



## Clinical trial results:

### A Study to Assess the Anamnestic Immune Response 4 to 8 Years After a Primary Vaccination Series With HBVAXPRO™

#### Summary

EudraCT number	2006-001639-23
Trial protocol	ES
Global end of trial date	23 June 2008

#### Results information

Result version number	v1 (current)
This version publication date	05 January 2017
First version publication date	05 January 2017

#### Trial information

##### Trial identification

Sponsor protocol code	V232-058
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00393523
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: V232-058

Notes:

##### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	23 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2008
Global end of trial reached?	Yes
Global end of trial date	23 June 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess the safety and immunogenicity of a booster dose of hepatitis B vaccine in children who have received a 3-dose primary series of either RECOMBIVAX HB™ vaccine or ENGERIX-B™ vaccine. The primary vaccination series was given 4 to 8 years prior to study entry and consisted of a licensed hepatitis B vaccine product (either RECOMBIVAX HB™ vaccine or ENGERIX-B™ vaccine). The booster dose given in this study was either an investigational Merck product (Modified Process Hepatitis B Vaccine) or licensed ENGERIX-B™ vaccine.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Spain: 1458
Worldwide total number of subjects	1478
EEA total number of subjects	1458

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)	1478
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:

This study was conducted at 77 primary study sites in Spain and 1 study site in Canada. Date of first participant visit: 26-Sep-2006; Date of last participant visit: 23-June-2008

### Pre-assignment

Screening details:

To be eligible for enrollment in the study, participants must have received a primary series of 3 doses of hepatitis B vaccine (either RECOMBIVAX HB™ vaccine or ENGERIX-B™ vaccine) during the first year of life.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)

Arm description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose))

Arm type	Experimental
Investigational medicinal product name	V232 Vaccine (Modified Process Hepatitis B Vaccine Booster)
Investigational medicinal product code	
Other name	V232
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

5 µg/0.5 mL, intramuscular

<b>Arm title</b>	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)
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Arm description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)

Arm type	Active comparator
Investigational medicinal product name	ENGERIX-B™ Vaccine Booster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

10 µg/0.5 mL, intramuscular

<b>Arm title</b>	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)
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Arm description:

Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose))

Arm type	Experimental
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Investigational medicinal product name	V232 Vaccine (Modified Process Hepatitis B Vaccine Booster)
Investigational medicinal product code	
Other name	V232
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: 5 µg/0.5 mL, intramuscular	
<b>Arm title</b>	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)

Arm description:

Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)

Arm type	Active comparator
Investigational medicinal product name	ENGERIX-B™ Vaccine Booster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: 10 µg/0.5 mL, intramuscular	
<b>Arm title</b>	V232 Vaccine (no prior Hepatitis B vaccine) (Group 5)

Arm description:

Participants did not receive a prior vaccination with a hepatitis B vaccine. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232), 5 µg.

Arm type	Experimental
Investigational medicinal product name	V232 Vaccine (Modified Process Hepatitis B Vaccine)
Investigational medicinal product code	
Other name	V232
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: 5 µg/0.5 mL, intramuscular	

<b>Number of subjects in period 1</b>	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)
Started	376	375	353
Vaccination Visit 1	374	375	349
Completed	364	366	349
Not completed	12	9	4
Consent withdrawn by subject	6	7	2
Difficulties in specimen collection	-	-	1
Vaccine supply issue	-	-	1
Lost to follow-up	-	-	-
Protocol deviation	6	2	-

<b>Number of subjects in period 1</b>	<b>ENGERIX-B™ Booster (ENGERIX- B™ in infancy) (Group 4)</b>	<b>V232 Vaccine (no prior Hepatitis B vaccine) (Group 5)</b>
Started	354	20
Vaccination Visit 1	352	20
Completed	348	19
Not completed	6	1
Consent withdrawn by subject	3	-
Difficulties in specimen collection	-	-
Vaccine supply issue	-	-
Lost to follow-up	2	1
Protocol deviation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)
Reporting group description:	Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose)
Reporting group title	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)
Reporting group description:	Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)
Reporting group title	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)
Reporting group description:	Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose)
Reporting group title	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)
Reporting group description:	Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)
Reporting group title	V232 Vaccine (no prior Hepatitis B vaccine) (Group 5)
Reporting group description:	Participants did not receive a prior vaccination with a hepatitis B vaccine. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232), 5 µg.

Reporting group values	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)
Number of subjects	376	375	353
Age categorical Units: Subjects			
Children (2-11 years)	376	375	353
Age Continuous   Units: years			
arithmetic mean	5.7	5.7	5.3
standard deviation	± 0.92	± 0.97	± 1.05
Gender, Male/Female Units: participants			
Female	172	186	179
Male	204	189	174

Reporting group values	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)	V232 Vaccine (no prior Hepatitis B vaccine) (Group 5)	Total
Number of subjects	354	20	1478

Age categorical Units: Subjects			
Children (2-11 years)	354	20	1478
Age Continuous   Units: years			
arithmetic mean	5.4	4.3	
standard deviation	± 0.98	± 0.66	-
Gender, Male/Female Units: participants			
Female	161	13	711
Male	193	7	767

## End points

### End points reporting groups

Reporting group title	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)
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Reporting group description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose))

Reporting group title	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)
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Reporting group description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)

Reporting group title	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)
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Reporting group description:

Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose))

Reporting group title	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)
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Reporting group description:

Participants received a primary series of 3 doses of ENGERIX-B™ vaccine (10 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose)

Reporting group title	V232 Vaccine (no prior Hepatitis B vaccine) (Group 5)
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Reporting group description:

Participants did not receive a prior vaccination with a hepatitis B vaccine. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232), 5 µg.

Subject analysis set title	Modified Process Hepatitis B Vaccine
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose)).

Subject analysis set title	ENGERIX-B™ Vaccine
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose).

### Primary: Participants With an Antibody Response to Hepatitis B Surface Antigen in Participants Who Received a 3-dose Primary Series of RECOMBIVAX HB™ in Infancy

End point title	Participants With an Antibody Response to Hepatitis B Surface Antigen in Participants Who Received a 3-dose Primary Series of RECOMBIVAX HB™ in Infancy <sup>[1][2]</sup>
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End point description:

Participants who received a 3-dose primary series of RECOMBIVAX HB™ in infancy and who demonstrated antibodies to hepatitis B surface antigen  $\geq 10$  mIU/mL at 1 month after receiving a booster dose of modified process hepatitis B vaccine or ENGERIX-B™. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

End point type	Primary
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End point timeframe:

4 weeks (1 month) after booster dose

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: No statistical analysis was planned or performed for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	333		
Units: Participants				
number (not applicable)	323	305		

## Statistical analyses

No statistical analyses for this end point

### **Primary: Seroprotection rate (SPR) to Hepatitis B Surface Antigen in Participants Who Received a 3-dose Primary Series of RECOMBIVAX HB™ in Infancy**

End point title	Seroprotection rate (SPR) to Hepatitis B Surface Antigen in Participants Who Received a 3-dose Primary Series of RECOMBIVAX HB™ in Infancy <sup>[3][4]</sup>
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End point description:

Participants received a 3-dose primary series of RECOMBIVAX HB™ in infancy. Seroprotection rate (SPR) was defined as the percentage of participants who demonstrated antibodies to hepatitis B surface antigen  $\geq 10$  mIU/mL at 1 month after receiving a booster dose of modified process hepatitis B vaccine or ENGERIX-B™. The statistical criterion for an adequate SPR required the lower bound of the 2-sided multiplicity adjusted 95.2% confidence interval for the anti-HBs SPR 4 weeks after the booster dose for participants to be greater than 90%. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

End point type	Primary
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End point timeframe:

4 weeks (1 month) after booster 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: No statistical analysis was planned or performed for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	333		
Units: Percentage of participants				
number (confidence interval 95%)	95 (92.1 to 97.1)	91.6 (88.1 to 94.3)		

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Who Experienced One or More Adverse Events (AEs)

End point title	Percentage of Participants Who Experienced One or More Adverse Events (AEs) <sup>[5]</sup>
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The safety population consisted of all participants who received at least one dose of Modified Process Hepatitis B Vaccine or ENGERIX-B™.

End point type	Primary
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End point timeframe:

Up to 14 days following booster vaccination with modified process hepatitis B vaccine or ENGERIX-B™ vaccine

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: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	Modified Process Hepatitis B Vaccine	ENGERIX-B™ Vaccine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	742	717		
Units: Percentage of participants				
number (not applicable)	58	55.9		

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Who Discontinued the Study Due to an AE

End point title	Percentage of Participants Who Discontinued the Study Due to an AE <sup>[6]</sup>
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**End point description:**

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The safety population consisted of all participants who received at least one dose of Modified Process Hepatitis B Vaccine or ENGERIX-B™.

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End point type	Primary
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**End point timeframe:**

Up to 14 days following booster vaccination with modified process hepatitis B vaccine or ENGERIX-B™ vaccine

**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: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	Modified Process Hepatitis B Vaccine	ENGERIX-B™ Vaccine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	742	717		
Units: Percentage of Participants				
number (not applicable)	0	0		

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Participants With an Antibody Response to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy**

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End point title	Participants With an Antibody Response to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy <sup>[7]</sup>
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**End point description:**

Participants who received a 3-dose primary series of ENGERIX™ in infancy and who demonstrated antibodies to hepatitis B surface antigen  $\geq 10$  mIU/mL at 1 month after receiving a booster dose of modified process hepatitis B vaccine or ENGERIX-B™. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

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End point type	Secondary
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**End point timeframe:**

4 weeks (1 month) after booster dose

**Notes:**

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	328		
Units: Participants				
number (not applicable)	329	313		

### Statistical analyses

No statistical analyses for this end point

### Secondary: SPR to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy

End point title	SPR to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy <sup>[8]</sup>
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End point description:

Participants received a 3-dose primary series of ENGERIX™ in infancy. SPR was defined as the percentage of participants who demonstrated antibodies to hepatitis B surface antigen  $\geq 10$  mIU/mL at 1 month after receiving a booster dose of modified process hepatitis B vaccine or ENGERIX-B™. The statistical criterion for an adequate SPR required the lower bound of the 2-sided multiplicity adjusted 95.2% confidence interval for the anti-HBs SPR 4 weeks after the booster dose for participants to be greater than 90%. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

End point type	Secondary
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End point timeframe:

4 weeks (1 month) after booster dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	328		
Units: Percentage of participants				
number (confidence interval 95%)	97.3 (95 to 98.8)	95.4 (92.6 to 97.4)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Geometric Mean Titer (GMT) for Antibodies to Hepatitis B

## Surface Antigen in Participants Who Received a 3-Dose Primary Series of RECOMBIVAX HB™ in Infancy

End point title	Geometric Mean Titer (GMT) for Antibodies to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of RECOMBIVAX HB™ in Infancy <sup>[9]</sup>
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### End point description:

GMT (in milli-international units per milliliter [mIU/mL]) for all participants who completed a 3-dose primary vaccination series of RECOMBIVAX HB™ and who received a booster dose of either modified process hepatitis B vaccine or ENGERIX-B™. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

End point type	Other pre-specified
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### End point timeframe:

4 weeks (1 month) after booster dose

### Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was planned or performed for this endpoint.

End point values	V232 Vaccine Booster (RECOMBIVAX HB™ in infancy) (Group 1)	ENGERIX-B™ Booster (RECOMBIVAX HB™ in infancy) (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	333		
Units: mIU/mL				
geometric mean (confidence interval 95%)	476.9 (380.7 to 597.3)	561.2 (435.6 to 723.1)		

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: GMT for Antibodies to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy

End point title	GMT for Antibodies to Hepatitis B Surface Antigen in Participants Who Received a 3-Dose Primary Series of ENGERIX-B™ in Infancy <sup>[10]</sup>
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### End point description:

GMT for all participants who completed a 3-dose primary vaccination series of ENGERIX-B™ and who received a booster dose of modified process hepatitis B vaccine or ENGERIX-B™. Per protocol population was defined as the participants that completed the study as defined by the protocol. Participants were excluded from the analysis population mainly because they did not receive the primary series vaccination series as defined in the protocol or the study vaccine was not maintained at proper temperature as defined in the protocol.

End point type	Other pre-specified
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### End point timeframe:

4 weeks (1 month) after booster dose

### Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

<b>End point values</b>	V232 Vaccine Booster (ENGERIX-B™ in infancy) (Group 3)	ENGERIX-B™ Booster (ENGERIX-B™ in infancy) (Group 4)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	328		
Units: mIU/mL				
geometric mean (confidence interval 95%)	1424 (1131.1 to 1792.8)	1216.1 (923.6 to 1601.2)		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 32 days following booster vaccination with modified process hepatitis B vaccine or ENGERIX-B™ vaccine

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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### Reporting groups

Reporting group title	ENGERIX-B™ Vaccine
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Reporting group description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of ENGERIX-B™ vaccine (10 µg per dose) (Booster Dose).

Reporting group title	Modified Process Hepatitis B Vaccine
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Reporting group description:

Participants received a primary series of 3 doses of RECOMBIVAX HB™ vaccine (5 µg per dose) during the first year of life outside of the context of the study. On Day 1 of the study, participants received one dose of Modified Process Hepatitis B Vaccine (V232, 5 µg (Booster Dose)).

<b>Serious adverse events</b>	ENGERIX-B™ Vaccine	Modified Process Hepatitis B Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

<b>Non-serious adverse events</b>	<b>ENGERIX-B™ Vaccine</b>	<b>Modified Process Hepatitis B Vaccine</b>	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	401 / 717 (55.93%)	430 / 742 (57.95%)	
<b>Vascular disorders</b>			
<b>Haematoma</b>			
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)	
occurrences (all)	1	1	
<b>Pallor</b>			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
<b>General disorders and administration site conditions</b>			
<b>Asthenia</b>			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
<b>Discomfort</b>			
subjects affected / exposed	2 / 717 (0.28%)	4 / 742 (0.54%)	
occurrences (all)	2	4	
<b>Injection site erythema</b>			
subjects affected / exposed	64 / 717 (8.93%)	70 / 742 (9.43%)	
occurrences (all)	64	71	
<b>Injection site bruising</b>			
subjects affected / exposed	2 / 717 (0.28%)	2 / 742 (0.27%)	
occurrences (all)	2	2	
<b>Hypothermia</b>			
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)	
occurrences (all)	0	1	
<b>Fatigue</b>			
subjects affected / exposed	5 / 717 (0.70%)	4 / 742 (0.54%)	
occurrences (all)	5	4	
<b>Injection site haematoma</b>			
subjects affected / exposed	6 / 717 (0.84%)	3 / 742 (0.40%)	
occurrences (all)	6	3	
<b>Injection site hypersensitivity</b>			
subjects affected / exposed	5 / 717 (0.70%)	4 / 742 (0.54%)	
occurrences (all)	5	4	

Injection site induration subjects affected / exposed occurrences (all)	3 / 717 (0.42%) 3	4 / 742 (0.54%) 4
Injection site oedema subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1
Injection site pain subjects affected / exposed occurrences (all)	207 / 717 (28.87%) 208	231 / 742 (31.13%) 241
Injection site pruritus subjects affected / exposed occurrences (all)	7 / 717 (0.98%) 7	9 / 742 (1.21%) 9
Injection site paraesthesia subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	1 / 742 (0.13%) 1
Injection site scar subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1
Injection site vesicles subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1
Injection site swelling subjects affected / exposed occurrences (all)	66 / 717 (9.21%) 66	98 / 742 (13.21%) 99
Injection site warmth subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	3 / 742 (0.40%) 3
Malaise subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	4 / 742 (0.54%) 5
Irritability subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1
Pain subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	2 / 742 (0.27%) 3

Vessel puncture site pain subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Pyrexia subjects affected / exposed occurrences (all)	53 / 717 (7.39%) 55	42 / 742 (5.66%) 46	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Reproductive system and breast disorders Balinitis subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	5 / 717 (0.70%) 6	4 / 742 (0.54%) 4	
Cough subjects affected / exposed occurrences (all)	23 / 717 (3.21%) 24	36 / 742 (4.85%) 38	
Epistaxis subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 3	3 / 742 (0.40%) 3	
Dysphonia subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	1 / 742 (0.13%) 1	
Increased upper airway secretion subjects affected / exposed occurrences (all)	5 / 717 (0.70%) 5	4 / 742 (0.54%) 4	
Nasal oedema subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	4 / 717 (0.56%) 4	3 / 742 (0.40%) 3	

Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	12 / 717 (1.67%) 13	16 / 742 (2.16%) 16	
Rhinalgia subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 717 (0.42%) 3	1 / 742 (0.13%) 1	
Rhinitis seasonal subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	0 / 742 (0.00%) 0	
Nightmare subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	2 / 742 (0.27%) 3	
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	2 / 742 (0.27%) 2	
Arthropod sting subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	

Chillblains			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Bite			
subjects affected / exposed	2 / 717 (0.28%)	1 / 742 (0.13%)	
occurrences (all)	2	1	
Excoriation			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 717 (0.28%)	4 / 742 (0.54%)	
occurrences (all)	2	4	
Face injury			
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)	
occurrences (all)	1	1	
Head injury			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Open wound			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Joint sprain			
subjects affected / exposed	1 / 717 (0.14%)	2 / 742 (0.27%)	
occurrences (all)	1	2	
Wound			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 717 (4.46%)	35 / 742 (4.72%)	
occurrences (all)	38	38	
Aphonia			
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Lymphadenitis subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	2 / 742 (0.27%) 2	
Ear and labyrinth disorders			
Motion sickness subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	2 / 742 (0.27%) 2	
Ear pain subjects affected / exposed occurrences (all)	10 / 717 (1.39%) 10	12 / 742 (1.62%) 12	
Otorrhoea subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 717 (0.42%) 3	4 / 742 (0.54%) 4	
Eye discharge subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Conjunctivitis allergic subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	3 / 742 (0.40%) 3	
Eye swelling subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	1 / 742 (0.13%) 1	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 717 (0.56%) 4	6 / 742 (0.81%) 8	
Abdominal pain subjects affected / exposed occurrences (all)	16 / 717 (2.23%) 17	8 / 742 (1.08%) 8	
Aphthous stomatitis			

subjects affected / exposed	3 / 717 (0.42%)	1 / 742 (0.13%)
occurrences (all)	3	1
Constipation		
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)
occurrences (all)	1	1
Dental caries		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Diarrhoea		
subjects affected / exposed	10 / 717 (1.39%)	17 / 742 (2.29%)
occurrences (all)	11	18
Flatulence		
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)
occurrences (all)	1	1
Gastritis		
subjects affected / exposed	2 / 717 (0.28%)	1 / 742 (0.13%)
occurrences (all)	2	1
Lip dry		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Lip haemorrhage		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Lip swelling		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Nausea		
subjects affected / exposed	2 / 717 (0.28%)	2 / 742 (0.27%)
occurrences (all)	2	2
Stomatitis		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Odynophagia		
subjects affected / exposed	1 / 717 (0.14%)	2 / 742 (0.27%)
occurrences (all)	1	2
Toothache		

subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 2	4 / 742 (0.54%) 4	
Vomiting subjects affected / exposed occurrences (all)	14 / 717 (1.95%) 14	21 / 742 (2.83%) 24	
<b>Skin and subcutaneous tissue disorders</b>			
Acne subjects affected / exposed occurrences (all)	3 / 717 (0.42%) 3	0 / 742 (0.00%) 0	
Dermatitis subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Dermatitis atopic subjects affected / exposed occurrences (all)	8 / 717 (1.12%) 8	6 / 742 (0.81%) 6	
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	0 / 742 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	2 / 742 (0.27%) 2	
Erythema subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	2 / 742 (0.27%) 2	
Rash subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 3	4 / 742 (0.54%) 4	
Pruritus subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	0 / 742 (0.00%) 0	
Prurigo subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	0 / 742 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	2 / 742 (0.27%) 2	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 717 (0.28%)	6 / 742 (0.81%)	
occurrences (all)	3	7	
Bone pain			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Epiphysiolysis			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 717 (0.00%)	9 / 742 (1.21%)	
occurrences (all)	0	9	
Neck pain			
subjects affected / exposed	3 / 717 (0.42%)	1 / 742 (0.13%)	
occurrences (all)	3	1	
Myalgia			
subjects affected / exposed	1 / 717 (0.14%)	3 / 742 (0.40%)	
occurrences (all)	1	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 717 (0.42%)	2 / 742 (0.27%)	
occurrences (all)	3	2	
Acute tonsillitis			
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)	
occurrences (all)	0	1	
Bronchopneumonia			
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)	
occurrences (all)	0	1	
Ear infection			

subjects affected / exposed	8 / 717 (1.12%)	7 / 742 (0.94%)
occurrences (all)	8	7
Enterobiasis		
subjects affected / exposed	2 / 717 (0.28%)	0 / 742 (0.00%)
occurrences (all)	2	0
Gastroenteritis		
subjects affected / exposed	7 / 717 (0.98%)	13 / 742 (1.75%)
occurrences (all)	7	13
Fungal infection		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Herpes virus infection		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Impetigo		
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)
occurrences (all)	1	1
Infection parasitic		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Infectious mononucleosis		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Laryngitis		
subjects affected / exposed	3 / 717 (0.42%)	1 / 742 (0.13%)
occurrences (all)	3	1
Influenza		
subjects affected / exposed	1 / 717 (0.14%)	6 / 742 (0.81%)
occurrences (all)	1	6
Nasopharyngitis		
subjects affected / exposed	27 / 717 (3.77%)	32 / 742 (4.31%)
occurrences (all)	27	32
Otitis media		
subjects affected / exposed	3 / 717 (0.42%)	1 / 742 (0.13%)
occurrences (all)	3	1
Otitis media acute		

subjects affected / exposed	2 / 717 (0.28%)	5 / 742 (0.67%)
occurrences (all)	2	5
Pharyngitis		
subjects affected / exposed	9 / 717 (1.26%)	17 / 742 (2.29%)
occurrences (all)	9	17
Pharyngotonsillitis		
subjects affected / exposed	3 / 717 (0.42%)	2 / 742 (0.27%)
occurrences (all)	3	2
Respiratory tract infection		
subjects affected / exposed	2 / 717 (0.28%)	0 / 742 (0.00%)
occurrences (all)	2	0
Pneumonia		
subjects affected / exposed	1 / 717 (0.14%)	1 / 742 (0.13%)
occurrences (all)	1	1
Rhinitis		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Scarlet fever		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Skin infection		
subjects affected / exposed	0 / 717 (0.00%)	1 / 742 (0.13%)
occurrences (all)	0	1
Sinusitis		
subjects affected / exposed	1 / 717 (0.14%)	2 / 742 (0.27%)
occurrences (all)	1	2
Tonsillitis		
subjects affected / exposed	20 / 717 (2.79%)	11 / 742 (1.48%)
occurrences (all)	20	11
Tooth infection		
subjects affected / exposed	1 / 717 (0.14%)	0 / 742 (0.00%)
occurrences (all)	1	0
Tonsillitis streptococcal		
subjects affected / exposed	2 / 717 (0.28%)	1 / 742 (0.13%)
occurrences (all)	2	1
Upper respiratory tract infection		

subjects affected / exposed occurrences (all)	11 / 717 (1.53%) 11	11 / 742 (1.48%) 11	
Varicella subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	2 / 742 (0.27%) 2	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 717 (0.28%) 2	3 / 742 (0.40%) 3	
Viral infection subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	2 / 742 (0.27%) 2	
Vulvovaginitis subjects affected / exposed occurrences (all)	1 / 717 (0.14%) 1	1 / 742 (0.13%) 1	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	0 / 717 (0.00%) 0	3 / 742 (0.40%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2006	AM1 - The protocol was amended to include only participants who received the primary series of hepatitis B vaccine through the birth, 1, and 6 months of age and birth, 2, and 6 months of age schedules for Cohorts A and B. Additionally, this amendment clarified that participants in Cohort C were to be enrolled in Canada or other countries, as needed, and that the study design was changed from single-blind to open-label for Cohorts A and B.
25 July 2007	AM2 - The protocol was amended to include healthy male and female children 4 to 7 years of age and born between 2000 and 2002.
01 November 2007	AM3 - The protocol was amended to include healthy male and female children 4 to 8 years of age and born between 2000 and 2003.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported