Pharyngitis			
subjects affected / exposed	11 / 132 (8.33%)	15 / 131 (11.45%)	
occurrences (all)	11	15	
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed	54 / 132 (40.91%)	58 / 131 (44.27%)	
occurrences (all)	54	58	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2007	Changes were implemented to: Clarify the term Pregnant women (or mothers within 4 weeks post partum) and their screening visits, and revision of visit intervals; Revision of inclusion/exclusion criteria; Change of the Sponsor's Responsible Medical Officer, Clinical Scientist, and CRA; Extension of the planned trial period and the revision of the benefit/risk statement and the addition of a Secondary immunogenicity objective and endpoint concerning the detection of PRP Abs (anti Hib)
20 December 2007	Changes were implemented to: Modify the screening period of mothers; follow changes in internal standards for the Phase III studies randomization process and the use of an IVRS system; revise study duration; SAE reporting period; the revision and clarification of the per-protocol analysis set.
25 February 2008	Further clarification of the maternal screening period to define and other minor changes to IVRS text and study procedures.
08 December 2008	Change of PRP assessment method to RIA and revision of descriptions for some antigen assessment methods and a note on the change in Sponsor's organization.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable.

Notes: