Clinical trial results:
Persistence of Anti-HBs Antibodies at 6 to 7 Years of Age in Subjects Having Received a DTaP-IPV-HB-PRP~T Hexavalent Vaccine at 3, 5, and 11 to 12 Months of Age, and Evaluation of Their Immune Memory Following a Challenge Vaccination with a Standalone Hepatitis B Vaccine

Summary

EudraCT number	2017-004069-29
Trial protocol	FI
Global end of trial date	20 June 2019

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020

Trial information

Trial identification

Sponsor protocol code	A3L00052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1183-6489

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	30 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To describe the persistence of anti-hepatitis B surface (HBs) antibodies at 6 to 7 years of age in subjects having received an hexavalent vaccine at 3, 5 and 11 to 12 months of age according to the vaccine received during Study A3L38 (Hexyon [Group 1] or Infanrix hexa [Group 2]).
2) To evaluate the immune response against HBs antigen one month after a vaccination with a standalone monovalent HB vaccine (challenge dose).

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	13 February 2019
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	Finland: 225
Worldwide total number of subjects	225
EEA total number of subjects	225

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)	0
Children (2-11 years)	225
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 10 sites in Finland from 13 February 2019 to 20 June 2019.

Pre-assignment

Screening details:

All subjects who were previously vaccinated in study A3L38 (2012-001054-26) (3 doses of either DTaP-IPV-HB-PRP~T hexavalent combined vaccine [Hexyon® {Group 1}] or DTaP-IPV-HB/Hib combined vaccine [Infanrix® hexa {Group 2}]) were enrolled in this study A3L00052.

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	Group 1: Hexyon®/Engerix® B

Arm description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB-PRP~T hexavalent combined vaccine (Hexyon® vaccine) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Arm type	Experimental
Investigational medicinal product name	Engerix® B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 millilitre (mL), intramuscular, 1 injection on Day 0.

Arm title	Group 2: Infanrix® hexa/Engerix® B

Arm description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB/Hib combined vaccine (Infanrix® hexa) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Arm type	Experimental
Investigational medicinal product name	Engerix® B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection on Day 0.

Number of subjects in period 1	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B
Started	111	114
Completed	108	113
Not completed	3	1
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: Hexyon®/Engerix® B
Reporting group description:	
Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB-PRP~T hexavalent combined vaccine (Hexyon® vaccine) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.	
Reporting group title	Group 2: Infanrix® hexa/Engerix® B
Reporting group description:	
Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB/Hib combined vaccine (Infanrix® hexa) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.	

Reporting group values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B	Total
Number of subjects	111	114	225
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	6.00	6.00	
standard deviation	± 0	± 0	-
Gender categorical			
Units: Subjects			
Female	52	58	110
Male	59	56	115

End points

End points reporting groups

Reporting group title	Group 1: Hexyon®/Engerix® B

Reporting group description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB-PRP~T hexavalent combined vaccine (Hexyon® vaccine) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Reporting group title	Group 2: Infanrix® hexa/Engerix® B

Reporting group description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB/Hib combined vaccine (Infanrix® hexa) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Primary: Geometric Mean Concentrations (GMCs) of Anti-HBs Antibody at Day 0

End point title	Geometric Mean Concentrations (GMCs) of Anti-HBs Antibody at Day 0[1]

End point description:

GMCs of anti-HBs antibodies was measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the per-protocol analysis set (PPAS) population which included subjects who received the challenge dose and had no protocol deviation.

End point type	Primary

End point timeframe:

At Baseline (Day 0)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
		Reporting group		

End point description:

Anti-HBs antibodies concentration >= 10 mIU/mL was measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

At Baseline (Day 0)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: subjects				
number (confidence interval 95%)	49 (43.1 to 64.4)	72 (63.6 to 81.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Anti-HBs Antibody Concentration >=100 mIU/mL at Day 0

End point title	Number of Subjects With Anti-HBs Antibody Concentration >=100 mIU/mL at Day 0[3]

End point description:

Anti-HBs antibodies concentration >=100 mIU/mL was measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

At Baseline (Day 0)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: subjects				
number (confidence interval 95%)	17 (11.3 to 28.2)	36 (27.2 to 47.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Concentrations of Anti-HBs Antibody at Day 28

End point title	Geometric Mean Concentrations of Anti-HBs Antibody at Day

End point description:

GMCs of anti-HBs antibodies were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

Post vaccination (Day 28)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: Titers (1/dilution)				
geometric mean (confidence interval 95%)	1816 (1100 to 2998)	7036 (4591 to 10783)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Anti-HBs Antibody Concentration >=10 mIU/mL at Day 28

End point title	Percentage of Subjects With Anti-HBs Antibody Concentration >=10 mIU/mL at Day 28[5]

End point description:

Anti-HBs antibodies concentration >=10 mIU/mL was measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

Post vaccination (Day 28)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: percentage of subjects				
number (confidence interval 95%)	96.7 (90.7 to 99.3)	99.0 (94.4 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Anti-HBs Antibody Concentration >=100 mIU/mL at Day 28

End point title	Number of Subjects With Anti-HBs Antibody Concentration >=100 mIU/mL at Day 28[6]

End point description:

Anti-HBs antibodies concentration >=100 mIU/mL was measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

Post vaccination (Day 28)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: subjects				
number (confidence interval 95%)	79 (78.1 to 93.0)	94 (89.9 to 98.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Concentration Ratio (GMCR) of Anti-HBs Antibody Concentrations

End point title	Geometric Mean Concentration Ratio (GMCR) of Anti-HBs Antibody Concentrations[7]

End point description:

GMCs of anti-HBs antibodies at Day 0 and Day 28 were measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System assay using chemiluminescence detection technology. GMCRs were calculated as the ratio of GMTs at post-vaccination (Day 28)/baseline (Day 0). The analysis was performed on the PPAS population.

End point type	Primary

End point timeframe:

At Baseline (Day 0) and Day 28

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: ratio				
geometric mean (confidence interval 95%)	90.1 (63.8 to 127)	163 (126 to 211)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Anamnestic Response to the Challenge Dose for Anti-HBs Antibodies

End point title	Percentage of Subjects With Anamnestic Response to the Challenge Dose for Anti-HBs Antibodies[8]

End point description:

Anamnestic response was defined as anti-HBs antibody concentrations >=4-fold increase from pre-challenge dose (Day 0) to post-challenge dose (Day 28) in subjects seroprotected (>=10 mIU/mL) prior to challenge dose or anti-HB antibody concentrations >=10 mIU/mL post-challenge dose in subjects not seroprotected prior to challenge dose (greater than [<] 10 mIU/mL). Analysis was performed on PPAS population.

End point type	Primary

End point timeframe:

Post vaccination (Day 28)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: percentage of subjects				
number (confidence interval 95%)	96.7 (90.7 to	99.0 (94.4 to		

99.3)	100)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs)

End point title	Number of Subjects With Serious Adverse Events (SAEs)

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 full analysis set (FAS) population which included subjects who received the challenge dose.

End point type	Secondary

End point timeframe:

From Day 0 up to Day 28

End point values	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	113		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

SAEs were collected throughout the study (from Day 0 through Day 28 after vaccination).

Adverse event reporting additional description:

Analysis was performed on FAS population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Group 1: Hexyon®/Engerix® B

Reporting group description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB-PRP~T hexavalent combined vaccine (Hexyon® vaccine) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Reporting group title	Group 2: Infanrix® hexa/Engerix® B

Reporting group description:

Subjects who were vaccinated in the prior study A3L38 with 3 doses of DTaP-IPV-HB/Hib combined vaccine (Infanrix® hexa) received a single dose (challenge dose) of Engerix® B (purified monovalent HBs antigen) vaccine on Day 0, in this study.

Serious adverse events	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Group 1: Hexyon®/Engerix® B	Group 2: Infanrix® hexa/Engerix® B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events were not collected in this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2018	Following changes were made: • The statement on the subject's parent consent for future use was deleted. • A statement on the destruction of blood samples was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported