

**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 | v2 (current) |
| This version publication date | 28 March 2023 |
| First version publication date | 01 August 2015 |
| Version creation reason | • Correction of full data set Correction of full data set and alignment between registries. |

Trial information**Trial identification**

| | |
|-----------------------|------------------------------------|
| Sponsor protocol code | 103860/280,101695,101696,/697,/698 |
|-----------------------|------------------------------------|

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 vaccination.

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 |
|------------------|----------------|

Arm description:

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

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------------------------------|
| 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 |
| 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. | |

| 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 20 μ g 2-dose vs. HBV 10 μ g 3-dose |
| Statistical analysis description: Non-inferiority of the immune response induced by thiomersal-free HBV (20 μ g HBsAg per dose) administered as a 2-dose vaccination schedule compared to preservative-free HBV (10 μ g 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] |
|-----------------|--|

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 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] |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 |
|-----------------|--|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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) |
|-----------------|--|

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 |
|----------------|-----------|

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) |
|-----------------|---|

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).
The total number of participants at risk is the number of participants with at least one documented dose.
The total number of participants at risk is the number of participants with at least one documented dose.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 8.1 |

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 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 ^[2] | 30 / 253 (11.86%) | 10 / 121 (8.26%) | |
| occurrences (all) | 30 | 10 | |
| Swelling; Dose 1 | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[3] | 18 / 253 (7.11%) | 8 / 121 (6.61%) | |
| occurrences (all) | 18 | 8 | |
| Pain; Dose 2 | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[4] | 42 / 252 (16.67%) | 38 / 119 (31.93%) | |
| occurrences (all) | 42 | 38 | |
| Redness; Dose 2 | | | |
| alternative assessment type: Systematic | | | |

| | | |
|---|--------------------|-------------------|
| subjects affected / exposed ^[5] | 15 / 252 (5.95%) | 15 / 119 (12.61%) |
| occurrences (all) | 15 | 15 |
| Swelling; Dose 2 | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[6] | 8 / 252 (3.17%) | 5 / 119 (4.20%) |
| occurrences (all) | 8 | 5 |
| Pain; Dose 3 | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[7] | 106 / 250 (42.40%) | 35 / 118 (29.66%) |
| occurrences (all) | 106 | 35 |
| Redness; Dose 3 | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[8] | 29 / 250 (11.60%) | 11 / 118 (9.32%) |
| occurrences (all) | 29 | 11 |
| Swelling; Dose 3 | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[9] | 14 / 250 (5.60%) | 6 / 118 (5.08%) |
| occurrences (all) | 14 | 6 |
| Pain; Across Doses | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[10] | 155 / 253 (61.26%) | 74 / 121 (61.16%) |
| occurrences (all) | 155 | 74 |
| Redness; Across Doses | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[11] | 50 / 253 (19.76%) | 28 / 121 (23.14%) |
| occurrences (all) | 50 | 28 |
| Swelling; Across Doses | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[12] | 27 / 253 (10.67%) | 15 / 121 (12.40%) |
| occurrences (all) | 27 | 15 |
| Fatigue; Dose 1 | | |
| alternative assessment type: Systematic | | |
| subjects affected / exposed ^[13] | 50 / 253 (19.76%) | 26 / 121 (21.49%) |
| occurrences (all) | 50 | 26 |

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

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed ^[22] occurrences (all) | 5 / 252 (1.98%) 5 | 5 / 119 (4.20%) 5 | |
| Fever; Dose 3 alternative assessment type: Systematic subjects affected / exposed ^[23] occurrences (all) | 13 / 250 (5.20%) 13 | 9 / 118 (7.63%) 9 | |
| Fever; Across Doses alternative assessment type: Systematic subjects affected / exposed ^[24] 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 ^[25] occurrences (all) | 26 / 253 (10.28%) 26 | 4 / 121 (3.31%) 4 | |
| Gastrointestinal symptoms; Dose 2 alternative assessment type: Systematic subjects affected / exposed ^[26] occurrences (all) | 20 / 252 (7.94%) 20 | 7 / 119 (5.88%) 7 | |
| Gastrointestinal symptoms; Dose 3 alternative assessment type: Systematic subjects affected / exposed ^[27] occurrences (all) | 17 / 250 (6.80%) 17 | 14 / 118 (11.86%) 14 | |
| Gastrointestinal symptoms; Across Doses alternative assessment type: Systematic subjects affected / exposed ^[28] occurrences (all) | 36 / 253 (14.23%) 36 | 21 / 121 (17.36%) 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 | 26 / 257 (10.12%) | 22 / 125 (17.60%) | |
| occurrences (all) | 26 | 22 | |

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

[22] - 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).

[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).

[26] - 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).

[27] - 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).

[28] - 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 | The protocol was amended to include the addition of long term follow-up (LTFU) study visits at Month 30 (Visit 6), Month 42 (Visit 7), Month 54 (Visit 8) and Month 66 (Visit 9) after the first dose of primary vaccination, as well as the administration of an additional vaccination and blood sampling at Visits 10 and 11 respectively for subjects who had anti-HBs antibody concentrations < 10 mIU/ml. |
| 08 December 2006 | The protocol was amended and stated that subjects who had anti-HBs antibody concentrations < 10 mIU/ml would not receive any additional vaccine dose as all the subjects in the study (irrespective of their seroprotective status) would be approached to participate in the 108988 (HBV-314 BST:280) study. In this study, all subjects who were primed in the HBV-280 study would receive an additional vaccine dose to evaluate immunological memory to hepatitis B antigen. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported