Clinical trial results:
Immunogenicity Study of a DTaP IPV Hep B PRP T Combined Vaccine in Comparison to CombAct Hib™ Concomitantly Administered with Engerix B™ Pediatric and OPV at 6, 10, and 14 Weeks of Age in South African Infants.

Summary

EudraCT number	2011-004433-14
Trial protocol	Outside EU/EEA
Global end of trial date	18 August 2009

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	A3L15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00362336
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
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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	21 December 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 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 does not induce a lower immune response than CombAct-Hib™ with Engerix B™ Pediatric and OPV in terms of seroprotection rates to D, T, polio, Hep B, and polyribosyl ribitol phosphate (PRP), 1 month after a three-dose primary series (at 6, 10, and 14 weeks) with no Hep B vaccination at birth.

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: -

Evidence for comparator: -

Actual start date of recruitment	28 August 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	South Africa: 622
Worldwide total number of subjects	622
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)	622
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 28 August 2006 to 11 February 2007 in 2 clinical centers in South Africa.

Pre-assignment

Screening details:

A total of 622 of the 715 recruited participants who met the inclusion and 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	Not blinded

Blinding implementation details:

Not applicable

Arms

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

Arm description:

Participants received a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular(aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 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 at age 6, 10, and 14 weeks, and a booster dose at age 15 to 18 months

Arm title	CombAct-Hib™ + Engerix B™ + OPV Group

Arm description:

Participants received a primary series of 3 doses of commercial CombAct-Hib™ vaccine, Engerix B™ vaccine, and oral poliovirus vaccine, with 1 dose of each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Arm type	Active comparator
Investigational medicinal product name	CombAct-Hib™
Investigational medicinal product code	Tetract-Hib
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, 3 priming doses of CombAct Hib™ + Engerix B™ Oral Poliovirus Vaccine (OPV) at 6, 10, and 14 weeks, and a booster dose of CombAct Hib™ + OPV at 15 to 18 months.

Investigational medicinal product name	OPVERO
Investigational medicinal product code	Oral Poliomyelitis Vaccine
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

0.1 mL, 3 priming doses at age 6, 10, and 14 weeks, and a booster dose at age 15 to 18 months

Investigational medicinal product name	Engerix B™
Investigational medicinal product code	Hepatitis B Surface antigen
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, Intramuscular injection into the anterolateral area of the right thigh. Three priming doses at age 6, 10, and 14 weeks

Arm title	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group

Arm description:

Participants received Engerix B™ vaccine at birth, followed by a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular (aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Arm type	Active comparator
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, at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age.

Investigational medicinal product name	Engerix B™
Investigational medicinal product code	Hepatitis B Surface antigen
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, at birth.

Number of subjects in period 1	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group
Started	243	242	137
Completed	233	235	134
Not completed	10	7	3
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	3	3	1
Adverse event, non-fatal	1	-	-
Lost to follow-up	6	4	-

Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	DTaP-IPV-Hep B-PRP~T Group
Reporting group description:	
Participants received a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular(aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.	
Reporting group title	CombAct-Hib™ + Engerix B™ + OPV Group
Reporting group description:	
Participants received a primary series of 3 doses of commercial CombAct-Hib™ vaccine, Engerix B™ vaccine, and oral poliovirus vaccine, with 1 dose of each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.	
Reporting group title	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group
Reporting group description:	
Participants received Engerix B™ vaccine at birth, followed by a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular (aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.	

Reporting group values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group
Number of subjects	243	242	137
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	243	242	137
Infants and toddlers (28 days-23 months)	0	0	0
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: days			
arithmetic mean	1.04	1.07	1.11
standard deviation	± 0.729	± 0.762	± 0.773
Gender categorical Units: Subjects			
Female	131	118	68
Male	112	124	69

Reporting group values	Total		
Number of subjects	622		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	622		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: days			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	317		
Male	305		

End points

End points reporting groups

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

Reporting group description:

Participants received a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular(aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Reporting group title	CombAct-Hib™ + Engerix B™ + OPV Group

Reporting group description:

Participants received a primary series of 3 doses of commercial CombAct-Hib™ vaccine, Engerix B™ vaccine, and oral poliovirus vaccine, with 1 dose of each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Reporting group title	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group

Reporting group description:

Participants received Engerix B™ vaccine at birth, followed by a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular (aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Primary: Number of Participants With Seroprotection After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point title	Number of Participants With Seroprotection After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)[1]

End point description:

Antibodies were measured by the following methods: anti-Hepatitis B (Hep B) by enhanced chemiluminescence detection, anti-Haemophilus influenzae type b (Hib) by Farr type radio immunoassay, anti-Diphtheria (D) by toxin neutralization assay, anti-Tetanus (T) by indirect enzyme-linked immunosorbent assay (ELISA), and anti-Poliovirus types 1, 2, and 3 by neutralization assay. Seroprotection was defined as the following antibody titers: Anti-Tetanus ≥ 0.01 International Unit (IU)/mL; Anti-Diphtheria ≥ 0.01 IU/mL; Anti-Hepatitis B ≥ 10 mIU/mL; Anti-Polyribosyl ribitol phosphate ≥ 0.15 µg/mL; Anti-polio 1, 2, and 3 ≥ 8 (1/dil).

End point type	Primary

End point timeframe:

1 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: 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-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	212	123	
Units: Participants				

Anti-Hep B	176	185	97	
Anti-PRP	209	212	119	
Anti-Diphtheria	201	198	116	
Anti-Tetanus	213	210	122	
Anti-Polio Type 1	186	174	103	
Anti-Polio Type 2	193	192	111	
Anti-Polio Type 3	182	176	98	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Attaining Other Seroprotection and Seroconversion Titers After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point title	Number of Participants Attaining Other Seroprotection and Seroconversion Titers After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point description:

Anti-Hepatitis B (Hep B) was measured by enhanced chemiluminescence detection, anti-Haemophilus influenzae type b (Hib) by Farr type radio immunoassay, anti diphtheria by toxin neutralization assay, anti-Tetanus (T) by indirect enzyme-linked immunosorbent assay (ELISA), and anti-Pertussis toxoid (PT) and anti-Filamentous hemagglutinin (FHA) by ELISA. Seroprotection was defined as a titer ≥ 100 mIU/mL for anti-Hep B; ≥ 1 µg/mL for anti-PRP; ≥ 0.1 IU/mL (Level 1) and ≥ 1.0 IU/mL (Level 2) for anti-Diphtheria and anti-Tetanus. Seroconversion for anti-PT and anti-FHA was a ≥ 4-fold increase from baseline.

End point type	Secondary

End point timeframe:

1 month post-Dose 3

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	220	212	123	
Units: Participants				
Anti-Hep B	145	127	95	
Anti-PRP	174	196	97	
Anti-Diphtheria Level 1	82	28	48	
Anti-Diphtheria Level 2	3	0	4	
Anti-Tetanus Level 1	213	210	122	
Anti-Tetanus Level 2	158	173	83	
Anti-Pertussis Toxoid	161	114	98	
anti-Filamentous hemagglutinin	149	75	81	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point title	Geometric Mean Titers (GMTs) of Antibodies After Primary Series Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point description:

Anti-Hepatitis B (Hep B) was measured by enhanced chemiluminescence detection, anti-Haemophilus influenzae type b (Hib) by Farr type radio-immunoassay, anti-Diphtheria by toxin neutralization assay, anti-Tetanus by indirect enzyme-linked immunosorbent assay (ELISA), anti-Poliovirus types 1, 2, and 3 by neutralization assay, and anti-Pertussis toxoid (PT) and anti-Filamentous hemagglutinin (FHA) by ELISA.

End point type	Secondary

End point timeframe:

Day 42 before Dose 1 and 1 month post-Dose 3

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	220	212	123	
Units: titre				
geometric mean (confidence interval 95%)				
Anti-Hep B Post-dose 3	330 (259 to 420)	148 (120 to 181)	1913 (1457 to 2513)	
Anti-PRP Post-dose 3	3.31 (2.69 to 4.08)	5.18 (4.47 to 6)	3.83 (2.92 to 5.02)	
Anti-Diphtheria Post-dose 3	0.074 (0.062 to 0.088)	0.04 (0.035 to 0.046)	0.074 (0.059 to 0.094)	
Anti-Tetanus Post-dose 3	1.51 (1.37 to 1.65)	1.88 (1.7 to 2.07)	1.33 (1.17 to 1.51)	
Anti-Polio Type 1 Post-dose 3	579 (478 to 702)	198 (153 to 256)	557 (410 to 756)	
Anti-Polio Type 2 Post-dose 3	620 (512 to 750)	446 (374 to 533)	371 (281 to 489)	
Anti-Polio Type 3 Post-dose 3	975 (812 to 1170)	228 (185 to 280)	811 (645 to 1020)	
Anti-PT Pre-Dose 1	7.77 (6.56 to 9.21)	7.66 (6.23 to 9.42)	6.62 (5.29 to 8.3)	
Anti-PT Post-dose 3	332 (304 to 362)	191 (147 to 249)	288 (256 to 323)	
Anti-Filamentous hemagglutinin Pre-dose 1	9.27 (8.02 to 10.7)	8.02 (6.82 to 9.42)	8.3 (6.8 to 10.1)	
Anti-Filamentous hemagglutinin Post-dose 3	207 (190 to 226)	37.4 (33.4 to 41.9)	188 (166 to 212)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Antibody Persistence Pre-Booster and Response Post-Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + OPV

End point title	Number of Participants With Antibody Persistence Pre-Booster and Response Post-Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + OPV

End point description:

Antibodies were measured by the following methods: anti-Hepatitis B (Hep B) by enhanced chemiluminescence detection, anti-Haemophilus influenzae type b (PRP) by Farr type radio immunoassay, anti-Diphtheria by toxin neutralization assay, anti-Tetanus by indirect enzyme-linked immunosorbent assay (ELISA), anti-poliovirus types 1, 2, and 3 by neutralization assay. Persistence and response were defined as a titer ≥ 10 mIU/mL for anti-Hep B, ≥ 0.15 µg/mL for anti-PRP, ≥ 0.01 IU/mL for anti-Diphtheria and anti-Tetanus, ≥ 8 (1/dil) for anti-Poliovirus, and ≥ 4 EU/mL for anti-PT and anti-FHA.

End point type	Secondary

End point timeframe:

Day 540 pre-booster and Day 570 post-booster

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	202	116	
Units: Participants				
Anti-Hep B pre-booster	157	183	107	
Anti-Hep B post-booster	194	0	113	
Anti-PRP pre-booster	166	185	88	
Anti-PRP post-booster	203	201	115	
Anti-Diphtheria pre-booster	184	173	98	
Anti-Diphtheria post-booster	195	200	111	
Anti-Tetanus pre-booster	189	195	116	
Anti-Tetanus post-booster	200	199	114	
Anti-Polio Type 1 pre-booster	185	178	108	
Anti-Polio Type 1 post-booster	189	186	108	
Anti-Polio Type 2 pre-booster	187	190	109	
Anti-Polio Type 2 post-booster	191	190	107	
Anti-Polio Type 3 pre-booster	186	185	110	
Anti-Polio Type 3 post-booster	188	185	108	
Anti-PT pre-booster	151	100	95	
Anti-PT post-booster	187	173	109	
Anti-PT post/pre-booster ratio	145	111	93	
Anti-FHA pre-booster	170	99	102	
Anti-FHA post-booster	184	190	105	
Anti-FHA post/pre-booster ratio	145	138	89	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Antibodies Pre- and Post-Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + OPV

End point title	Geometric Mean Titers (GMTs) of Antibodies Pre- and Post-Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + OPV

End point description:

Anti-Hepatitis B (Hep B) was measured by enhanced chemiluminescence detection, anti-Haemophilus influenzae type b (PRP) by Farr type radio immunoassay, anti-Diphtheria by toxin neutralization assay, anti-Tetanus (T) by indirect enzyme-linked immunosorbent assay (ELISA), anti-Poliovirus types 1, 2, and 3 by neutralization assay, and anti-Pertussis toxoid (PT) and anti-Filamentous hemagglutinin (FHA) by ELISA.

End point type	Secondary

End point timeframe:

Day 540 pre-booster and Day 570, post-booster

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	202	116	
Units: titre				
geometric mean (confidence interval 95%)				
Anti-Hep B pre-booster	51.3 (40 to 65.8)	103 (83.3 to 127)	228 (172 to 303)	
Anti-Hep B post-booster	4630 (3402 to 6302)	86.2 (69.2 to 107)	44893 (33652 to 59890)	
Anti-Hep B post/pre-booster ratio	88.7 (74 to 106)	0 (0 to 0)	191 (157 to 231)	
Anti-PRP pre-booster	0.757 (0.585 to 0.98)	1.19 (0.948 to 1.48)	0.631 (0.448 to 0.889)	
Anti-PRP post-booster	68.5 (55.7 to 84.2)	52.2 (43.9 to 62.2)	63.1 (47.6 to 83.8)	
Anti-PRP post/pre-booster ratio	89 (71.4 to 111)	43.6 (34.5 to 55)	97.4 (71.7 to 132)	
Anti-Diphtheria pre-booster	0.06 (0.05 to 0.073)	0.027 (0.023 to 0.032)	0.045 (0.033 to 0.059)	
Anti-Diphtheria post-booster	9.37 (8.05 to 10.9)	3.33 (2.92 to 3.8)	7 (5.61 to 8.72)	
Anti-Diphtheria post/pre-booster ratio	158 (137 to 182)	123 (108 to 140)	153 (125 to 189)	

Anti-Tetanus pre-booster	0.219 (0.189 to 0.254)	0.311 (0.276 to 0.352)	0.173 (0.143 to 0.208)	
Anti-Tetanus post-booster	10 (8.65 to 11.7)	8.23 (7.49 to 9.04)	8.13 (6.68 to 9.89)	
Anti-Tetanus post/pre-booster ratio	45.5 (40 to 51.8)	26.5 (23.5 to 29.9)	47.4 (39.8 to 56.3)	
Anti-Polio Type 1 pre-booster	127 (104 to 155)	151 (118 to 192)	142 (107 to 190)	
Anti-Polio Type 1 post-booster	7298 (6202 to 8588)	329 (260 to 417)	5346 (4309 to 6633)	
Anti-Polio Type 1 post/pre-booster ratio	59 (47 to 74)	2.27 (1.8 to 2.85)	38.4 (27.4 to 53.7)	
Anti-Polio Type 2 pre-booster	210 (170 to 260)	246 (204 to 296)	191 (144 to 255)	
Anti-Polio Type 2 post-booster	6637 (5745 to 7668)	863 (665 to 1118)	4190 (3460 to 5074)	
Anti-Polio Type 2 post/pre-booster ratio	32.4 (24.9 to 42.3)	3.82 (2.9 to 5.04)	23.2 (16.2 to 33.3)	
Anti-Polio Type 3 pre-booster	161 (130 to 199)	114 (96.4 to 135)	127 (97.9 to 165)	
Anti-Polio Type 3 post-booster	6411 (5525 to 7493)	315 (245 to 404)	5144 (4156 to 6367)	
Anti-Polio Type 3 post/pre-booster ratio	40.5 (31 to 53)	2.92 (2.26 to 3.77)	41.2 (29.3 to 57.9)	
Anti-Pertussis toxoid pre-booster	11.6 (9.88 to 13.6)	10.4 (8.03 to 13.6)	12 (9.62 to 14.9)	
Anti-Pertussis toxoid post-booster	288 (260 to 318)	110 (88.7 to 137)	235 (206 to 268)	
Anti-Pertussis toxoid post/pre-booster ratio	26.1 (21.8 to 31.1)	10.6 (8.56 to 13.1)	20.5 (16.5 to 25.4)	
Anti-FHA pre-booster	30.5 (25.4 to 36.7)	5.43 (4.52 to 6.53)	25.1 (19.7 to 31.9)	
Anti-FHA post-booster	570 (514 to 630)	211 (193 to 231)	472 (419 to 533)	
Anti-FHA post/pre-booster ratio	18.9 (15.8 to 22.6)	40.8 (34.5 to 48.1)	20.3 (16.5 to 24.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Solicited Injection Site and Systemic Reactions After Primary Vaccination Series With With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point title	Number of Participants With Solicited Injection Site and Systemic Reactions After Primary Vaccination Series With With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point description:

Solicited Injection Site Reactions: Pain, Erythema, Swelling. Solicited System Reactions: Fever (Temperature), Vomiting, Crying, Somnolence, Anorexia, Irritability. Grade 3 was defined as: Pain - crying when injected limb is moved or the movement reduced; Erythema and Swelling - ≥ 5 cm; Fever - temperature ≥ 39.0ºC; Vomiting - ≥ 6 episodes/24 hours or requiring parenteral hydration; Crying abnormal - > 3 hours; Somnolence - sleeping most of the time or difficulty to wake up; Anorexia - refusing ≥ 3 feeds or refusing most feeds/meals; and Irritability - inconsolable.

End point type	Secondary

End point timeframe:
Day 0 up to Day 7 post each dose

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	242	137	
Units: Participants				
Pain post-dose 1	166	177	95	
Pain post-dose 2	171	171	97	
Pain post-dose 3	143	162	83	
Grade 3 Pain post-any dose	17	24	7	
Erythema post-dose 1	112	133	69	
Erythema post-dose 2	116	114	59	
Erythema post-dose 3	103	106	56	
Grade 3 Erythema post-any dose	9	15	2	
Swelling post-dose 1	87	102	48	
Swelling post-dose 2	88	109	43	
Swelling post-dose 3	74	89	39	
Grade 3 Swelling post-any dose	9	10	4	
Pyrexia post-dose 1	50	38	27	
Pyrexia post-dose 2	43	35	18	
Pyrexia post-dose 3	48	34	21	
Grade 3 Pyrexia post-any dose	4	1	0	
Vomiting post-dose 1	59	59	30	
Vomiting post-dose 2	52	56	35	
Vomiting post-dose 3	56	49	31	
Grade 3 Vomiting post-any dose	14	7	6	
Crying post-dose 1	138	154	91	
Crying post-dose 2	131	135	74	
Crying post-dose 3	106	116	66	
Grade 3 Crying post-any dose	15	20	9	
Somnolence post-dose 1	100	103	57	
Somnolence post-dose 2	79	90	47	
Somnolence post-dose 3	72	69	43	
Grade 3 Somnolence post-any dose	9	9	8	
Anorexia post-dose 1	62	87	42	
Anorexia post-dose 2	66	68	39	
Anorexia post-dose 3	64	76	39	
Grade 3 Anorexia post-any dose	9	13	5	
Irritability post-dose 1	128	137	77	
Irritability post-dose 2	114	118	66	
Irritability post-dose 3	94	99	53	
Grade 3 Irritability post-any dose	18	16	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Solicited Injection Site (Study Vaccine Site) and Systemic Reactions After Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point title	Number of Participants With Solicited Injection Site (Study Vaccine Site) and Systemic Reactions After Booster Vaccination With DTaP-IPV-Hep B-PRT~T (With or Without Engerix B™ at Birth) or CombAct Hib™ + Engerix B™ + Oral Polio Vaccine (OPV)

End point description:

Solicited Injection Site Reactions: Pain, Erythema, Swelling, and Extensive swelling of vaccinated limb. Solicited System Reactions: Fever (Temperature), Vomiting, Crying, Somnolence, Anorexia, and Irritability. Grade 3 was defined as: Pain, crying when injected limb is moved or the movement reduced; Erythema and Swelling, ≥ 5 cm; Fever, temperature ≥ 39.0ºC; Vomiting, ≥ 6 episodes/24 hours or requiring parenteral hydration; Crying, > 3 hours; Somnolence, sleeping most of the time or difficulty to wake up; Anorexia, refusing ≥ 3 feeds or refusing most feeds/meals; and Irritability, inconsolable.

End point type	Secondary

End point timeframe:

Day 0 up to 7 post-booster vaccination

End point values	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	218	219	130	
Units: Participants				
Injection site Pain	138	149	84	
Grade 3 injection site Pain	5	4	1	
Injection site Erythema	102	104	54	
Grade 3 injection site Erythema	3	2	2	
Injection site Swelling	75	98	48	
Grade 3 injection site Swelling	2	11	5	
Extensive Swelling of vaccinated limb	0	0	0	
Grade 3 extensive Swelling of vaccinated limb	0	0	0	
Pyrexia	61	50	37	
Grade 3 Pyrexia	1	2	2	
Vomiting	22	28	14	
Grade 3 Vomiting	0	2	0	
Crying	106	115	58	
Grade 3 Crying	3	0	2	
Somnolence	85	80	43	
Grade 3 Somnolence	3	1	1	
Anorexia	88	99	55	
Grade 3 Anorexia	8	4	4	
Irritability	98	103	52	
Grade 3 Irritability	2	1	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 the time of each vaccination up to 28 days after each primary and the booster vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

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

Reporting group description:

Participants received a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular(aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Reporting group title	CombAct-Hib™ + Engerix B™ + OPV Group

Reporting group description:

Participants received a primary series of 3 doses of commercial CombAct-Hib™ vaccine, Engerix B™ vaccine, and oral poliovirus vaccine, with 1 dose of each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Reporting group title	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group

Reporting group description:

Participants received Engerix B™ vaccine at birth, followed by a primary series of 3 doses of diphtheria (D), tetanus (T), pertussis (2 component acellular (aP), recombinant hepatitis B Hansenula (Hep B) and inactivated poliomyelitis vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) vaccine, polyribosyl ribitol phosphate (PRP) conjugated to tetanus protein (DTaP-IPV-Hep B-PRP-T), with 1 dose each at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age. Participants also received Trimovax™ and Varilrix™ vaccines at 15 to 18 months of age.

Serious adverse events	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 243 (2.88%)	6 / 242 (2.48%)	5 / 137 (3.65%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Heart disease congenital			
subjects affected / exposed	1 / 243 (0.41%)	1 / 242 (0.41%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular septal defect			

subjects affected / exposed	0 / 243 (0.00%)	0 / 242 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pulmonary Valve Stenosis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (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
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (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
Renal Impairment			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (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
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 243 (0.00%)	1 / 242 (0.41%)	0 / 137 (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
Bronchiolitis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (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	2 / 243 (0.82%)	2 / 242 (0.83%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysentery			
subjects affected / exposed	0 / 243 (0.00%)	0 / 242 (0.00%)	1 / 137 (0.73%)
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 / 243 (0.82%)	1 / 242 (0.41%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 242 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 242 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 242 (0.41%)	0 / 137 (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
Respiratory Tract Infection			
subjects affected / exposed	0 / 243 (0.00%)	1 / 242 (0.41%)	0 / 137 (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
Urinary tract infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (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
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 243 (0.41%)	0 / 242 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

Non-serious adverse events	DTaP-IPV-Hep B-PRP~T Group	CombAct-Hib™ + Engerix B™ + OPV Group	DTaP-IPV-Hep B-PRP~T (Engerix B™ at Birth) Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 243 (83.13%)	210 / 242 (86.78%)	119 / 137 (86.86%)
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed[1]	143 / 236 (60.59%)	143 / 238 (60.08%)	78 / 135 (57.78%)
occurrences (all)	143	143	78
General disorders and administration site conditions			
Injection-site bruising			
alternative assessment type: Systematic			
subjects affected / exposed[2]	6 / 237 (2.53%)	9 / 238 (3.78%)	9 / 136 (6.62%)
occurrences (all)	6	9	9
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	160 / 236 (67.80%)	173 / 238 (72.69%)	91 / 135 (67.41%)
occurrences (all)	160	173	91
Injection site pain			
subjects affected / exposed[4]	202 / 237 (85.23%)	210 / 238 (88.24%)	119 / 136 (87.50%)
occurrences (all)	202	210	119
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed[5]	130 / 236 (55.08%)	150 / 238 (63.03%)	65 / 136 (47.79%)
occurrences (all)	130	150	65
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[6]	157 / 236 (66.53%)	165 / 238 (69.33%)	94 / 135 (69.63%)
occurrences (all)	157	165	94
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed[7]	105 / 236 (44.49%)	79 / 238 (33.19%)	45 / 136 (33.09%)
occurrences (all)	105	79	45

Gastrointestinal disorders Vomiting alternative assessment type: Systematic subjects affected / exposed[8] occurrences (all)	106 / 243 (43.62%) 106	100 / 242 (41.32%) 100	54 / 135 (40.00%) 54
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed[9] occurrences (all)	13 / 237 (5.49%) 13	4 / 238 (1.68%) 4	4 / 136 (2.94%) 4
Psychiatric disorders Crying abnormal alternative assessment type: Systematic subjects affected / exposed[10] occurrences (all)	180 / 236 (76.27%) 180	186 / 238 (78.15%) 186	112 / 135 (82.96%) 112
Infections and infestations Upper respiratory tract infection subjects affected / exposed[11] occurrences (all)	11 / 237 (4.64%) 11	13 / 238 (5.46%) 13	4 / 136 (2.94%) 4
Metabolism and nutrition disorders Anorexia alternative assessment type: Systematic subjects affected / exposed[12] occurrences (all)	110 / 236 (46.61%) 110	133 / 238 (55.88%) 133	67 / 136 (49.26%) 67

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.
[10] - 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.
[11] - 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.
[12] - 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
21 June 2007	The protocol amendment includes an extension of the age group for MMR and varicella vaccinations and timing of the booster dose to 15 to 18 months; revision of the Informed consent form, addition of inclusion criteria for booster phase, addition solicited adverse event and clarification immunogenicity and points and analyses.
29 November 2007	The amendment include an increase in the sample size, revision of timing of blood sample storage and clotting in line with new sample preparation procedures, and removal of 'height' from Visit 01 demographic characteristics.
20 December 2007	The amendment includes the addition of a secondary endpoint, revision of assay procedure, and inclusion of five protocol violation criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21289531