



## Clinical trial results:

**An open, phase IV, single-group, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B (HBV) vaccine challenge in adolescents 12-13 years of age who were vaccinated in infancy with GSK Biologicals' HBV vaccine (Engerix™-B).**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-012117-21 |
| Trial protocol           | DE             |
| Global end of trial date | 07 April 2010  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 27 April 2016    |
| First version publication date | 28 February 2015 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 112682 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00984139 |
| 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                                       | Final           |
| Date of interim/final analysis                       | 25 October 2010 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 07 April 2010   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To assess the anti-HBs antibody response to a challenge dose of HBV vaccine (Engerix-B Kinder) in subjects 12-13 years of age, vaccinated with three doses of Engerix-B in infancy.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of the vaccine.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 12 October 2009 |
| 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 | Germany: 306 |
| Worldwide total number of subjects   | 306          |
| EEA total number of subjects         | 306          |

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)                 | 306 |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### 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

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Engerix-B Group |
|------------------|-----------------|

Arm description:

Subjects who were vaccinated with 3 doses of Engerix-B in infancy and who received a single challenge dose of Engerix-B , intramuscularly in the deltoid region of the non-dominant arm, at 12-13 years of age (Day 0).

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | Biological: Engerix™-B Kinder |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Injection                     |
| Routes of administration               | Intramuscular use             |

Dosage and administration details:

All subjects received a single-dose of HBV vaccine at 12-13 years of age (Day 0). The vaccine was administered as an intramuscular injection into the deltoid region of the non-dominant arm.

|                                       |                 |
|---------------------------------------|-----------------|
| <b>Number of subjects in period 1</b> | Engerix-B Group |
| Started                               | 306             |
| Completed                             | 306             |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Engerix-B Group |
|-----------------------|-----------------|

Reporting group description:

Subjects who were vaccinated with 3 doses of Engerix-B in infancy and who received a single challenge dose of Engerix-B , intramuscularly in the deltoid region of the non-dominant arm, at 12-13 years of age (Day 0).

| Reporting group values                                | Engerix-B Group | Total |  |
|---|-----------------|-------|--|
| Number of subjects                                    | 306             | 306   |  |
| Age categorical<br>Units: Subjects                    |                 |       |  |
| In utero  |                 | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |                 | 0     |  |
| Newborns (0-27 days)                                  |                 | 0     |  |
| Infants and toddlers (28 days-23<br>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<br>Units: years                        |                 |       |  |
| arithmetic mean                                       | 12.4            |       |  |
| standard deviation                                    | ± 0.49          | -     |  |
| Gender categorical<br>Units: Subjects                 |                 |       |  |
| Female  | 152             | 152   |  |
| Male  | 154             | 154   |  |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | Engerix-B Group |
| Reporting group description:<br>Subjects who were vaccinated with 3 doses of Engerix-B in infancy and who received a single challenge dose of Engerix-B , intramuscularly in the deltoid region of the non-dominant arm, at 12-13 years of age (Day 0). |                 |

### Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations as measured by ELISA equal to or above cut-off value

|                 |   |
|-----------------|---|
| End point title | Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations as measured by ELISA equal to or above cut-off value <sup>[1]</sup> |
|-----------------|---|

End point description:

The cut-off value was defined as 100 milli-international units per milliliter (mIU/mL).

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

End point timeframe:

One month after the challenge dose (Month 1)

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                                   | Engerix-B Group |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 284             |  |  |  |
| Units: Subjects                                    |                 |  |  |  |
| post challenge dose 100 mIU/mL<br>[Units:subjects] | 266             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations as measured by ChemiLuminescence ImmunoAssay (CLIA) equal to or above cut-off value.

|                 |   |
|-----------------|---|
| End point title | Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations as measured by ChemiLuminescence ImmunoAssay (CLIA) equal to or above cut-off value. <sup>[2]</sup> |
|-----------------|---|

End point description:

The cut-off value was defined as 100 milli-international units per milliliter (mIU/mL).

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

End point timeframe:

One month after the challenge dose (Month 1)

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                                   | Engerix-B Group |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 276             |  |  |  |
| Units: Subjects                                    |                 |  |  |  |
| post challenge dose 100 mIU/mL<br>[Units:Subjects] | 257             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anti-HBs antibody concentrations as measured by ELISA equal to or above cut-off values

|                 |  |
|-----------------|--|
| End point title | Number of subjects with anti-HBs antibody concentrations as measured by ELISA equal to or above cut-off values |
|-----------------|--|

End point description:

The cut-off values were defined as 3.3 mIU/mL, 10 mIU/mL and 100 mIU/mL. Note: the number of subjects with anti-HBs antibody concentrations equal to or above 100 mIU/mL on month post-challenge dose data are presented as a primary outcome measure.

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

End point timeframe:

Before (Day 0) and one month (Month 1) after the challenge dose

| End point values                          | Engerix-B Group |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 284             |  |  |  |
| Units: Subjects                           |                 |  |  |  |
| pre challenge dose 3.3 mIU/mL<br>(N=282)  | 259             |  |  |  |
| post challenge dose 3.3 mIU/mL<br>(N=284) | 283             |  |  |  |
| pre challenge dose 10 mIU/mL (N=282)      | 220             |  |  |  |
| post challenge dose 10 mIU/mL<br>(N=284)  | 281             |  |  |  |
| pre challenge dose 100 mIU/mL<br>(N=282)  | 70              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of subjects with anti-HBs antibody concentrations as measured by CLIA equal to or above cut-off values**

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|                 |   |
|-----------------|---|
| End point title | Number of subjects with anti-HBs antibody concentrations as measured by CLIA equal to or above cut-off values |
|-----------------|---|

End point description:

The cut-off values were defined as 6.2 mIU/mL, 10 mIU/mL and 100 mIU/mL. Note: the number of subjects with anti-HBs antibody concentrations equal to or above 100 mIU/mL on month post-challenge dose data are presented as a primary outcome measure.

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

End point timeframe:

Before (Day 0) and one month (Month 1) after the challenge dose

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| End point values                       | Engerix-B Group |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 279             |  |  |  |
| Units: Subjects                        |                 |  |  |  |
| pre challenge dose 6.2 mIU/mL (N=279)  | 201             |  |  |  |
| post challenge dose 6.2 mIU/mL (N=276) | 271             |  |  |  |
| pre challenge dose 10 mIU/mL (N=279)   | 181             |  |  |  |
| post challenge dose 10 mIU/mL (N=276)  | 271             |  |  |  |
| pre challenge dose 100 mIU/mL (N=279)  | 67              |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of subjects with solicited local and general symptoms**

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|                 |  |
|-----------------|--|
| End point title | Number of subjects with solicited local and general symptoms |
|-----------------|--|

End point description:

Solicited local symptoms were pain, redness and swelling. Solicited general symptoms were fatigue, gastrointestinal symptoms, headache and fever. Fever was defined as axillary temperature greater than or equal to 37.5 degrees Celsius.

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

End point timeframe:

During the 4-day (Day 0-3) follow-up period following the challenge dose vaccination

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| End point values            | Engerix-B Group |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 306             |  |  |  |
| Units: Subjects             |                 |  |  |  |
| pain                        | 104             |  |  |  |
| redness                     | 56              |  |  |  |
| swelling                    | 26              |  |  |  |
| fatigue                     | 63              |  |  |  |
| gastrointestinal symptoms   | 14              |  |  |  |
| headache                    | 56              |  |  |  |
| fever                       | 9               |  |  |  |

## 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:  |   |
| SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| After the challenge dose of the vaccine (Day 0) up to the study end (Month 1)   |   |

| End point values                                   | Engerix-B Group |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 306             |  |  |  |
| Units: Subjects                                    |                 |  |  |  |
| Number of subjects with serious adverse events [Un | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with unsolicited adverse events (AEs)

|   |  |
|---|--|
| End point title   | Number of subjects with unsolicited adverse events (AEs) |
| End point description:  |  |
| Unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. |  |
| End point type  | Secondary  |



End point timeframe:

During the 31-day (Day 0-30) follow-up period following the challenge dose vaccination

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                            | Engerix-B Group |  |  |  |
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 306             |  |  |  |
| Units: Subjects                                    |                 |  |  |  |
| Number of subjects with unsolicited adverse events | 64              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anamnestic response to the challenge dose as measured by ELISA.

|                 |   |
|-----------------|---|
| End point title | Number of subjects with anamnestic response to the challenge dose as measured by ELISA. |
|-----------------|---|

End point description:

Anamnestic response was defined as: - At least (i.e. greater than or equal to) a 4-fold rise in post-challenge vaccine dose anti-HBs antibody concentrations in subjects seropositive (i.e. with anti-HBs antibody concentration equal to or greater than 3.3 mIU/mL) at the pre-challenge dose time point. - Post-challenge dose anti-HBs antibody concentrations equal to or greater than 10 mIU/mL in subjects seronegative (i.e. with anti-HBs antibody concentrations less than 3.3 mIU/mL) at the pre-challenge dose time point.

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

End point timeframe:

One month after the challenge dose (Month 1)

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                         | Engerix-B Group |  |  |  |
| Subject group type                              | Reporting group |  |  |  |
| Number of subjects analysed                     | 282             |  |  |  |
| Units: Subjects                                 |                 |  |  |  |
| post challenge dose 3.3 mIU/mL [Units:subjects] | 274             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anamnestic response to the challenge dose as measured by CLIA.

|  |  |
|--|--|
| End point title  | Number of subjects with anamnestic response to the challenge dose as measured by CLIA. |
| End point description:   |  |
| Anamnestic response was defined as: - At least (i.e. greater than or equal to) a 4-fold rise in post-challenge vaccine dose anti-HBs antibody concentrations in subjects seropositive (i.e. with anti-HBs antibody concentration $\geq 6.2$ mIU/mL) at the pre-challenge dose time point. - Post-challenge dose anti-HBs antibody concentrations equal to or greater than 10 mIU/mL in subjects seronegative (i.e. with anti-HBs antibody concentrations $< 6.2$ mIU/mL) at the pre-challenge dose time point. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| One month after the challenge dose (Month 1)   |  |

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                            | Engerix-B Group |  |  |  |
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 271             |  |  |  |
| Units: Subjects                                    |                 |  |  |  |
| post challenge dose 6.2 mIU/mL<br>[Units:Subjects] | 267             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited local and general symptoms = During the 4-day (Day 0 to Day 3) post-vaccination period.

Unsolicited AEs = During the 31-day (Day 0-30) follow-up period after the HBV challenge dose.

Adverse event reporting additional description:

For the systematically assessed other (non-serious) adverse events, number of participants at risk included those from Total Vaccinated cohort who had the symptom sheet completed.

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 13 |
|--------------------|----|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Engerix-B Group |
|-----------------------|-----------------|

Reporting group description:

Subjects who were vaccinated with 3 doses of Engerix-B in infancy and who received a single challenge dose of Engerix-B , intramuscularly in the deltoid region of the non-dominant arm, at 12-13 years of age (Day 0).

| Serious adverse events                            | Engerix-B Group |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 0 / 306 (0.00%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |

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

| Non-serious adverse events                            | Engerix-B Group    |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 104 / 306 (33.99%) |  |  |
| General disorders and administration site conditions  |                    |  |  |
| Pain  |                    |  |  |
| alternative assessment type: Systematic               |                    |  |  |
| subjects affected / exposed                           | 104 / 306 (33.99%) |  |  |
| occurrences (all)                                     | 104                |  |  |
| Redness   |                    |  |  |
| alternative assessment type: Systematic               |                    |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                | 56 / 306 (18.30%) |  |  |
| occurrences (all)                          | 56                |  |  |
| Swelling                                   |                   |  |  |
| alternative assessment type:<br>Systematic |                   |  |  |
| subjects affected / exposed                | 26 / 306 (8.50%)  |  |  |
| occurrences (all)                          | 26                |  |  |
| Fatigue                                    |                   |  |  |
| alternative assessment type:<br>Systematic |                   |  |  |
| subjects affected / exposed                | 63 / 306 (20.59%) |  |  |
| occurrences (all)                          | 63                |  |  |
| Headache                                   |                   |  |  |
| alternative assessment type:<br>Systematic |                   |  |  |
| subjects affected / exposed                | 56 / 306 (18.30%) |  |  |
| occurrences (all)                          | 56                |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported