Clinical trial results:
Lot to Lot Consistency Study of DTaP-IPV-Hep B-PRP~T Vaccine Administered at 2- 4-6 Months of Age in Healthy Mexican Infants

Summary

EudraCT number	2011-004455-39
Trial protocol	Outside EU/EEA
Global end of trial date	13 June 2008

Results information

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

Trial information

Trial identification

Sponsor protocol code	A3L11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00404651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon cedex, France, F-69367
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	24 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 June 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the equivalence of three batches of DTaP-IPV-Hep B-PRP-T vaccine second Drug Product Generation in terms of seroprotection rates for D, T, Hep B, PRP, and polio and seroconversion rates for anti-pertussis toxoid (PT) and anti-filamentous hemagglutinin (FHA), 1 month after a three-dose primary series (at 2, 4, and 6 months of age).

Protection of trial subjects:

Subjects in the study received three injections of a single dose of the study vaccine DTaP-IPV-HB-PRP~T or the comparator DTaP-HBV-IPV vaccine supplied in a prefilled 0.5 mL syringe that was administered by qualified study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After each vaccination, subjects were also kept under observation for 30 minutes to ensure their safety. Appropriate equipment were also available on site in case of any immediate allergic reactions.

Background therapy:

Not Applicable

Evidence for comparator:

A fourth treatment group (Infanrix hexa - DTaP-HB-IPV/Hib) was added in order to provide an estimate of the immunogenicity and safety profile of a reference licensed vaccine.

Actual start date of recruitment	14 November 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	Mexico: 1189
Worldwide total number of subjects	1189
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)	1189

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 14 November 2006 to 13 July 2007 in 6 clinical centers in Mexico.

Pre-assignment

Screening details:

A total of 1189 participants who met all the inclusion but none 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	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The Investigator (blind observer or assessor) and the subjects' parents did not know the vaccine administered. The assessor was in charge of safety assessment, held in a separate room to one in which the vaccines were prepared. A nurse/vaccinator was in charge of the preparation and administration of the vaccine(s) only, in another room away from the assessor. A scratch off emergency decoding procedure described in the study protocol was followed.

Arms

Are arms mutually exclusive?	Yes
Arm title	DTaP-IPV-HB-PRP~T Batch 1

Arm description:

Participants received 3 doses of Batch 1 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 4, and 6 months of age.

Arm type	Experimental
Investigational medicinal product name	Hexaxim
Investigational medicinal product code	DTaP-IPV-Hep B-PRP-T
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, 4, and 6 months of age.

Arm title	DTaP-IPV-HB-PRP~T Batch 2

Arm description:

Participants received 3 doses of Batch 2 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.

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, 4, and 6 months of age.

Arm title	DTaP-IPV-HB-PRP~T Batch 3

Arm description:

Participants received 3 doses of Batch 3 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.

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:

.5 mL, intramuscular. One dose each at 2, 4, and 6 months of age.

Arm title	Infanrix hexa™

Arm description:

Participants received 3 doses of diphtheria (D), tetanus (T), pertussis (3 component acellular), recombinant hepatitis B (Hep B) and poliomyelitis (IPV) vaccine adsorbed, plus Haemophilus influenzae type b (Hib) vaccine conjugated to tetanus protein (Infanrix hexa™), a dose each at 2, 4, and 6 months of age.

Arm type	Active comparator
Investigational medicinal product name	Infanrix hexa™
Investigational medicinal product code	DTaP-HBV-IPV 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, 4, and 6 months of age.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The Investigator served as blind observer or assessor in this study design.

Number of subjects in period 1	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3
Started	340	343	339
Completed	301	315	294
Not completed	39	28	45
Consent withdrawn by subject	14	12	16
Adverse event, non-fatal	-	-	2
Lost to follow-up	15	11	13
Protocol deviation	10	5	14

Number of subjects in period 1	Infanrix hexa™
Started	167
Completed	146
Not completed	21
Consent withdrawn by subject	6
Adverse event, non-fatal	-
Lost to follow-up	10

Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	DTaP-IPV-HB-PRP~T Batch 1
Reporting group description:	
Participants received 3 doses of Batch 1 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 4, and 6 months of age.	
Reporting group title	DTaP-IPV-HB-PRP~T Batch 2
Reporting group description:	
Participants received 3 doses of Batch 2 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.	
Reporting group title	DTaP-IPV-HB-PRP~T Batch 3
Reporting group description:	
Participants received 3 doses of Batch 3 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.	
Reporting group title	Infanrix hexa™
Reporting group description:	
Participants received 3 doses of diphtheria (D), tetanus (T), pertussis (3 component acellular), recombinant hepatitis B (Hep B) and poliomyelitis (IPV) vaccine adsorbed, plus Haemophilus influenzae type b (Hib) vaccine conjugated to tetanus protein (Infanrix hexa™), a dose each at 2, 4, and 6 months of age.	

Reporting group values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3
Number of subjects	340	343	339
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)	340	343	339
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	2	2.01
standard deviation	± 0.2	± 0.197	± 0.193
Gender categorical Units: Subjects			
Female	160	163	167
Male	180	180	172

Reporting group values	Infanrix hexa™	Total	

Number of subjects	167	1189	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	167	1189	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
arithmetic mean	1.98		
standard deviation	± 0.189	-	
Gender categorical Units: Subjects			
Female	82	572	
Male	85	617	

End points

End points reporting groups

Reporting group title	DTaP-IPV-HB-PRP~T Batch 1

Reporting group description:

Participants received 3 doses of Batch 1 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	DTaP-IPV-HB-PRP~T Batch 2

Reporting group description:

Participants received 3 doses of Batch 2 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	DTaP-IPV-HB-PRP~T Batch 3

Reporting group description:

Participants received 3 doses of Batch 3 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-HB-PRP~T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	Infanrix hexa™

Reporting group description:

Participants received 3 doses of diphtheria (D), tetanus (T), pertussis (3 component acellular), recombinant hepatitis B (Hep B) and poliomyelitis (IPV) vaccine adsorbed, plus Haemophilus influenzae type b (Hib) vaccine conjugated to tetanus protein (Infanrix hexa™), a dose each at 2, 4, and 6 months of age.

Primary: Equivalence of Seroprotection Against Vaccine Antigens in Study Participants After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T or Infanrix Hexa™ Vaccine

End point title	Equivalence of Seroprotection Against Vaccine Antigens in Study Participants After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T or Infanrix Hexa™ Vaccine[1]

End point description:

Antibody titers were measured for hepatitis B (Hep B) by enhanced chemiluminescence detection, for Haemophilus influenzae type b (PRP) by Farr type radioimmunoassay, for diphtheria (D) by toxin neutralization test, and for tetanus by enzyme linked immunosorbent assay (ELISA). Seroprotection was defined as a titer ≥ 0.10 mIU/mL for Hep B, ≥ 0.15 µg/mL for PRP, and ≥ 0.01 IU/mL for D and T antibodies.

End point type	Primary

End point timeframe:

Day 150 (one month post-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: This outcome presented and compared the values among the groups.

End point values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3	Infanrix hexa™
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	231	231	228	117
Units: Participants				
Anti-Hep B	226	231	221	119
Anti-PRP	229	232	226	118
Anti-Diphtheria	220	228	222	118
Anti-Tetanus	231	236	227	119

Statistical analyses

No statistical analyses for this end point

Primary: Equivalence of Seroprotection Against Pertussis in Study Participants After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T or Infanrix Hexa™ Vaccine.

End point title	Equivalence of Seroprotection Against Pertussis in Study Participants After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T or Infanrix Hexa™ Vaccine.[2]

End point description:

Antibody titers were measured for pertussis toxoid (PT) and filamentous hemagglutinin (FHA) by enzyme linked immunosorbent assay (ELISA). Seroconversion was defined as a ≥ 4 fold increase in titer from Day 0 (before dose 1) to Day 150, one month post-dose 3.

End point type	Primary

End point timeframe:

Day 150 (one month post-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: This outcome presented and compared the values among the groups.

End point values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3	Infanrix hexa™
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	231	236	228	119
Units: Participants				
Anti-Pertussis	223	226	218	113
Anti-FHA	225	229	216	111

Statistical analyses

No statistical analyses for this end point

Primary: Equivalence of Seroprotection Against Poliovirus Types 1, 2, and 3 in Study Participants After Vaccination With Either One of the Batches of DTaP-IPV- Hep B-PRP~T or Infanrix Hexa™ Vaccine

End point title	Equivalence of Seroprotection Against Poliovirus Types 1, 2, and 3 in Study Participants After Vaccination With Either One of

	the Batches of DTaP-IPV- Hep B-PRP~T or Infanrix Hexa™ Vaccine[3]

End point description:

Antibody titers were measured for poliovirus types 1, 2, and 3 by neutralization assay. Seroprotection against Poliovirus Types 1, 2, and 3 was defined as a titer ≥ 8 (1/dilutions).

End point type	Primary

End point timeframe:

Day 150 (one month post-dose 3)

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: This outcome presented and compared the values among the groups.

End point values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3	Infanrix hexa™
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	231	236	228	119
Units: Participants				
Anti-Polio 1	230	236	225	119
Anti-Polio 2	230	236	226	118
Anti-Polio 3	229	235	226	117

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Antibodies After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T Vaccine or Infanrix Hexa™ Vaccine

End point title	Geometric Mean Titers of Antibodies After Vaccination With Either One of the Batches of DTaP-IPV-HB-PRP~T Vaccine or Infanrix Hexa™ Vaccine

End point description:

Antibody titers were measured for hepatitis B (Hep B) by enhanced chemiluminescence detection, for Haemophilus influenzae type b (PRP) by Farr type radioimmunoassay, for diphtheria (D) by toxin neutralization test, and for tetanus by enzyme linked immunosorbent assay. Antibody titers were measured for poliovirus types 1, 2, and 3 by neutralization assay. Antibody titers were measured for pertussis toxoid (PT) and filamentous hemagglutinin (FHA) by enzyme linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Day 150 (one month post-dose 3)

End point values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3	Infanrix hexa™
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	231	236	228	119
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Hep B	935 (755 to 1158)	1566 (1288 to 1905)	1009 (814 to 1252)	1576 (1283 to 1934)

Anti-PRP	11.9 (9.77 to 14.5)	13.1 (10.7 to 16)	11.5 (9.26 to 14.3)	6.68 (5.1 to 8.74)
Anti-Diphtheria	0.176 (0.143 to 0.217)	0.246 (0.194 to 0.311)	0.173 (0.139 to 0.214)	0.173 (0.132 to 0.226)
Anti-Tetanus	1.9 (1.67 to 2.15)	1.86 (1.64 to 2.1)	1.77 (1.57 to 2.01)	2.2 (1.93 to 2.52)
Anti-Polio 1	860 (725 to 1021)	945 (809 to 1102)	843 (712 to 999)	1370 (1082 to 1736)
Anti-Polio 2	1689 (1429 to 1996)	1665 (1416 to 1957)	1612 (1374 to 1892)	2337 (1878 to 2909)
Anti-Polio 3	1198 (1015 to 1413)	1170 (995 to 1377)	962 (809 to 1143)	2186 (1752 to 2727)
Anti-Pertusiss toxoid	242 (226 to 260)	238 (220 to 258)	241 (222 to 262)	228 (205 to 254)
Anti-FHA	243 (228 to 259)	256 (237 to 277)	220 (202 to 239)	182 (165 to 200)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Solicited Injection Site or Systemic Reactions After Vaccination With Either One of the Batches of DTaP-IPV-HB- PRP~T Vaccine or Infanrix Hexa™ Vaccine

End point title	Number of Participants Reporting Solicited Injection Site or Systemic Reactions After Vaccination With Either One of the Batches of DTaP-IPV-HB- PRP~T Vaccine or Infanrix Hexa™ Vaccine

End point description:

Solicited Injection Site Reactions: Pain, Erythema, and Swelling. Solicited Systemic Reactions: Fever ([pyrexia] - temperature), Vomiting, Crying, Somnolence, Anorexia, and Irritability.

End point type	Secondary

End point timeframe:

Day 0 (pre-each vaccination) up to 7 days post-each dose

End point values	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-HB-PRP~T Batch 2	DTaP-IPV-HB-PRP~T Batch 3	Infanrix hexa™
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	340	343	339	167
Units: Participants				
Solicited Injection site Pain post-dose 1	220	237	225	95
Solicited Injection site Pain post-dose 2	191	220	199	88
Solicited Injection site Pain post-dose 3	188	209	198	87
Solicited Injection site Erythema post-dose 1	92	97	97	41
Solicited Injection site Erythema post-dose 2	94	101	96	33
Solicited Injection site Erythema post-dose 3	95	94	101	43
Solicited Injection site Swelling post-dose 1	67	86	80	35

Solicited Injection site Swelling post-dose 2	74	70	60	26
Solicited Injection site Swelling post-dose 3	66	65	72	22
Solicited Pyrexia post-dose 1	63	77	82	17
Solicited Pyrexia Post-dose 2	75	84	85	32
Solicited Pyrexia Post-dose 3	69	85	70	28
Solicited Vomiting Post-dose 1	68	63	56	27
Solicited Vomiting post-dose 2	37	46	34	18
Solicited Vomiting post-dose 3	51	46	47	20
Solicited Crying post-dose 1	160	156	148	62
Solicited Crying post-dose 2	133	145	134	59
Solicited Crying post-dose 3	110	118	122	40
Solicited Somnolence post-dose 1	93	110	102	45
Solicited Somnolence post-dose 2	69	78	65	24
Solicited Somnolence post-dose 3	56	57	54	20
Solicited Anorexia post-dose 1	62	75	70	27
Solicited Anorexia post-dose 2	56	64	65	25
Solicited Anorexia post-dose 3	61	58	65	29
Solicited Irritability post-dose 1	188	198	193	83
Solicited Irritability post-dose 2	158	192	174	72
Solicited Irritability post-dose 3	158	167	165	69

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 vaccination and up to 6 months after the third infant dose

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	DTaP-IPV-HB-PRP~T Batch 1

Reporting group description:

Participants received 3 doses of Batch 1 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP~T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	DTaP-IPV-Hep B-PRP-T Batch 2

Reporting group description:

Participants received 3 doses of Batch 2 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	DTaP-IPV-Hep B-PRP-T Batch 3

Reporting group description:

Participants received 3 doses of Batch 3 of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed, and Haemophilus influenzae type b (Hib) vaccine, conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with one dose each at 2, 4, and 6 months of age.

Reporting group title	Infanrix hexa™

Reporting group description:

Participants received 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular), recombinant hepatitis B Hansenula (Hep B) and poliomyelitis (IPV) vaccine adsorbed (Infanrix hexa™), plus Haemophilus influenzae type b (Hib) vaccine conjugated to tetanus protein , with one dose each at 2, 4, and 6 months of age.

Serious adverse events	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-Hep B-PRP-T Batch 2	DTaP-IPV-Hep B-PRP-T Batch 3
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 337 (1.48%)	5 / 345 (1.45%)	12 / 340 (3.53%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	0 / 337 (0.00%)	1 / 345 (0.29%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			

subjects affected / exposed	0 / 337 (0.00%)	1 / 345 (0.29%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Heart Disease Congenital			
subjects affected / exposed	0 / 337 (0.00%)	1 / 345 (0.29%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile Convulsion			
subjects affected / exposed	1 / 337 (0.30%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infantile Spasms			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	1 / 337 (0.30%)	0 / 345 (0.00%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear Infection			
subjects affected / exposed	0 / 337 (0.00%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 337 (0.59%)	2 / 345 (0.58%)	5 / 340 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 337 (0.30%)	0 / 345 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Food Intolerance			
subjects affected / exposed	1 / 337 (0.30%)	0 / 345 (0.00%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Infanrix hexa™		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 167 (3.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head Injury			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple Fractures			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Heart Disease Congenital			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile Convulsion			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infantile Spasms			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Partial Seizures			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asphyxia			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear Infection			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Food Intolerance			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DTaP-IPV-HB-PRP~T Batch 1	DTaP-IPV-Hep B-PRP-T Batch 2	DTaP-IPV-Hep B-PRP-T Batch 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 337 (65.28%)	237 / 345 (68.70%)	225 / 340 (66.18%)
Nervous system disorders			
Solicited Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed[1]	93 / 323 (28.79%)	110 / 336 (32.74%)	102 / 329 (31.00%)
occurrences (all)	93	110	102
General disorders and administration site conditions			
Solicited injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[2]	95 / 302 (31.46%)	101 / 319 (31.66%)	101 / 306 (33.01%)
occurrences (all)	95	101	101
Solicited injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[3]	220 / 323 (68.11%)	237 / 336 (70.54%)	225 / 329 (68.39%)
occurrences (all)	220	237	225
Solicited injetion site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	74 / 310 (23.87%)	86 / 336 (25.60%)	80 / 329 (24.32%)
occurrences (all)	74	86	80
Solicited Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[5]	188 / 323 (58.20%)	198 / 336 (58.93%)	193 / 329 (58.66%)
occurrences (all)	188	198	193
Solicited Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed[6]	75 / 310 (24.19%)	85 / 317 (26.81%)	85 / 315 (26.98%)
occurrences (all)	75	85	85
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[7]	68 / 323 (21.05%)	63 / 336 (18.75%)	56 / 329 (17.02%)
occurrences (all)	68	63	56
Psychiatric disorders			

Solicited Crying			
alternative assessment type: Systematic			
subjects affected / exposed[8]	160 / 323 (49.54%)	156 / 336 (46.43%)	148 / 329 (44.98%)
occurrences (all)	160	156	148
Metabolism and nutrition disorders			
Solicited Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed[9]	62 / 323 (19.20%)	75 / 336 (22.32%)	70 / 329 (21.28%)
occurrences (all)	62	75	70

Non-serious adverse events	Infanrix hexa™		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 167 (56.89%)		
Nervous system disorders			
Solicited Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed[1]	45 / 156 (28.85%)		
occurrences (all)	45		
General disorders and administration site conditions			
Solicited injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[2]	43 / 149 (28.86%)		
occurrences (all)	43		
Solicited injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[3]	95 / 155 (61.29%)		
occurrences (all)	95		
Solicited injetion site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	35 / 156 (22.44%)		
occurrences (all)	35		
Solicited Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[5]	83 / 156 (53.21%)		
occurrences (all)	83		
Solicited Pyrexia			

alternative assessment type: Systematic subjects affected / exposed[6] occurrences (all)	32 / 153 (20.92%) 32		
Gastrointestinal disorders Vomiting alternative assessment type: Systematic subjects affected / exposed[7] occurrences (all)	27 / 156 (17.31%) 27		
Psychiatric disorders Solicited Crying alternative assessment type: Systematic subjects affected / exposed[8] occurrences (all)	62 / 156 (39.74%) 62		
Metabolism and nutrition disorders Solicited Anorexia alternative assessment type: Systematic subjects affected / exposed[9] occurrences (all)	29 / 149 (19.46%) 29		

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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card

during the solicited events 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: The number presented are those exposed subjects that retured the safety diary card during the solicited events period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2006	Amendment 1 of Protocol (Version 7.0) was produced to align the study with prevailing immunization of pregnant women practice in Mexico and the addition of a secondary objective on non-inferiority of anti-Dihtheria seroprotection. The collection of maternal vaccination history was also included.
15 November 2007	Amendment 4 of Protocol (Version 10.0) was produced to extend the time intervals between vaccinations and between vaccination and blood samples to be used for the primary series in order to maintain the defined attrition rate for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported