Clinical trial results:
An open-label, controlled, multi-centre study of the immunogenicity and safety of a challenge dose of HBVAXPRO® to explore the anamnestic immune response in healthy children vaccinated 10 years ago with a primary series (3 doses) of either HEXAVAC® or INFANRIX®-HEXA

Summary

EudraCT number	2013-001602-28
Trial protocol	IT
Global end of trial date	04 February 2015

Results information

Result version number	v2 (current)
This version publication date	02 July 2016
First version publication date	23 April 2016
Version creation reason	• Correction of full data set Global end of trial date corrected to comply with protocol definition (date of final collection of data for the primary endpoint).

Trial information

Trial identification

Sponsor protocol code	HXV02C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02012998
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur MSD S.N.C.
Sponsor organisation address	162 avenue Jean Jaurès - CS 50712, Lyon Cedex 07, France, 69367
Public contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com
Scientific contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.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	04 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2015
Global end of trial reached?	Yes
Global end of trial date	04 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe, in subjects vaccinated with 3 doses of HEXAVAC® as infants, the percentage of subjects with an anti-HBs concentration ≥10 mIU/mL 1 month after a challenge dose of HBVAXPRO® 5 µg given at least 10 years later
To describe, in subjects vaccinated with 3 doses of INFANRIX®-HEXA as infants, the percentage of subjects with an anti-HBs concentration ≥10 mIU/mL 1 month after a challenge dose of HBVAXPRO® 5 µg given at least 10 years later
Note: "HBVAXPRO® 5 µg" was referred to "HBVAXPRO" to facilitate reading.

Protection of trial subjects:

Healthy subjects with sensitivity and/or allergy to any component of HBVAXPRO were excluded.
Vaccine was administered by qualified study personnel.
After each vaccination, subjects were kept under observation for at least 20 minutes to ensure their safety.

Background therapy:

Subjects were previously vaccinated with a 3-doses primary series of HEXAVAC or a 3-doses primary series of INFANRIX-HEXA as infants (at about 3, 5, and 12 months of life). They received the 3rd dose of HEXAVAC or INFANRIX-HEXA at least 10 years before the challenge dose of HBVAXPRO.

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
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	Italy: 751
Worldwide total number of subjects	751
EEA total number of subjects	751

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)	451
Adolescents (12-17 years)	300
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled in 8 active centres in Italy.

Pre-assignment

Screening details:

753 subjects were screened.
751 subjects were enrolled and vaccinated.
749 subjects completed the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study was open-label as all the subjects received 1 dose of HBVAXPRO.
Nevertheless, subjects were recruited from 2 different cohorts based on their vaccination history: vaccination with a 3-doses primary series of HEXAVAC or INFANRIX-HEXA during infancy.
Immunogenicity assays were performed by laboratory staff (personnel and the analysts) who were blinded for the vaccine each subject had received as primo-vaccination.

Arms

Are arms mutually exclusive?	Yes
Arm title	HEXAVAC / HBVAXPRO

Arm description:

Subjects previously vaccinated with a 3-doses primary series of HEXAVAC (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular (IM) route at least 10 years after the 3rd dose of the primary series.
Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).

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

Dosage and administration details:

0.5 mL, IM route (deltoid region), 1 dose at least 10 years after the 3rd dose of the primary series.

Arm title	INFANRIX-HEXA / HBVAXPRO

Arm description:

Subjects previously vaccinated with a 3-doses primary series of INFANRIX-HEXA (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by IM route at least 10 years after the 3rd dose of the primary series.
Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).

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

Dosage and administration details:
0.5 mL, IM route (deltoid region), 1 dose at least 10 years after the 3rd dose of the primary series.

Number of subjects in period 1	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO
Started	409	342
Completed	408	341
Not completed	1	1
Subject not available to continue (other city)	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	HEXAVAC / HBVAXPRO
Reporting group description:	
# Subjects previously vaccinated with a 3-doses primary series of HEXAVAC (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular (IM) route at least 10 years after the 3rd dose of the primary series. # Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).	
Reporting group title	INFANRIX-HEXA / HBVAXPRO
Reporting group description:	
# Subjects previously vaccinated with a 3-doses primary series of INFANRIX-HEXA (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by IM route at least 10 years after the 3rd dose of the primary series. # Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).	

Reporting group values	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO	Total
Number of subjects	409	342	751
Age categorical			
Age at challenge dose			
Units: Subjects			
10.9-13.4 years (min-max)	409	342	751
Age continuous			
Age at challenge dose			
Units: years			
arithmetic mean	11.9	11.8	
standard deviation	± 0.5	± 0.5	-
Gender categorical			
Units: Subjects			
Female	222	198	420
Male	187	144	331
Time interval between the 3rd and the challenge doses			
Time interval between the last Hexavalent dose (HEXAVAC or INFANRIX-HEXA) and the challenge dose of HBVAXPRO			
Units: Years			
median	11	10.8	
full range (min-max)	10 to 12.3	10 to 12.2	-

End points

End points reporting groups

Reporting group title	HEXAVAC / HBVAXPRO

Reporting group description:

Subjects previously vaccinated with a 3-doses primary series of HEXAVAC (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular (IM) route at least 10 years after the 3rd dose of the primary series.
Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).

Reporting group title	INFANRIX-HEXA / HBVAXPRO

Reporting group description:

Subjects previously vaccinated with a 3-doses primary series of INFANRIX-HEXA (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO (Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by IM route at least 10 years after the 3rd dose of the primary series.
Blood samples were collected on Day 0 (D0) before challenge dose (pre-challenge dose) and 1 month (D21 to D35) after the challenge dose (post-challenge dose).

Subject analysis set title	HEXAVAC / HBVAXPRO anti-HBs <10 mIU/mL at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects previously vaccinated with a 3-doses primary series of HEXAVAC (at 3, 5, and 12 months of life) with anti-HBs antibody (Ab) concentration <10 mIU/mL at baseline, i.e., at D0 before HBVAXPRO challenge dose.

Subject analysis set title	HEXAVAC / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects previously vaccinated with a 3-doses primary series of HEXAVAC (at 3, 5, and 12 months of life) with anti-HBs Ab concentration ≥10 mIU/mL at baseline, i.e., at D0 before HBVAXPRO challenge dose.

Subject analysis set title	INFANRIX-HEXA / HBVAXPRO anti-HBs <10 mIU/mL at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects previously vaccinated with a 3-doses primary series of INFANRIX-HEXA (at 3, 5, and 12 months of life) with anti-HBs Ab concentration <10 mIU/mL at baseline, i.e., at D0 before HBVAXPRO challenge dose.

Subject analysis set title	INFANRIX-HEXA / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects previously vaccinated with a 3-doses primary series of INFANRIX-HEXA (at 3, 5, and 12 months of life) with anti-HBs Ab concentration ≥10 mIU/mL at baseline, i.e., at D0 before HBVAXPRO challenge dose.

Subject analysis set title	All subjects
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of HBVAXPRO and who had any safety follow-up data.

Primary: Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)

End point title	Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)[1]

End point description:

Percentage of subjects with an anti-HBs Ab concentration ≥10 mIU/mL measured by Microparticle

Enzyme Immunoassay (MEIA) - AxSYM® AUSAB 1 month after HBVAXPRO challenge dose, given at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Primary

End point timeframe:

1 month after HBVAXPRO challenge dose (post-challenge).

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: Objectives were only descriptive. Thus no formal statistical hypothesis was tested in this study.

End point values	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	336		
Units: Percentage of subjects				
number (confidence interval 95%)				
Post-challenge anti-HBs ≥10 mIU/mL	83.6 (79.6 to 87.1)	96.4 (93.8 to 98.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL before HBVAXPRO challenge dose (PRE-CHALLENGE)

End point title	Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL before HBVAXPRO challenge dose (PRE-CHALLENGE)

End point description:

Percentage of subjects with an anti-HBs Ab concentration ≥10 mIU/mL measured by MEIA - AxSYM® AUSAB at Day 0 (D0) before HBVAXPRO challenge dose (pre-challenge), at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Secondary

End point timeframe:

Before HBVAXPRO challenge dose (pre-challenge).

End point values	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394[2]	336		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pre-challenge anti-HBs ≥10 mIU/mL	23.9 (19.7 to 28.4)	69 (63.8 to 74)		

Notes:

[2] - Pre-challenge blood samples of 2 subjects were considered as missing due to suspected inversion.

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations (GMCs) of anti-HBs Abs before (PRE-CHALLENGE) and 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)

End point title	Geometric Mean Concentrations (GMCs) of anti-HBs Abs before (PRE-CHALLENGE) and 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)

End point description:

Anti-HBs Ab concentrations were measured by MEIA - AxSYM® AUSAB before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge), given at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Ab concentrations are expressed in mIU/mL.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "HEXAVAC / HBVAXPRO" and "INFANRIX-HEXA / HBVAXPRO" groups, respectively.

End point type	Secondary

End point timeframe:

Before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge).

End point values	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	336		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Pre-challenge anti-HBs GMC (N=394, 336)	7.7 (7 to 8.3)	26.8 (22.9 to 31.4)		
Post-challenge anti-HBs GMC (N=396, 336)	191.9 (152.8 to 241)	1823.8 (1449 to 2295.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMCs of anti-HBs Abs before (PRE-CHALLENGE) and 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) by subset of subjects defined according to pre-challenge anti-HBs Ab concentrations (<10 or ≥10 mIU/mL)

End point title	GMCs of anti-HBs Abs before (PRE-CHALLENGE) and 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) by subset

	of subjects defined according to pre-challenge anti-HBs Ab concentrations (<10 or ≥10 mIU/mL)

End point description:

Anti-HBs Ab concentrations were measured by MEIA - AxSYM® AUSAB before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge), given at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Ab concentrations are expressed in mIU/mL.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Secondary

End point timeframe:

Before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge).

End point values	HEXAVAC / HBVAXPRO anti-HBs <10 mIU/mL at baseline	HEXAVAC / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline	INFANRIX-HEXA / HBVAXPRO anti-HBs <10 mIU/mL at baseline	INFANRIX-HEXA / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	300	94	104	232
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Pre-challenge anti-HBs GMC	5 (5 to 5)	29.8 (25.2 to 35.2)	5 (5 to 5)	56.8 (49 to 65.9)
Post-challenge anti-HBs GMC	91.1 (72.5 to 114.5)	2113.4 (1608.2 to 2777.5)	221.6 (148.7 to 330.3)	4691.6 (3927.4 to 5604.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of individual anti-HBs Ab Concentration post-/pre-challenge Ratios (GMCRs) 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)

End point title	Geometric Mean of individual anti-HBs Ab Concentration post-/pre-challenge Ratios (GMCRs) 1 month after HBVAXPRO challenge dose (POST-CHALLENGE)

End point description:

Anti-HBs Ab concentrations were measured by MEIA - AxSYM® AUSAB before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge), given at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Individual post- (1 month)/pre-challenge (D0) anti-HBs Ab concentration ratios were calculated.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Secondary

End point timeframe:

1 month after HBVAXPRO challenge dose (post-challenge).

End point values	HEXAVAC / HBVAXPRO	INFANRIX-HEXA / HBVAXPRO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	336		
Units: Not applicable				
number (confidence interval 95%)				
Anti-HBs GMCR	25.2 (20.8 to 30.6)	68.1 (57.6 to 80.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of individual anti-HBs Ab Concentration post-/pre-challenge Ratios (GMCRs) 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) by subset of subjects defined according to pre-challenge anti-HBs Ab concentrations (<10 or ≥10 mIU/mL)

End point title	Geometric Mean of individual anti-HBs Ab Concentration post-/pre-challenge Ratios (GMCRs) 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) by subset of subjects defined according to pre-challenge anti-HBs Ab concentrations (<10 or ≥10 mIU/mL)

End point description:

Anti-HBs Ab concentrations were measured by MEIA - AxSYM® AUSAB before (pre-challenge) and 1 month after HBVAXPRO challenge dose (post-challenge), given at least 10 years after the 3rd dose of either HEXAVAC or INFANRIX-HEXA.
Individual post- (1 month)/pre-challenge (D0) anti-HBs Ab concentration ratios were calculated.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Secondary

End point timeframe:

1 month after HBVAXPRO challenge dose (post-challenge).

End point values	HEXAVAC / HBVAXPRO anti-HBs <10 mIU/mL at baseline	HEXAVAC / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline	INFANRIX-HEXA / HBVAXPRO anti-HBs <10 mIU/mL at baseline	INFANRIX-HEXA / HBVAXPRO anti-HBs ≥10 mIU/mL at baseline
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	300	94	104	232
Units: Not applicable				
number (confidence interval 95%)				
Anti-HBs GMCR	18.2 (14.5 to 22.9)	70.9 (54.3 to 92.6)	44.3 (29.7 to 66.1)	82.6 (70.5 to 96.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) in subjects with pre-challenge anti-HBs concentration <10 mIU/mL

End point title	Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/mL 1 month after HBVAXPRO challenge dose (POST-CHALLENGE) in subjects with pre-challenge anti-HBs concentration <10 mIU/mL

End point description:

Percentage of subjects with an anti-HBs concentration ≥10 mIU/mL measured by MEIA - AxSYM® AUSAB 1 month after HBVAXPRO challenge dose (post-challenge) in subjects with pre-challenge anti-HBs concentration <10 mIU/mL.
Analysis was done on the Per Protocol Set (PPS), i.e. all the vaccinated subjects excluding those with a serology-confirmed diagnosis of Hepatitis B infection or with important protocol deviations which may have interfered with the immunogenicity evaluation.

End point type	Secondary

End point timeframe:

1 month after HBVAXPRO challenge dose (post-challenge).

End point values	HEXAVAC / HBVAXPRO anti-HBs <10 mIU/mL at baseline	INFANRIX-HEXA / HBVAXPRO anti-HBs <10 mIU/mL at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	300	104		
Units: Percentage of subjects				
number (confidence interval 95%)				
Post-challenge anti-HBs ≥10 mIU/mL	78.7 (73.6 to 83.2)	88.5 (80.7 to 93.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global summary of safety from D0 to D14 after HBVAXPRO challenge dose

End point title	Global summary of safety from D0 to D14 after HBVAXPRO challenge dose

End point description:

Adverse events (AEs) were recorded as follows.

1/ From D0 to D4 after vaccination: # solicited injection-site adverse reactions (ISRs: injection-site erythema, injection-site swelling, and injection-site pain), and # solicited systemic AE pyrexia (defined as body temperature ≥38.0°C).
2/ From D0 to D14 after vaccination: unsolicited ISRs (including erythema, swelling, and pain from D5 to D14), and # unsolicited systemic AEs.
AEs at injection sites were always considered as vaccine-related (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not to HBVAXPRO.
The percentage of subjects presenting at least once the considered events is reported hereafter.
Analysis was done on the Safety Analysis Set, i.e., all subjects who received at least 1 dose of HBVAXPRO and who had any safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D14 after HBVAXPRO challenge dose.

End point values	All subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	750			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 AE (D0-D14)	46.1 (42.5 to 49.8)			
At least 1 vaccine-related AE (D0-D14)	41.3 (37.8 to 45)			
At least 1 ISR (D0-D14)	40.7 (37.1 to 44.3)			
At least 1 solicited ISR (D0-D4)	40.5 (37 to 44.1)			
At least 1 other ISR (D0-D14)	0.3 (0 to 1)			
At least 1 systemic AE (D0-D14)	11.7 (9.5 to 14.3)			
At least 1 pyrexia (D0-D4)	0.8 (0.3 to 1.7)			
At least 1 other systemic AE (D0-D14)	11.6 (9.4 to 14.1)			
At least 1 vaccine-related systemic AE (D0-D14)	1.9 (1 to 3.1)			
At least 1 vaccine-related pyrexia (D0-D4)	0.3 (0 to 1)			
At least 1 other vaccine-related syst. AE (D0-D14)	1.7 (0.9 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting ISRs from D0 to D14 after HBVAXPRO challenge dose

End point title	Percentage of subjects reporting ISRs from D0 to D14 after HBVAXPRO challenge dose

End point description:

ISRs occurring after HBVAXPRO challenge dose were recorded as follows:
From D0 to D4 after vaccination: solicited ISRs, i.e., injection-site erythema, injection-site swelling, and injection-site pain.
From D0 to D14 after vaccination: unsolicited ISRs (including erythema, swelling, and pain from D5 to

D14).
AEs at injection-site were always considered as related to vaccine (ISRs).
The percentage of subjects presenting at least once the considered events is reported hereafter.
Analysis was done on the Safety Analysis Set, i.e., all subjects who received at least 1 dose of HBVAXPRO and who had any safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D14 after HBVAXPRO challenge dose.

End point values	All subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	750			
Units: Percentage of subjects				
number (not applicable)				
Solicited injection-site erythema (D0-D4)	2.4			
Solicited injection-site swelling (D0-D4)	3.5			
Solicited injection-site pain (D0-D4)	39.3			
Unsolicited injection-site bruising (D0-D14)	0.1			
Unsolicited injection-site swelling (D5-D14)	0.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Systemic adverse events (AEs) were collected from D0 to D14 after HBVAXPRO challenge dose.
Serious AEs (SAEs) and deaths were collected throughout the study.

Adverse event reporting additional description:

Analysis was done on the Safety Analysis Set, i.e., all subjects who received at least 1 dose of HBVAXPRO and who had any safety follow-up data.
Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence ≥1% are presented hereafter.
2 subjects reported 1 SAE each; none of them was assessed as related to HBVAXPRO challenge dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects previously vaccinated with a 3-doses primary series of HEXAVAC or INFANRIX-HEXA (at 3, 5, and 12 months of life) received 1 challenge dose of HBVAXPRO by IM route at least 10 years after the 3rd dose of the primary series.
Respectively, 87 (11.6%) subjects reported at least 1 unsolicited systemic AE, and 13 (1.7%) subjects reported at least 1 vaccine-related unsolicited systemic AE within 14 days after vaccination.
Note: Unsolicited non-serious systemic AEs with incidence ≥1% are presented hereafter. If each non-serious systemic AE with incidence ≥1% had been reported by a different subject, the number of subjects reporting at least 1 non-serious systemic AE with incidence ≥1% would have been 51.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 750 (0.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Schwannoma			
subjects affected / exposed	1 / 750 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 750 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events subjects affected / exposed	51 / 750 (6.80%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	27 / 750 (3.60%) 28		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	5 / 750 (0.67%) 5		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	12 / 750 (1.60%) 12		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 750 (0.93%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported