



Clinical trial results:

A phase III, single-blinded, randomized, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals' thiomersal-free 2-dose Engerix™-B (20 mcg) and 3-dose preservative-free Engerix™-B (10 mcg) vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).

Summary

EudraCT number	2015-001531-20
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	27 April 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	103860/280,101695,101696,/697,/698
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00343915
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.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	Interim
Date of interim/final analysis	30 November 2005
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2004
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

For the primary Epoch:

To demonstrate non-inferiority of the immune response induced by (thiomersal-free) Engerix™-B (20 mcg HBsAg) administered as a 2-dose vaccination schedule compared to (preservative-free) Engerix™-B (10 mcg HBsAg) administered as a 3-dose vaccination schedule, one month after the full vaccination course (month 7).

For the long term follow-up (LTFU):

To evaluate anti-HBs antibody persistence at Months 30, 42, 54 and 66 after the first vaccine dose of primary vac-cination.

Protection of trial subjects:

The vaccinees were observed closely for at least 15 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 April 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	66 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 110
Country: Number of subjects enrolled	Belgium: 274
Worldwide total number of subjects	384
EEA total number of subjects	274

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)	0

Adolescents (12-17 years)	384
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects who participated in the primary vaccination study, in which they received either 2 or 3 doses of GSK Biologicals hepatitis B vaccine, and who consented to participate in the long-term follow-up were contacted by the investigators. No additional subjects were recruited during this long-term follow-up study.

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	2-dose Engerix

Arm description:

subjects received 2 doses of adult (thiomersal-free) HBV formulation, one at 0 and 6 months, respectively and placebo (physiological saline) at 1 month.

Arm type	Experimental
Investigational medicinal product name	Engerix™-B (thiomersal-free) 20µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In the primary study: 2 deep intramuscular injections (Months 0, & 6) in the deltoid region of the non-dominant arm.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In the primary study: 1 deep intramuscular injection (month 1) in the deltoid region of the non-dominant arm.

Arm title	3-dose Engerix
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Arm description:

Subjects received 3 doses of paediatric (preservative-free) HBV formulation one at 0, 1 and 6 months, respectively.

Arm type	Active comparator
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Investigational medicinal product name	10 µg Engerix™-B (preservative-free)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In the primary study: 3 deep intramuscular injections (months 0, 1 & 6) in the deltoid region of the non-dominant arm.

Number of subjects in period 1	2-dose Engerix	3-dose Engerix
Started	258	126
Completed	254	123
Not completed	4	3
Consent withdrawn by subject	1	-
Unspecified	1	-
Lost to follow-up	2	3

Baseline characteristics

Reporting groups

Reporting group title	2-dose Engerix
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Reporting group description:

subjects received 2 doses of adult (thiomersal-free) HBV formulation, one at 0 and 6 months, respectively and placebo (physiological saline) at 1 month.

Reporting group title	3-dose Engerix
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Reporting group description:

Subjects received 3 doses of paediatric (preservative-free) HBV formulation one at 0, 1 and 6 months, respectively.

Reporting group values	2-dose Engerix	3-dose Engerix	Total
Number of subjects	258	126	384
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	12.9	12.7	
standard deviation	± 1.23	± 1.32	-
Gender categorical			
Units: Subjects			
Female	132	61	193
Male	126	65	191

End points

End points reporting groups

Reporting group title	2-dose Engerix
Reporting group description: subjects received 2 doses of adult (thiomersal-free) HBV formulation, one at 0 and 6 months, respectively and placebo (physiological saline) at 1 month.	
Reporting group title	3-dose Engerix
Reporting group description: Subjects received 3 doses of paediatric (preservative-free) HBV formulation one at 0, 1 and 6 months, respectively.	

Primary: Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibody.

End point title	Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibody.
End point description: A seroprotected subject was defined as a subject with anti-HBs antibody concentrations ≥ 10 mIU/mL.	
End point type	Primary
End point timeframe: At Month 7	

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	113		
Units: Subjects				
Month 7 (N=241, 113)	233	111		

Statistical analyses

Statistical analysis title	Non-inf. of HBV 20µg 2-dose vs. HBV 10µg 3-dose
Statistical analysis description: Non-inferiority of the immune response induced by thiomersal-free HBV (20 µg HBsAg per dose) administered as a 2-dose vaccination schedule compared to preservative-free HBV (10 µg HBsAg per dose) administered as a 3-dose vaccination schedule, one month after the full vaccination course (Month 7).	
Comparison groups	2-dose Engerix v 3-dose Engerix
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in anti-HBs
Point estimate	-1.5

Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.4
upper limit	3.8

Primary: Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibody.

End point title	Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibody. ^[1]
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End point description:

A seroprotected subject was defined as a subject with anti-HBs antibody concentrations ≥ 10 mIU/mL.

End point type	Primary
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End point timeframe:

At Month 30, Month 42, Month 54 and Month 66

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	80		
Units: Subjects				
Month 30 (N=140, 64)	122	62		
Month 42 (N=166, 80)	139	74		
Month 54 (N=147, 76)	124	72		
Month 66 (N=132, 70)	105	64		

Statistical analyses

No statistical analyses for this end point

Primary: Antibody titers against hepatitis-B virus.

End point title	Antibody titers against hepatitis-B virus. ^[2]
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End point description:

Antibody titers were summarized by Geometric Mean Concentrations (GMCs) with their 95% CIs.

End point type	Primary
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End point timeframe:

At Month 30, Month 42, Month 54 and Month 66.

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	80		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Month 30 (N=140, 64)	229 (162.1 to 323.5)	708.3 (409.6 to 1224.8)		
Month 42 (N=166, 80)	159.7 (118.3 to 215.7)	417.9 (267.3 to 653.6)		
Month 54 (N=147, 76)	123.6 (92.7 to 165)	277.6 (176.5 to 436.7)		
Month 66 (N=132, 70)	82.1 (60.7 to 111)	225.2 (142.6 to 355.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody titers against hepatitis-B virus.

End point title	Antibody titers against hepatitis-B virus.
End point description:	
Antibody titers were summarized by Geometric Mean Concentrations (GMCs) with their 95% CIs.	
End point type	Secondary
End point timeframe:	
At Months 1, 2, 6 and 7	

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	113		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Month 1 (N=240, 112)	28.8 (16.8 to 49.2)	28.7 (9.4 to 87.8)		
Month 2 (N=240, 113)	17.6 (11.1 to 27.8)	29.4 (21.6 to 40.1)		
Month 6 (N=239, 113)	18.8 (14.7 to 24.1)	90 (68.6 to 117.9)		
Month 7 (N=241, 113)	2738.5 (2071.4 to 3620.5)	7238.3 (5247.3 to 9984.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seroprotected for anti-HBs antibody.

End point title	Number of subjects seroprotected for anti-HBs antibody.
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End point description:

A seroprotected subject was defined as a subject with anti-HBs antibody concentrations ≥ 10 mIU/mL.

End point type	Secondary
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End point timeframe:

At Months 1, 2 and 6.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	113		
Units: Subjects				
Month 1 (N=240, 112)	31	8		
Month 2 (N=240, 113)	27	63		
Month 6 (N=239, 113)	63	99		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited local symptoms.

End point title	Number of subjects with any and Grade 3 solicited local symptoms.
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = spontaneously painful. Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimeters (mm) of injection site.

End point type	Secondary
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End point timeframe:

During the 4-day (Day 0-3) follow-up period after each vaccination and overall.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	121		
Units: Subjects				
Any Pain; Dose 1 (N=253, 121)	121	44		
Grade 3 Pain; Dose 1 (N=253, 121)	6	3		
Any Redness; Dose 1 (N=253, 121)	30	10		
Grade 3 Redness; Dose 1 (N=253, 121)	0	1		
Any Swelling; Dose 1 (N=253, 121)	18	8		
Grade 3 Swelling; Dose 1 (N=253, 121)	2	2		
Any Pain; Dose 2 (N=252, 119)	42	38		
Grade 3 Pain; Dose 2 (N=252, 119)	3	2		

Any Redness; Dose 2 (N=252, 119)	15	15		
Grade 3 Redness; Dose 2 (N=252, 119)	1	0		
Any Swelling; Dose 2 (N=252, 119)	8	5		
Grade 3 Swelling; Dose 2 (N=252, 119)	1	0		
Any Pain; Dose 3 (N=250, 118)	106	35		
Grade 3 Pain; Dose 3 (N=250, 118)	4	1		
Any Redness; Dose 3 (N=250, 118)	29	11		
Grade 3 Redness; Dose 3 (N=250, 118)	0	0		
Any Swelling; Dose 3 (N=250, 118)	14	6		
Grade 3 Swelling; Dose 3 (N=250, 118)	0	0		
Any Pain; Across Doses (N=253, 121)	155	74		
Grade 3 Pain; Across Doses (N=253,121)	8	6		
Any Redness; Across Doses (N=253,121)	50	28		
Grade 3 Redness; Across Doses (N=253, 121)	0	1		
Any Swelling; Across Doses (N=253,121)	27	15		
Grade 3 Swelling; Across Doses (N=253, 121)	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited general symptoms.

End point title	Number of subjects with any, grade 3 and related solicited general symptoms.
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End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache, and fever. Any was defined as incidence of the specified symptoms regardless of intensity or relationship to study vaccine. Gastrointestinal symptoms included nausea, vomiting, diarrhea and abdominal pain. Grade 3 fever was defined as fever (axillary temperature) > 38.5°C. Grade 3 symptoms were defined as symptoms which prevented normal everyday activities. Related = general symptom assessed by the investigator as causally related to the vaccination.

End point type	Secondary
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End point timeframe:

During the 4-day (Day 0-3) follow-up period after each vaccination and overall.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	121		
Units: Subjects				
Any Fatigue; Dose 1 (N=253, 121)	50	26		
Grade 3 Fatigue; Dose 1 (N=253, 121)	1	1		
Related Fatigue; Dose 1 (N=253, 121)	29	16		
Any Gastrointestinal; Dose 1 (N=253,121)	26	4		

Grade 3 Gastrointestinal; Dose 1 (N=253, 121)	3	0		
Related Gastrointestinal; Dose 1 (N=253, 121)	11	3		
Any Headache; Dose 1 (N=253, 121)	57	29		
Grade 3 Headache; Dose 1 (N=253,121)	0	1		
Related Headache; Dose 1 (N=253,121)	33	15		
Any Temperature; Dose 1 (N=253,121)	4	2		
Grade 3 Temperature; Dose 1 (N=253,121)	0	0		
Related Temperature; Dose 1 (N=253,121)	3	2		
Any Fatigue; Dose 2 (N=252, 119)	37	18		
Grade 3 Fatigue; Dose 2 (N=252, 119)	2	0		
Related Fatigue; Dose 2 (N=252, 119)	23	13		
Any Gastrointestinal; Dose 2 (N=252,119)	20	7		
Grade 3 Gastrointestinal; Dose 2(N=252, 119)	0	0		
Related Gastrointestinal; Dose 2 (N=252, 119)	7	5		
Any Headache; Dose 2 (N=252, 119)	40	21		
Grade 3 Headache; Dose 2 (N=252,119)	0	0		
Related Headache; Dose 2 (N=252,119)	24	11		
Any Temperature; Dose 2 (N=252,119)	5	5		
Grade 3 Temperature; Dose 2 (N=252,119)	1	0		
Related Temperature; Dose 2 (N=252,119)	5	4		
Any Fatigue; Dose 3 (N=250, 118)	49	20		
Grade 3 Fatigue; Dose 3 (N=250, 118)	3	2		
Related Fatigue; Dose 3 (N=250, 118)	30	8		
Any Gastrointestinal; Dose 3 (N=250,118)	17	14		
Grade 3 Gastrointestinal; Dose 3 (N=250, 118)	3	2		
Related Gastrointestinal; Dose 3 (N=250, 118)	6	6		
Any Headache; Dose 3 (N=250, 118)	36	20		
Grade 3 Headache; Dose 3 (N=250,118)	1	1		
Related Headache; Dose 3 (N=250,118)	22	12		
Any Temperature; Dose 3 (N=250,118)	13	9		
Grade 3 Temperature; Dose 3 (N=250,118)	1	0		
Related Temperature; Dose 3 (N=250,118)	7	5		
Any Fatigue; Across Doses (N=253,121)	77	46		
Grade 3 Fatigue; Across Doses (N=253,121)	4	3		
Related Fatigue; Across Doses (N=253,121)	51	30		
Any Gastrointestinal; Across Doses (N=253, 121)	36	21		
Grade 3 Gastrointestinal; Across Doses (N=253,121)	6	2		

Related Gastrointestinal; Across Doses (N=253,121)	17	14		
Any Headache; Across Doses (N=253,121)	78	46		
Grade 3 Headache; Across Doses (N=253, 121)	1	2		
Related Headache; Across Doses (N=253, 121)	49	30		
Any Temperature; Across Doses (N=253, 121)	17	14		
Grade 3 Temperature; Across Doses (N=253, 121)	1	0		
Related Temperature; Across Doses (N=253, 121)	10	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related unsolicited adverse events (AEs).

End point title	Number of subjects reporting any, grade 3 and related unsolicited adverse events (AEs).
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End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

End point type	Secondary
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End point timeframe:

During the 31-day (Day 0-30) follow-up period after each vaccination and overall.

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	125		
Units: Subjects				
Any AE(s)	112	54		
Grade 3 AE(s)	31	15		
Related AE(s)	9	1		

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).
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that resulted in death, were life

threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary
End point timeframe:	
During the entire study period (Month 0 to Month 66).	

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	125		
Units: Subjects				
Any SAE(s)	4	1		

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:	
Serious adverse events (SAEs) assessed include medical occurrences that resulted in death, were life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject.	
End point type	Secondary
End point timeframe:	
At Month 30, Month 42, Month 54 & Month 66.	

End point values	2-dose Engerix	3-dose Engerix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	88		
Units: Subjects				
Month 30 (N=179, 88)	0	0		
Month 42 (N=174, 84)	0	0		
Month 54 (N=166, 79)	0	0		
Month 66 (N=158, 76)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events: during the entire study period (Month 0-66),

Solicited local and general symptoms: During the 4-day (Days 0-3) post vaccination period and unsolicited adverse events: up to Month 7.

Adverse event reporting additional description:

Non-serious adverse events were not assessed during the long term follow-up period (Month 30-66).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.1
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Reporting groups

Reporting group title	2-dose Engerix
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Reporting group description:

Subjects received 2 doses of adult (thiomersal-free) HBV formulation, one at 0 and 6 months, respectively and placebo (physiological saline) at 1 month.

Reporting group title	3-dose Engerix
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Reporting group description:

Subjects received 3 doses of pediatric (preservative-free) HBV formulation one at 0, 1 and 6 months, respectively.

Serious adverse events	2-dose Engerix	3-dose Engerix	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 257 (1.56%)	1 / 125 (0.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	1 / 257 (0.39%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 125 (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			
Arthritis			

subjects affected / exposed	1 / 257 (0.39%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection bacterial			
subjects affected / exposed	1 / 257 (0.39%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	2-dose Engerix	3-dose Engerix	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	155 / 257 (60.31%)	74 / 125 (59.20%)	
General disorders and administration site conditions			
Pain; Dose 1			
alternative assessment type: Systematic			
subjects affected / exposed ^[1]	121 / 253 (47.83%)	44 / 121 (36.36%)	
occurrences (all)	121	44	
Redness; Dose 1			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 257 (11.67%)	10 / 125 (8.00%)	
occurrences (all)	30	10	
Swelling; Dose 1			
alternative assessment type: Systematic			
subjects affected / exposed	18 / 257 (7.00%)	8 / 125 (6.40%)	
occurrences (all)	18	8	
Pain; Dose 2			
alternative assessment type: Systematic			
subjects affected / exposed ^[2]	42 / 252 (16.67%)	38 / 119 (31.93%)	
occurrences (all)	42	38	
Redness; Dose 2			
alternative assessment type: Systematic			
subjects affected / exposed ^[3]	15 / 252 (5.95%)	15 / 119 (12.61%)	
occurrences (all)	15	15	

Swelling; Dose 2		
alternative assessment type: Systematic		
subjects affected / exposed ^[4]	8 / 252 (3.17%)	5 / 119 (4.20%)
occurrences (all)	8	5
Pain; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[5]	106 / 250 (42.40%)	35 / 118 (29.66%)
occurrences (all)	106	35
Redness; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[6]	29 / 250 (11.60%)	11 / 118 (9.32%)
occurrences (all)	29	11
Swelling; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[7]	14 / 250 (5.60%)	6 / 118 (5.08%)
occurrences (all)	14	6
Pain; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed ^[8]	155 / 253 (61.26%)	74 / 121 (61.16%)
occurrences (all)	155	74
Redness; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed ^[9]	50 / 253 (19.76%)	28 / 121 (23.14%)
occurrences (all)	50	28
Swelling; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed ^[10]	27 / 253 (10.67%)	15 / 121 (12.40%)
occurrences (all)	27	15
Fatigue; Dose 1		
alternative assessment type: Systematic		
subjects affected / exposed ^[11]	50 / 253 (19.76%)	26 / 121 (21.49%)
occurrences (all)	50	26
Fatigue; Dose 2		
alternative assessment type: Systematic		

subjects affected / exposed ^[12]	37 / 252 (14.68%)	18 / 119 (15.13%)
occurrences (all)	37	18
Fatigue; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[13]	49 / 250 (19.60%)	20 / 118 (16.95%)
occurrences (all)	49	20
Fatigue; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed ^[14]	77 / 253 (30.43%)	46 / 121 (38.02%)
occurrences (all)	77	46
Headache; Dose 1		
alternative assessment type: Systematic		
subjects affected / exposed ^[15]	57 / 253 (22.53%)	29 / 121 (23.97%)
occurrences (all)	57	29
Headache; Dose 2		
alternative assessment type: Systematic		
subjects affected / exposed ^[16]	40 / 252 (15.87%)	21 / 119 (17.65%)
occurrences (all)	40	21
Headache, Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[17]	36 / 250 (14.40%)	20 / 118 (16.95%)
occurrences (all)	36	20
Headache; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed ^[18]	78 / 253 (30.83%)	46 / 121 (38.02%)
occurrences (all)	78	46
Fever; Dose 1		
alternative assessment type: Systematic		
subjects affected / exposed ^[19]	4 / 253 (1.58%)	2 / 121 (1.65%)
occurrences (all)	4	2
Fever; Dose 2		
alternative assessment type: Systematic		
subjects affected / exposed ^[20]	5 / 252 (1.98%)	5 / 119 (4.20%)
occurrences (all)	5	5

Fever; Dose 3 alternative assessment type: Systematic subjects affected / exposed ^[21] occurrences (all)	13 / 250 (5.20%) 13	9 / 118 (7.63%) 9	
Fever; Across Doses alternative assessment type: Systematic subjects affected / exposed ^[22] occurrences (all)	17 / 253 (6.72%) 17	14 / 121 (11.57%) 14	
Headache subjects affected / exposed occurrences (all)	28 / 257 (10.89%) 28	10 / 125 (8.00%) 10	
Gastrointestinal disorders Gastrointestinal symptoms; Dose 1 alternative assessment type: Systematic subjects affected / exposed ^[23] occurrences (all)	26 / 253 (10.28%) 26	4 / 121 (3.31%) 4	
Gastrointestinal symptoms; Dose 2 alternative assessment type: Systematic subjects affected / exposed ^[24] occurrences (all)	20 / 252 (7.94%) 20	7 / 119 (5.88%) 7	
Gastrointestinal symptoms; Dose 3 alternative assessment type: Systematic subjects affected / exposed ^[25] occurrences (all)	17 / 250 (6.80%) 17	14 / 118 (11.86%) 14	
Gastrointestinal symptoms; Across Doses alternative assessment type: Systematic subjects affected / exposed occurrences (all)	36 / 257 (14.01%) 36	21 / 125 (16.80%) 21	
Respiratory, thoracic and mediastinal disorders Pharyngitis subjects affected / exposed occurrences (all)	15 / 257 (5.84%) 15	5 / 125 (4.00%) 5	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	26 / 257 (10.12%) 26	22 / 125 (17.60%) 22	
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Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[23] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, non-evaluable measurements were not replaced. Therefore, an analysis excluded data points of subjects with missing or non-evaluable measurements (e.g., analysis of solicited symptoms excluded vaccinated subjects without documented symptom sheets).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2004	<p>The clinical study protocol 103860/280 (HBV-280) was designed to evaluate the immunogenicity of 3-dose primary vaccination course of preservative-free Engerix™-B (10 µg HBsAg) administered at 0, 1, 6 months compared to a 2-dose vaccination course of thiomersal-free Engerix™-B (20 µg HBsAg) administered at 0, 6 months.</p> <p>Results from the primary study have shown the vaccine to be safe with a good immune response. Anti-HBs seroprotection rate was 96.7% in group receiving thiomersal-free Engerix™-B (20 µg HBsAg) and 98.2% in group receiving preservative-free Engerix™-B (10 µg HBsAg), one month after the primary vaccination course i.e. at Month 7.</p> <p>The protocol is currently being amended to evaluate the persistence of humoral immune response at Month 30, 42, 54 and 66 after the first dose of primary vaccination.</p> <p>To evaluate the long-term antibody persistence, volunteers will be bled at Months 30, 42, 54 and 66 (intervals to be respected at ± 2 months) after the first vaccine dose of the primary vaccination course, to determine their anti-HBs antibody titres.</p> <p>If a subject loses seroprotective titres for anti-HBs antibodies (i.e. titres < 10 mIU/ml) at the long-term blood sampling time point (i.e. Month 30, 42, 54 and 66), he/ she will be offered an additional vaccine dose of commercial Engerix™-B (to be administered between 6 to 12 months after Month 66 time point), in order to assess the immune memory after a primary three-dose schedule of preservative-free Engerix™-B (10 µg HBsAg) or primary two -dose schedule of thiomersal-free Engerix™-B (20 µg HBsAg) administered at 0, 6 months (see Section 5.3). A blood sample will be taken on the day of the additional vaccination and after one month to evaluate the immune response following this vaccination.</p>
08 December 2006	<p>The protocol is currently being amended to state that subjects who had antibody concentrations <10 mIU/ml will not receive an additional vaccine dose in this study, as all subjects in this study (irrespective of their seroprotective status), will be approached to participate in another study, 108988 (HBV-314 BST:280). Study HBV-314, will be conducted in subjects primed in study HBV-280, after completion of the last follow-up (Month 66), and will evaluate immunological memory to hepatitis B in terms of the ability to mount an anamnestic response to an additional vaccine dose of hepatitis B vaccine . Thus, all study procedures related to additional vaccine dose in the second protocol amendment of study 103860 (HBV-280) dated 2 February 2004 are not applicable.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported