Clinical trial results:
Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Given as a Primary Series and a Second Year of Life Booster in HIV-Exposed Infected and in HIV-Exposed Uninfected Infants in Republic of South Africa

Summary

EudraCT number	2018-004708-21
Trial protocol	Outside EU/EEA
Global end of trial date	13 March 2019

Results information

Result version number	v2 (current)
This version publication date	22 January 2020
First version publication date	28 October 2019
Version creation reason	• Correction of full data set Correction of type of immunogenicity assay used to analyze antibody levels.

Trial information

Trial identification

Sponsor protocol code	A3L44

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02817451
WHO universal trial number (UTN)	U1111-1161-2610

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur
Sponsor organisation address	14 Espace Henry Vallée, Lyon, France, 69007
Public contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	13 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the immunogenicity of the study vaccine 1 month after the 3-dose primary series in Human Immunodeficiency Virus (HIV)-exposed infected and in HIV-exposed uninfected infants.
- To describe the persistence of all antibodies before receipt of the booster vaccination in HIV-exposed infected and in HIV-exposed uninfected infants.
- To evaluate the immunogenicity of the study vaccine 1 month after the booster dose in HIV-exposed infected and in HIV-exposed uninfected infants.

Protection of trial subjects:

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 was also available on site in case of any immediate allergic reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2016
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	South Africa: 64
Worldwide total number of subjects	64
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)	64
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 was conducted at 1 centre in South Africa from 14 July 2016 to 13 March 2019.

Pre-assignment

Screening details:

A total of 64 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and vaccinated in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	HIV-Exposed Infected Subjects

Arm description:

Subjects identified as polymerase chain reaction (PCR) positive for HIV received 3 doses of primary vaccination with Diphtheria (D), tetanus (T), pertussis (2-component acellular) (aP), recombinant Hepatitis B Hansenula polymorpha (Hep B) and inactivated poliovirus vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) (DTaP-IPV-HB-PRP-T) combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Arm type	Experimental
Investigational medicinal product name	DTaP-IPV-HB-PRP-T combined vaccine
Investigational medicinal product code	
Other name	Hexaxim®
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL (millilitre), intramuscular injection into the anterolateral area of the right thigh.

Arm title	HIV-Exposed Uninfected Subjects

Arm description:

Subjects identified as HIV-exposed during pregnancy but uninfected received 3 doses of primary vaccination with DTaP-IPV-HB-PRP-T combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Arm type	Experimental
Investigational medicinal product name	DTaP-IPV-HB-PRP-T combined vaccine
Investigational medicinal product code	
Other name	Hexaxim®
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the anterolateral area of the right thigh.

Number of subjects in period 1	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects
Started	14	50
Completed	12	40
Not completed	2	10
Consent withdrawn by subject	1	6
Receipt of a vaccine unacceptable for use	-	1
Lost to follow-up	1	-
Non-compliance with the protocol	-	3

Baseline characteristics

Reporting groups	
Reporting group title	HIV-Exposed Infected Subjects
Reporting group description:	
Subjects identified as polymerase chain reaction (PCR) positive for HIV received 3 doses of primary vaccination with Diphtheria (D), tetanus (T), pertussis (2-component acellular) (aP), recombinant Hepatitis B Hansenula polymorpha (Hep B) and inactivated poliovirus vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) (DTaP-IPV-HB-PRP-T) combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).	
Reporting group title	HIV-Exposed Uninfected Subjects
Reporting group description:	
Subjects identified as HIV-exposed during pregnancy but uninfected received 3 doses of primary vaccination with DTaP-IPV-HB-PRP-T combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).	

Reporting group values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects	Total
Number of subjects	14	50	64
Age categorical			
Units: subjects			
Age continuous			
Units: weeks			
arithmetic mean	6.07	5.76	
standard deviation	± 0.267	± 0.431	-
Gender categorical			
Units: Subjects			
Female	9	29	38
Male	5	21	26

End points

End points reporting groups

Reporting group title	HIV-Exposed Infected Subjects

Reporting group description:

Subjects identified as polymerase chain reaction (PCR) positive for HIV received 3 doses of primary vaccination with Diphtheria (D), tetanus (T), pertussis (2-component acellular) (aP), recombinant Hepatitis B Hansenula polymorpha (Hep B) and inactivated poliovirus vaccine (IPV) adsorbed, and Haemophilus influenzae type b (Hib) (DTaP-IPV-HB-PRP-T) combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Reporting group title	HIV-Exposed Uninfected Subjects

Reporting group description:

Subjects identified as HIV-exposed during pregnancy but uninfected received 3 doses of primary vaccination with DTaP-IPV-HB-PRP-T combined vaccine at 6, 10, and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Primary: Number of Subjects with Anti-Pertussis Toxoid (PT) and Anti-Filamentous Hemagglutinin (FHA) Antibody (Ab) Concentrations less than equal to (>=) Lower Limit of Quantification (LLOQ) and >=4*LLOQ at Baseline

End point title	Number of Subjects with Anti-Pertussis Toxoid (PT) and Anti-Filamentous Hemagglutinin (FHA) Antibody (Ab) Concentrations less than equal to (>=) Lower Limit of Quantification (LLOQ) and >=4*LLOQ at Baseline[1]

End point description:

Anti-PT and anti-FHA Ab concentrations were determined in terms of endotoxin units per millilitre (EU/mL). Analysis was performed on per-protocol analysis set which was a subset of the full analysis set (FAS) that included all subjects who had received at least one dose of study vaccine.

End point type	Primary

End point timeframe:

Day 0 (baseline)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	42		
Units: subjects				
number (not applicable)				
Anti-PT: >=LLOQ	2	23		
Anti-PT: >=4*LLOQ	1	6		
Anti-FHA: >=LLOQ	6	38		
Anti-FHA: >=4*LLOQ	2	23		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Means of Anti-Pertussis Toxoid and Anti-Filamentous Hemagglutinin Antibody Concentrations at Baseline

End point title	Geometric Means of Anti-Pertussis Toxoid and Anti-Filamentous Hemagglutinin Antibody Concentrations at Baseline[2]

End point description:

Anti-PT and anti-FHA Ab levels were measured by electrochemiluminescence immunoassay (ECL) and anti-PT and anti-FHA Ab concentrations were determined in terms of EU/mL. Analysis was performed on per protocol analysis set.

End point type	Primary

End point timeframe:

Day 0 (baseline)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	42		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Anti-PT	1.55 (0.774 to 3.10)	2.83 (1.95 to 4.11)		
Anti-FHA	3.82 (1.46 to 9.98)	9.62 (6.38 to 14.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Means of Antibody Titers/Concentrations After Primary Series Vaccination

End point title	Geometric Means of Antibody Titers/Concentrations After Primary Series Vaccination[3]

End point description:

Anti-diphtheria, anti-tetanus, anti-PT and anti-FHA Ab levels were measured by ECL. Anti-poliovirus types 1, 2, and 3 Ab levels were measured by neutralisation assay. Anti-Hep B Ab levels were measured by VITROS ECi/ECiQ Immunodiagnostic system using chemiluminescence detection technology. Anti-polyribosylribitol phosphate (PRP) Ab levels were measured using a Farr-type radioimmunoassay (RIA). Ab concentrations were determined as: anti-diphtheria >=0.01 international units (IU)/mL, >=0.1 IU/mL, 1.0 IU/mL, anti-tetanus >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-PT and anti-FHA EU/mL, anti-PRP >=0.15 microgram (mcg)/mL, >=1.0 mcg/mL, anti-Poliovirus types 1, 2, and 3 Ab titers >=8 (1/dilution [dil]), Anti-Hep B >=10 milli (m) IU/mL, and >=100 mIU/mL. Analysis was performed on per-protocol analysis set. Here, 'n' signifies subjects with available data for each specified category.

End point type	Primary

End point timeframe:

Day 90 (1 month after third dose)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	42		
Units: titers				
geometric mean (confidence interval 95%)				
Anti-Diphtheria; (IU/mL) (n= 8,42)	4.72 (3.42 to 6.53)	2.78 (2.40 to 3.22)		
Anti-Tetanus; (IU/mL) (n= 8,42)	4.81 (2.89 to 8.01)	1.37 (1.04 to 1.80)		
Anti-PT; (EU/mL) (n= 8,42)	287 (181 to 457)	151 (128 to 178)		
Anti-FHA; (EU/mL) (n= 8,42)	618 (303 to 1261)	315 (261 to 379)		
Anti-Polio 1; (1/dil) (n= 8,41)	3298 (1476 to 7369)	1523 (1139 to 2038)		
Anti-Polio 2; (1/dil) (n= 8,41)	3756 (1569 to 8989)	1365 (1009 to 1847)		
Anti-Polio 3; (1/dil) (n= 8,40)	4096 (1918 to 8747)	2253 (1647 to 3082)		
Anti-Hep B; (mIU/mL) (n= 8,42)	615 (212 to 1783)	244 (174 to 342)		
Anti-PRP; (mcg/mL) (n= 8,41)	3.72 (1.15 to 12.0)	2.48 (1.61 to 3.81)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Seroprotection After Primary Series Vaccination

End point title	Number of Subjects With Seroprotection After Primary Series Vaccination[4]

End point description:

Seroprotection was determined as: anti-diptheria Ab concentrations >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-tetanus Ab concentrations >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-PT and anti-FHA Ab concentrations EU/mL (>=LLOQ and >=4*LLOQ), anti-PRP Ab concentrations >=0.15 mcg/mL and >=1.0 mcg/mL, anti-poliovirus 1, 2, and 3 Ab titers >=8 (1/dil), anti-Hep B Ab concentrations >=10 mIU/mL and >=100 mIU/mL. Analysis was performed on per-protocol analysis set. Here, 'n' signifies subjects with available data for each specified category.

End point type	Primary

End point timeframe:

Day 90 (1 month after third dose)

Notes:

[4] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	42		
Units: subjects				
number (not applicable)				
Anti-Diphtheria; (>=0.01 IU/mL) (n=8,42)	8	42		
Anti-Diphtheria; (>=0.1 IU/mL) (n=8,42)	8	42		
Anti-Diphtheria; (>=1.0 IU/mL) (n=8,42)	8	41		
Anti-Tetanus; (>=0.01 IU/mL) (n=8,42)	8	42		
Anti-Tetanus; (>=0.1 IU/mL) (n=8,42)	8	42		
Anti-Tetanus; (>=1.0 IU/mL) (n=8,42)	8	29		
Anti-PT; (EU/mL, >=LLOQ) (n= 8,42)	8	42		
Anti-PT; (EU/mL, >=4*LLOQ) (n= 8,42)	8	42		
Anti-FHA; (EU/mL, >=LLOQ) (n= 8,42)	8	42		
Anti-FHA; (EU/mL, >=4*LLOQ) (n= 8,42)	8	42		
Anti-Polio 1; (>=8 [1/dil]) (n= 8,41)	8	41		
Anti-Polio 2; (>=8 [1/dil]) (n= 8,41)	8	41		
Anti-Polio 3; (>=8 [1/dil]) (n= 8,40)	8	40		
Anti-Hep B; (>=10 mIU/mL) (n= 8,42)	8	42		
Anti-Hep B; (>=100 mIU/mL) (n= 8,42)	7	35		
Anti-PRP; (>=0.15 mcg/mL) (n= 8,41)	8	40		
Anti-PRP; (>=1.0 mcg/mL) (n= 8,41)	7	30		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Vaccine Response or Seroconversion After Primary Series Vaccination

End point title	Number of Subjects with Vaccine Response or Seroconversion After Primary Series Vaccination[5]

End point description:

Vaccine response was defined for anti-PT and anti-FHA as Ab post-Dose 3 concentrations >=4*LLOQ, if pre-Dose (Day 0) Ab concentration is <4*LLOQ or 1 month after third dose (Day 90) concentrations >= pre-Dose Ab concentrations if pre-Dose (Day 0) concentrations >=4*LLOQ. Seroconversion for anti-PT and anti-FHA was defined as >=4-fold Ab concentrations increase from pre-Dose (Day 0) to 1 month after third dose (Day 90). Analysis was performed on per-protocol analysis set.

End point type	Primary

End point timeframe:

Day 0 (baseline), Day 90 (1 month after third dose)

Notes:

[5] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	42		
Units: subjects				
number (not applicable)				
Anti-PT; Day 90/ Day 0 (Vaccine Response)	8	42		
Anti-PT; Day 90/Day 0 (Seroconversion)	8	38		
Anti-FHA; Day 90/Day 0 (Vaccine Response)	8	42		
Anti-FHA; Day 90/Day 0 (Seroconversion)	8	37		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Means of Antibody Titers/Concentrations After Booster Vaccination

End point title	Geometric Means of Antibody Titers/Concentrations After Booster Vaccination[6]

End point description:

Anti-diphtheria, anti-tetanus, anti-PT, and anti-FHA Ab levels were measured by ECL. Anti-poliovirus types 1, 2, and 3 Ab levels were measured by neutralisation assay. Anti-Hep B Ab levels were measured by VITROS ECi/ECiQ Immunodiagnostic system using chemiluminescence detection technology. Anti-PRP Ab levels were measured using a Farr-type RIA. Ab concentrations: anti-diphtheria >=0.01 IU/mL, >=0.1 IU/mL, >=1.0 IU/mL, anti-tetanus >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-PT and anti-FHA EU/mL, anti-PRP >=0.15 mcg/mL, >=1.0 mcg/mL, anti-poliovirus 1, 2, and 3 Ab titers >=8 (1/dil), anti-Hep B >=10 mIU/mL, and >=100 mIU/mL. Analysis was performed on booster per-protocol analysis set which included subjects who received the booster dose of the vaccine, and with at least one antibody titer available pre-booster dose or one month post-booster.

End point type	Primary

End point timeframe:

Day 420 (1 month after booster vaccination)

Notes:

[6] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	29		
Units: titers				
geometric mean (confidence interval 95%)				
Anti-Diphtheria; (IU/mL)	9.72 (4.59 to 20.6)	6.20 (4.86 to 7.92)		
Anti-Tetanus; (IU/mL)	13.0 (7.11 to 23.9)	5.90 (4.30 to 8.10)		
Anti-PT; (EU/mL)	310 (165 to 582)	194 (149 to 252)		

Anti-FHA; (EU/mL)	369 (187 to 726)	229 (162 to 324)		
Anti-Polio 1; (1/dil)	3710 (944 to 14583)	3999 (2848 to 5617)		
Anti-Polio 2; (1/dil)	7420 (2153 to 25574)	7445 (5361 to 10340)		
Anti-Polio 3; (1/dil)	5247 (1543 to 17834)	6450 (4207 to 9889)		
Anti-Hep B; (mIU/mL)	2371 (394 to 14286)	2014 (945 to 4292)		
Anti-PRP; (mcg/mL)	40.1 (8.71 to 184)	39.8 (20.8 to 76.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Seroprotection After Booster Vaccination

End point title	Number of Subjects With Seroprotection After Booster Vaccination[7]

End point description:

Seroprotection: anti-diphtheria Ab concentrations >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-tetanus Ab concentrations >=0.01 IU/mL, >=0.1 IU/mL, and >=1.0 IU/mL, anti-PT and anti-FHA Ab concentrations EU/mL (>=LLOQ and >=4*LLOQ), anti-PRP Ab concentrations >=0.15 mcg/mL and >=1.0 mcg/mL, anti-poliovirus 1, 2, and 3 Ab titers >=8 (1/dil), and anti-Hep B Ab concentrations >=10 mIU/mL and >=100 mIU/mL. Analysis was performed on booster per-protocol analysis Set.

End point type	Primary

End point timeframe:

Day 420 (1 month after booster vaccination)

Notes:

[7] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	29		
Units: subjects				
number (not applicable)				
Anti-Diphtheria; (>=0.01 IU/mL)	7	29		
Anti-Diphtheria; (>=0.1 IU/mL)	7	29		
Anti-Diphtheria; (>=1.0 IU/mL)	7	29		
Anti-Tetanus; (>=0.01 IU/mL)	7	29		
Anti-Tetanus; (>=0.1 IU/mL)	7	29		
Anti-Tetanus; (>=1.0 IU/mL)	7	28		
Anti-PT; (EU/mL, >=LLOQ)	7	29		
Anti-PT; (EU/mL, >=4*LLOQ)	7	29		
Anti-FHA; (EU/mL, >=LLOQ)	7	29		
Anti-FHA; (EU/mL, >=4*LLOQ)	7	29		
Anti-Polio 1; (>=8 [1/dil])	7	29		
Anti-Polio 2; (>=8 [1/dil])	7	29		
Anti-Polio 3; (>=8 [1/dil])	7	29		

Anti-Hep B; (>=10 mIU/mL)	7	29		
Anti-Hep B; (>=100 mIU/mL)	7	26		
Anti-PRP; (>=0.15 mcg/mL)	7	29		
Anti-PRP; (>=1.0 mcg/mL)	7	28		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Vaccine Response or Seroconversion After Booster Vaccination

End point title	Number of Subjects With Vaccine Response or Seroconversion After Booster Vaccination[8]

End point description:

Vaccine response was defined for anti-PT and anti-FHA as >=4 fold Ab concentrations increase from pre-dose (Day 0) to 1 month after booster dose (Day 420), if pre-Dose (Day 0) Ab concentrations <4*LLOQ; or >=2 fold Ab concentrations increase from pre- dose (Day 0) to 1 month after booster dose (Day 420), if pre-dose (Day 0) Ab concentrations >=4*LLOQ. Seroconversion was defined for anti-PT and anti-FHA as >=4 fold Ab concentrations increase from pre-dose (Day 0) to 1 month after booster dose. Analysis was performed on booster per-protocol analysis set.

End point type	Primary

End point timeframe:

Day 0 (baseline), Day 420 (1 month after booster vaccination)

Notes:

[8] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	29		
Units: subjects				
number (not applicable)				
Anti-PT; Day 420/Day 0 (Vaccine Response)	7	29		
Anti-PT; Day 420/Day 0 (Seroconversion)	7	28		
Anti-FHA; Day 420/Day 0 (Vaccine Response)	7	28		
Anti-FHA; Day 420/Day 0 (Seroconversion)	7	26		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Booster Response After Booster Vaccination

End point title	Number of Subjects With Booster Response After Booster Vaccination[9]

End point description:

Booster response was defined for anti-PT and anti-FHA as >=4 fold Ab concentrations increase from pre-booster (Day 390) to 1 month after booster dose (Day 420), if pre-booster Ab concentrations <4*LLOQ; or >=2 fold Ab concentrations increase from pre-booster (Day 390) to 1 month after booster dose (Day 390) if pre-Booster Ab concentrations >=4*LLOQ. Analysis was performed on booster per-protocol analysis set.

End point type	Primary

End point timeframe:

Day 390 (pre-booster), Day 420 (1 month after booster dose)

Notes:

[9] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	29		
Units: subjects				
number (not applicable)				
Anti-PT; Day 420/Day 390 (Booster Response)	7	29		
Anti-FHA; Day 420/Day 390 (Booster Response)	6	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Immediate Unsolicited Adverse Events (AE) After Primary Series Vaccination

End point title	Number of Subjects With Immediate Unsolicited Adverse Events (AE) After Primary Series Vaccination

End point description:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the electronic case report form (eCRF) in terms of diagnosis and/or onset post-vaccination. Analysis was performed on safety analysis set which included subjects who had received at least one dose of study vaccine.

End point type	Secondary

End point timeframe:

Within 30 minutes after vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	49		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Solicited Injections Site or Systemic Reactions After Primary Series Vaccination

End point title	Number of Subjects With Solicited Injections Site or Systemic Reactions After Primary Series Vaccination

End point description:

A solicited reaction is an adverse reaction observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the eCRF and considered as related to vaccination. Solicited injection site reactions: injection site tenderness, erythema, and swelling. Solicited systemic reactions: fever, vomiting, crying abnormal, drowsiness, appetite lost, and irritability. Analysis was performed on safety analysis set. Here, number of subjects analysed signifies subjects evaluable for this end-point.

End point type	Secondary

End point timeframe:

Within 7 days after vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	48		
Units: subjects				
number (not applicable)				
Injection site tenderness	4	27		
Injection site erythema	0	2		
Injection site swelling	0	5		
Fever	2	3		
Vomiting	3	13		
Crying abnormal	7	30		
Drowsiness	4	19		
Appetite lost	6	10		
Irritability	5	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Unsolicited Adverse Events After Primary Series Vaccination

End point title	Number of Subjects With Unsolicited Adverse Events After

	Primary Series Vaccination

End point description:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset post-vaccination. An unsolicited non-serious AE is an unsolicited AE excluding serious adverse events (SAEs). Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site. Analysis was performed on safety analysis set.

End point type	Secondary

End point timeframe:

Within 30 days after vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	49		
Units: subjects				
number (not applicable)				
Unsolicited AE	7	29		
Unsolicited non-serious AE	6	29		
Unsolicited non-serious systemic AE	6	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events During the Study

End point title	Number of Subjects With Serious Adverse Events During the Study

End point description:

An SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is an important medical event. Analysis was performed on safety analysis set.

End point type	Secondary

End point timeframe:

Day 0 to Day 420

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	49		
Units: subjects				
number (not applicable)	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Immediate Unsolicited Adverse Events After Booster Vaccination

End point title	Number of Subjects With Immediate Unsolicited Adverse Events After Booster Vaccination

End point description:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset post-vaccination. Analysis was performed on booster safety analysis set which included the subjects who had received the booster dose of study vaccine.

End point type	Secondary

End point timeframe:

Within 30 minutes after booster vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	40		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Solicited Injection Site or Systemic Reactions After Booster Vaccination

End point title	Number of Subjects With Solicited Injection Site or Systemic Reactions After Booster Vaccination

End point description:

A solicited reaction is an adverse reaction observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the eCRF and considered as related to vaccination. Solicited injection site reactions: tenderness, erythema, swelling, and extensive limb swelling. Solicited systemic reactions: fever, vomiting, crying abnormal, drowsiness, appetite lost, and irritability. Analysis was performed on booster safety analysis set.

End point type	Secondary

End point timeframe:

Within 7 days after booster vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	40		
Units: subjects				
number (not applicable)				
Injection site tenderness	4	14		
Injection site erythema	0	1		
Injection site swelling	1	0		
Extensive swelling of vaccinated limb	0	0		
Fever	3	1		
Vomiting	2	1		
Crying abnormal	5	12		
Drowsiness	0	7		
Appetite lost	4	11		
Irritability	3	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Unsolicited Adverse Events After Booster Vaccination

End point title	Number of Subjects With Unsolicited Adverse Events After Booster Vaccination

End point description:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset post-vaccination. An unsolicited non-serious AE is an unsolicited AE excluding SAEs. Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site. Analysis was performed on booster safety analysis set.

End point type	Secondary

End point timeframe:

Within 30 days after booster vaccination

End point values	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	40		
Units: subjects				
number (not applicable)				
Unsolicited AE	0	10		
Unsolicited non-serious AE	0	10		

Unsolicited non-serious systemic AE	0	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited reactions (SR): collected up to Day 7 after each vaccination, non-serious unsolicited adverse events were collected up to Day 30 after each vaccination. SAEs: throughout the trial (up to 30 days after primary series and booster vaccination).

Adverse event reporting additional description:

SR: AE prelisted in eCRF, considered related to vaccination. SR was therefore, an adverse drug reaction observed, reported under conditions (symptom and onset) prelisted in eCRF. Unsolicited AE: an observed AE that does not fulfill conditions prelisted in eCRF in terms of diagnosis and/or onset post-vaccination. Analysis done on safety analysis set

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	HIV-Exposed Infected Subjects

Reporting group description:

Subjects identified as PCR positive for HIV received 3 doses of primary vaccination with DTaP-IPV-HB-PRP-T combined vaccine at 6, 10 and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Reporting group title	HIV-Exposed Uninfected Subjects

Reporting group description:

Subjects identified as HIV-exposed during pregnancy but uninfected received 3 doses of primary vaccination with DTaP-IPV-HB-PRP-T combined vaccine at 6, 10 and 14 weeks of age (Infant Series), followed by a booster dose approximately 12 months after the completion of the Infant Series (at 15 to 18 months of age).

Serious adverse events	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	4 / 49 (8.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 14 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Abscess			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup Infectious			
subjects affected / exposed	2 / 14 (14.29%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 14 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 14 (7.14%)	0 / 49 (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	HIV-Exposed Infected Subjects	HIV-Exposed Uninfected Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	46 / 49 (93.88%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	4 / 14 (28.57%)	22 / 49 (44.90%)	
occurrences (all)	43	61	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	8 / 14 (57.14%)	34 / 49 (69.39%)	
occurrences (all)	67	139	
Injection Site Pain			
subjects affected / exposed	5 / 14 (35.71%)	30 / 49 (61.22%)	
occurrences (all)	54	127	
Injection Site Swelling			
subjects affected / exposed	1 / 14 (7.14%)	5 / 49 (10.20%)	
occurrences (all)	8	21	
Pyrexia			
subjects affected / exposed	5 / 14 (35.71%)	4 / 49 (8.16%)	
occurrences (all)	10	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Vomiting			

subjects affected / exposed	4 / 14 (28.57%)	13 / 49 (26.53%)	
occurrences (all)	20	37	
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	1 / 14 (7.14%)	10 / 49 (20.41%)	
occurrences (all)	1	11	
Cough			
subjects affected / exposed	1 / 14 (7.14%)	6 / 49 (12.24%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Dermatitis Diaper			
subjects affected / exposed	0 / 14 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	1 / 14 (7.14%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Psychiatric disorders			
Irritability			
subjects affected / exposed	6 / 14 (42.86%)	26 / 49 (53.06%)	
occurrences (all)	54	96	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Fungal Skin Infection			
subjects affected / exposed	2 / 14 (14.29%)	2 / 49 (4.08%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	3 / 49 (6.12%)	
occurrences (all)	1	3	
Oral Candidiasis			
subjects affected / exposed	1 / 14 (7.14%)	5 / 49 (10.20%)	
occurrences (all)	1	5	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 14 (21.43%)	17 / 49 (34.69%)	
occurrences (all)	3	19	

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 63	16 / 49 (32.65%) 63	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2015	Following amendment changes were made: the table of procedures were edited to more accurately represent the intentions found in the protocol, the schedule of visits was edited to more accurately represent the procedures to be followed at each visit, in Section 6.5 of the protocol, information was added to more clearly describe the process of screening subjects in this study, the tympanic route temperature was replaced by the axillary route temperature to be used in this study for determining temperature. Note that the oral route could also be used.
12 February 2016	Following amendment changes were made: the exclusion criterion #7 was modified: the temperature was >=38.0 degree Celsius (°C) in lieu of >=37.4°C; the table of procedures was updated as follows: during the screening period, the demographic data of all the subjects were to be collected in the CRF, at Visit 1 (Day 0), the vaccination history of all the subjects' mother was to be collected in the CRF, memory aid checked – Visit 5 was added with a cross checked at Visit 5 (Day 390), Visit 5 (booster vaccine injection) was mentioned according to Visit 3 (last vaccine injection), section 5.1.4 visit procedures of the protocol was updated according to the table of procedures.
20 October 2016	Following amendment changes were made: the period of detection was extended to 6 weeks of age in lieu of 4 to 6 weeks of age, subject's inclusion was modified, infants detected HIV+ outside the study screening process could be included, the screening criterion #2 was modified: self-reported or maternity-reported of HIV infection in the mother, not only documented proof HIV infection in the mother, the inclusion #1 and #3 were modified: infants born to an adult mother and aged 35 to 56 days (not 49 days) (between 5 and 8 weeks (not 7 weeks) of age) on the day of inclusion and born with a birth weight >=2.0 kg (not 2.5 kg), the table of procedure was updated according to the extension of the screening phase and the subject's age at inclusion (inclusion criterion #1), the number of countries, where the product has been licensed, was modified: 104 countries in lieu of 78 countries, the visit procedures was updated according to the additional way of selection of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported