Clinical trial results:
Immunogenicity of DTaP-IPV-Hep B-PRP-T Combined Vaccine Compared with PENTAXIM and ENGERIX B® at 2, 3, and 4 Months Primary Schedule in Healthy Turkish Infants

Summary

EudraCT number	2011-004454-26
Trial protocol	Outside EU/EEA
Global end of trial date	18 June 2007

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	12 September 2014

Trial information

Trial identification

Sponsor protocol code	A3L10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00315055
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?	Yes
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	30 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2007
Global end of trial reached?	Yes
Global end of trial date	18 June 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immune response to Hep B antigen of the DTaP-IPV-Hep B-PRP-T is non-inferior to that of the association of PENTAXIM™ + ENGERIX B® 1 month after a three-dose primary series at 2, 3, and 4 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:

All subjects participating in the study were to have received the DTaP-IPV-Hep B-PRP-T vaccine at 2, 3, and 4 months of age which is in agreement with the national immunization program in Turkey.

Evidence for comparator:

PENTAXIM + ENGERIX B® vaccines were chosen as the control vaccines for this trial as they are part of the standard range of vaccines currently used in Turkey. In addition, PENTAXIM contains the same D, T, aP, IPV, and PRP-T antigens as the investigational vaccine while ENGERIX B® contains the same amount of HBsAg as the investigational vaccine.

Actual start date of recruitment	01 June 2006
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: 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:

Subjects were enrolled and treated from 01 June 2006 to 18 June 2007 in 1 clinical center in Turkey.

Pre-assignment

Screening details:

A total of 310 subjects who met the inclusion but non of the exclusion criteria were enrolled and vaccinated.

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:

Participants received 3 vaccinations with Diphtheria (D) and tetanus (T) toxoids, acellular pertussis (2-component) (aP), recombinant Hepatitis B surface antigen (HBsAg), inactivated poliomyelitis virus (IPV), and Hemophilus influenzae type b (Hib) polysaccharide conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).

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, intramuscular, one dose each at 2, 3, and 4 months of age.

Arm title	PENTAXIM™ and ENGERIX®

Arm description:

Participants received 3 vaccinations with DTaP-IPV-PRP~T (PENTAXIM™) and recombinant Hepatitis B (ENGERIX® PEDIATRIC) vaccines, with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).

Arm type	Active comparator
Investigational medicinal product name	Pentaxim
Investigational medicinal product code	DTaP-IPV-PRP-T vaccine
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, one dose at 2, 3, and 4 months of age.

Investigational medicinal product name	ENGERIX B
Investigational medicinal product code	Recombinant Hep B vaccine
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, one dose each at 2, 3, and 4 months of age.

Number of subjects in period 1	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®
Started	155	155
Completed	152	150
Not completed	3	5
Lost to follow-up	1	1
Protocol deviation	2	4

Baseline characteristics

Reporting groups	
Reporting group title	DTaP-IPV-Hep B-PRP~T
Reporting group description:	
Participants received 3 vaccinations with Diphtheria (D) and tetanus (T) toxoids, acellular pertussis (2-component) (aP), recombinant Hepatitis B surface antigen (HBsAg), inactivated poliomyelitis virus (IPV), and Hemophilus influenzae type b (Hib) polysaccharide conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).	
Reporting group title	PENTAXIM™ and ENGERIX®
Reporting group description:	
Participants received 3 vaccinations with DTaP-IPV-PRP~T (PENTAXIM™) and recombinant Hepatitis B (ENGERIX® PEDIATRIC) vaccines, with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).	

Reporting group values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®	Total
Number of subjects	155	155	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)	155	155	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: months			
arithmetic mean	2.08	2.08	
standard deviation	± 0.09	± 0.102	-
Gender categorical Units: Subjects			
Female	67	72	139
Male	88	83	171

	Hep B-PRP~T or PENTAXIM™ + ENGERIX B®

End point description:

Antibodies to hepatitis B surface antigen (HBs) were measured by means of automated enhanced chemoluminescence assay. Antibodies to Polyribosyl ribitol phosphate and tetanus were measured by enzyme linked immunosorbent assay (ELISA), and antibodies to diphtheria were measured by a neutralization test using crystal violet. Seroprotection was defined as: titers ≥ 100 mIU/mL for HBs; ≥ 0.01 and ≥ 0.1 IU/mL for anti-Tetanus and anti-diphtheria, and ≥ 0.15 µg/mL and ≥ 1.0 µg/mL for anti-PRP.

End point type	Secondary

End point timeframe:

Day 90 post first dose

End point values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Percentage of subjects				
Anti-HBs (≥ 100 mIU/mL)	65	78		
Anti-PRP (≥ 0.15 µg/mL)	91	98		
Anti-PRP (≥ 1.0 µg/mL)	73	77		
Anti-Diphtheria (≥0.01 IU/mL)	99	97		
Anti-Diphtheria (≥0.1 IU/mL)	34	44		
Anti-Tetanus (≥0.01 IU/mL)	100	100		
Anti-Tetanus (≥0.1 IU/mL)	100	99		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection Against Poliovirus Antigens After the 3 Dose Primary Series Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point title	Percentage of Subjects With Seroprotection Against Poliovirus Antigens After the 3 Dose Primary Series Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point description:

Antibodies to poliovirus types 1, 2, and 3 were measured by microneutralization on Vero cell culture. Seroprotection was defined as titers ≥8 1/dil.

End point type	Secondary

End point timeframe:

Day 90 post first dose

End point values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Percentage of subjects				
Anti-Polio 1	98	98		
Anti-Polio 2	95	94		
Anti-Polio 3	97	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Pertussis Seroconversion After the 3 Dose Primary Series Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point title	Percentage of Subjects With Anti-Pertussis Seroconversion After the 3 Dose Primary Series Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point description:

Antibodies to pertussis toxoid (PT) and filamentous hemagglutinin (FHA) were measured by means of enzyme linked immunosorbent assay (ELISA). Seroconversion was defined as a ≥ 4-fold increase in titer between baseline (Day 0 pre-vaccination and Day 30 post-dose 3 (Day 90).

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 30 post-dose 3

End point values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Percentage of subjects				
Anti-PT (Pre-dose 1)	55	48		
Anti-PT (Post-dose 3)	100	100		
Anti-FHA (Pre-dose 1)	65	62		
Anti-FHA (Post-dose 3)	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Antibodies After the 3 Dose Primary Series With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point title	Geometric Mean Titers of Antibodies After the 3 Dose Primary Series With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point description:	
Antibodies to hepatitis B surface antigen (HBs) were measured by means of automated enhanced chemoluminescence assay. Antibodies to PRP, tetanus, pertussis toxoid (PT), and filamentous hemagglutinin (FHA) were measured by enzyme linked immunosorbent assay (ELISA), and antibodies to diphtheria were measured by a neutralization test using crystal violet.	
End point type	Secondary
End point timeframe:	
Day 90 (30 Days post-dose 3)	

End point values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-HBs	149 (115 to 191)	265 (205 to 342)		
Anti-PRP	2.12 (1.62 to 2.77)	2.37 (1.91 to 2.94)		
Anti-Diphtheria	0.071 (0.06 to 0.084)	0.091 (0.075 to 0.11)		
Anti-Tetanus	0.839 (0.731 to 0.962)	0.709 (0.625 to 0.804)		
Anti-Polio 1	102 (74.9 to 138)	112 (85.4 to 147)		
Anti-Polio 2	73.5 (52.9 to 102)	78.2 (58.2 to 105)		
Anti-Polio 3	133 (93 to 190)	214 (159 to 288)		
Anti-PT	123 (109 to 139)	138 (122 to 155)		
Anti-FHA	102 (90.4 to 114)	69.3 (62 to 77.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least a Solicited Injection Site or Systemic Reaction After Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®

End point title	Number of Subjects With at Least a Solicited Injection Site or Systemic Reaction After Vaccination With Either DTaP-IPV-HB-PRP~T or PENTAXIM™ + ENGERIX B®
End point description:	
Solicited Injection Site Reactions: Pain, Erythema, Swelling. Solicited Systemic Reactions: Pyrexia (Temperature), Vomiting, Crying, Somnolence, Anorexia, Irritability	
End point type	Secondary
End point timeframe:	
Day 0 to Day 7 post any dose	

End point values	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	152		
Units: Subjects				
number (not applicable)				
Injection site Pain Post-dose 1	70	55		
Injection site Pain Post-dose 2	66	58		
Injection site Pain Post-dose 3	57	48		
Injection site Erythema Post-dose 1	23	17		
Injection site Erythema Post-dose 2	25	17		
Injection site Erythema Post-dose 3	30	17		
Injection site Swelling Post-dose 1	21	16		
Injection site Swelling Post Dose 2	21	12		
Injection site Sweling Post Dose 3	17	11		
Pyrexia Post-dose 1	15	12		
Pyrexia Post-dose 2	33	23		
Pyrexia Post-dose 3	41	24		
Vomiting Post-dose 1	57	44		
Vomiting Post-dose 2	55	48		
Vomiting Post-dose 3	44	40		
Crying Post-dose 1	51	41		
Crying Post-dose 2	54	38		
Crying Post-dose 3	45	30		
Somnolence Post-dose 1	51	45		
Somnolence Post-dose 2	35	38		
Somnolence Post-dose 3	26	36		
Anorexia Post-dose 1	43	27		
Anorexia Post-dose 2	48	35		
Anorexia Post-dose 3	42	40		
Irritability Post-dose 1	83	67		
Irritability Post-dose 2	81	74		
Irritability Post-dose 3	71	64		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed following the administration first dose of study vaccine (Day 0) through 6 months after the last dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

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

Reporting group description:

Participants received 3 vaccinations with Diphtheria (D) and tetanus (T) toxoids, acellular pertussis (2-component) (aP), recombinant Hepatitis B surface antigen (HBsAg), inactivated poliomyelitis virus (IPV), and Hemophilus influenzae type b (Hib) polysaccharide conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).

Reporting group title	PENTAXIM™ and ENGERIX®

Reporting group description:

Participants received 3 vaccinations with DTaP-IPV-PRP~T (PENTAXIM™) and recombinant Hepatitis B (ENGERIX® PEDIATRIC) vaccines, with one dose each at 2, 3, and 4 months of age (Days 0, 30, and 60).

Serious adverse events	DTaP-IPV-Hep B-PRP~T	PENTAXIM™ and ENGERIX®	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 153 (1.31%)	3 / 152 (1.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 153 (0.65%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 152 (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	PENTAXIM™ and ENGERIX®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 153 (54.25%)	74 / 152 (48.68%)	
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	51 / 153 (33.33%)	45 / 152 (29.61%)	
occurrences (all)	51	45	
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	70 / 153 (45.75%)	58 / 152 (38.16%)	
occurrences (all)	70	58	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 153 (19.61%)	17 / 152 (11.18%)	
occurrences (all)	30	17	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 153 (13.73%)	16 / 152 (10.53%)	
occurrences (all)	21	16	
Irritability			
alternative assessment type: Systematic			

subjects affected / exposed	83 / 153 (54.25%)	74 / 152 (48.68%)	
occurrences (all)	83	74	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	41 / 153 (26.80%)	24 / 152 (15.79%)	
occurrences (all)	41	24	
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	57 / 153 (37.25%)	48 / 152 (31.58%)	
occurrences (all)	57	48	
Psychiatric disorders			
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	54 / 153 (35.29%)	41 / 152 (26.97%)	
occurrences (all)	54	41	
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed	48 / 153 (31.37%)	40 / 152 (26.32%)	
occurrences (all)	48	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2006	Prior to the enrollment of subjects in the study, the protocol was updated to include (i) the incorporation of an Independent Data Monitoring Committee (ii) the requirements for collection of baseline, immunogenicity, and safety data and analysis.
16 April 2007	A modification to remove all study procedures related to the booster vaccination, include another secondary immunogenicity assessment, and a change to the type of assays used to detect antibody levels at qualified contract laboratories.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported