



Clinical trial results:

An open, phase IV, multicentre, study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B vaccine challenge in healthy children aged 11-12 years, previously vaccinated with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™) or GSK Biologicals' DTPa-IPV/Hib and HBV (Engerix™- B) vaccines at the ages of 3, 5 and 11 months in clinical trial DTPa-HBV-IPV-031 (217744/031).

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-016911-39 |
| Trial protocol | SK |
| Global end of trial date | 26 November 2010 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 18 April 2016 |
| First version publication date | 30 October 2014 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 113954 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01138098 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, 1330 |
| Public contact | Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, +44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, +44 2089904466, 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 | 20 June 2011 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 June 2010 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 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 in subjects aged 11-12 years, vaccinated in infancy with three doses of Infanrix hexa or Engerix-B at 3, 5 and 11 months of age.

Protection of trial subjects:

Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 07 June 2010 |
| 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 | Slovakia: 185 |
| Worldwide total number of subjects | 185 |
| EEA total number of subjects | 185 |

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) | 185 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

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 | Infanrix-hexa/Engerix-B Group |

Arm description:

Subjects aged 11-12 year old received 3 doses of Infanrix-hexa vaccine in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

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

Dosage and administration details:

Intramuscular, single dose

| | |
|------------------|----------------------------------|
| Arm title | Infanrix-IPV+Hib/Engerix-B Group |
|------------------|----------------------------------|

Arm description:

Subjects aged 11-12 year old received 3 doses of Infanrix-IPV+Hib and Engerix-B vaccines in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Engerix™-B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Intramuscular, single dose

| Number of subjects in period 1 | Infanrix- hexa/Engerix-B Group | Infanrix- IPV+Hib/Engerix-B Group |
|---------------------------------------|--------------------------------------|---|
| Started | 95 | 90 |
| Completed | 95 | 90 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Infanrix-hexa/Engerix-B Group |
|-----------------------|-------------------------------|

Reporting group description:

Subjects aged 11-12 year old received 3 doses of Infanrix-hexa vaccine in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Infanrix-IPV+Hib/Engerix-B Group |
|-----------------------|----------------------------------|

Reporting group description:

Subjects aged 11-12 year old received 3 doses of Infanrix-IPV+Hib and Engerix-B vaccines in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

| Reporting group values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | Total |
|--|-------------------------------|----------------------------------|-------|
| Number of subjects | 95 | 90 | 185 |
| 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 | | | |
| geometric mean | 11.3 | 11.3 | |
| standard deviation | ± 0.46 | ± 0.47 | - |
| Gender categorical Units: Subjects | | | |
| Female | 45 | 35 | 80 |
| Male | 50 | 55 | 105 |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Infanrix-hexa/Engerix-B Group |
| Reporting group description: Subjects aged 11-12 year old received 3 doses of Infanrix-hexa vaccine in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm. | |
| Reporting group title | Infanrix-IPV+Hib/Engerix-B Group |
| Reporting group description: Subjects aged 11-12 year old received 3 doses of Infanrix-IPV+Hib and Engerix-B vaccines in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm. | |

Primary: Number of subjects with anti-hepatitis B (anti-HBs) antibody concentration equal to or above (\geq) 100 milli-International units per milliliter (mIU/mL)

| | |
|---|--|
| End point title | Number of subjects with anti-hepatitis B (anti-HBs) antibody concentration equal to or above (\geq) 100 milli-International units per milliliter (mIU/mL) ^[1] |
| End point description: A decrease in the specificity of the anti-HB enzyme-linked immunosorbent assay (ELISA) had been observed in some studies for low levels of antibody (10-100 mIU/mL). All the available blood samples initially tested with ELISA were re-tested using the Chemi Luminescence Immuno Assay (CLIA) approved by the US Food and Drug Administration (FDA). The table shows updated results following partial or complete retesting/reanalysis. | |
| End point type | Primary |
| End point timeframe: One month after a challenge dose of Engerix™-B vaccine | |
| 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 | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 89 | | |
| Units: Subjects | | | | |
| Anti-HBs \geq 100 mIU/mL | 88 | 84 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with an anamnestic response to a challenge dose

| | |
|-----------------|--|
| End point title | Number of subjects with an anamnestic response to a challenge dose |
|-----------------|--|

End point description:

The anamnestic response was defined as: at least (\geq) a 4-fold rise in post-challenge dose anti-HBs antibody concentrations in subjects seropositive at the pre-challenge dose time point. - Post-challenge dose anti-HBs antibody concentrations ≥ 10 mIU/mL in seronegative subjects at the pre-challenge dose time point. A seropositive/seronegative subject is a subject with anti-HBs antibody concentration \geq /lower than ($<$) 6.2 mIU/mL. A decrease in the specificity of the anti-HB ELISA had been observed in some studies for low levels of antibody (10-100 mIU/mL). All the available blood samples initially tested with ELISA were re-tested using the Chemi Luminescence Immuno Assay (CLIA) approved by the US Food and Drug Administration (FDA). The table shows updated results following partial or complete retesting/reanalysis and the initial 3.3 mIU/mL seropositivity cut-off was revised into the new 6.2 mIU/mL cut-off.

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

End point timeframe:

Before and one month after a challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 89 | | |
| Units: Subjects | | | | |
| Anamnestic response | 91 | 86 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentration ≥ 6.2 mIU/mL

| | |
|-----------------|---|
| End point title | Number of subjects with anti-HBs antibody concentration ≥ 6.2 mIU/mL |
|-----------------|---|

End point description:

A seropositive subject was defined as a subject with anti-HBs antibody concentration \geq the 6.2 mIU/mL cut-off. A decrease in the specificity of the anti-HB ELISA had been observed in some studies for low levels of antibody (10-100 mIU/mL). All the available blood samples initially tested with ELISA were re-tested using the Chemi Luminescence Immuno Assay (CLIA) approved by the US Food and Drug Administration (FDA). The table shows updated results following partial or complete retesting/reanalysis and the initial 3.3 mIU/mL seropositivity cut-off was revised into the new 6.2 mIU/mL cut-off.

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

End point timeframe:

Before and one month after a challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|---|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 89 | | |
| Units: Subjects | | | | |
| ≥ 6.2 mIU/mL [pre-challenge dose] (N=95, 89) | 53 | 57 | | |

| | | | | |
|--|----|----|--|--|
| ≥ 6.2 mIU/mL [post-challenge dose] (N=94, 89) | 92 | 88 | | |
|--|----|----|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentration ≥ 10 mIU/mL

| | |
|-----------------|---|
| End point title | Number of subjects with anti-HBs antibody concentration ≥ 10 mIU/mL |
|-----------------|---|

End point description:

A seroprotected subject was defined as a subject with anti-HBs antibody concentration ≥ 10 mIU/mL. A decrease in the specificity of the anti-HB enzyme-linked immunosorbent assay (ELISA) had been observed in some studies for low levels of antibody (10-100 mIU/mL). All the available blood samples initially tested with ELISA were re-tested using the Chemi Luminescence Immuno Assay (CLIA) approved by the US Food and Drug Administration (FDA). The table shows updated results following partial or complete retesting/reanalysis.

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

End point timeframe:

Before and one month after a challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|---|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 89 | | |
| Units: Subjects | | | | |
| ≥ 10 mIU/mL [pre-challenge dose] (N=95, 89) | 46 | 52 | | |
| ≥ 10 mIU/mL [post-challenge dose] (N=94, 89) | 91 | 88 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentration ≥ 100 mIU/mL

| | |
|-----------------|--|
| End point title | Number of subjects with anti-HBs antibody concentration ≥ 100 mIU/mL |
|-----------------|--|

End point description:

A seroprotected subject was defined as a subject with anti-HBs antibody concentration ≥ 10 mIU/mL. A decrease in the specificity of the anti-HB ELISA had been observed in some studies for low levels of antibody (10-100 mIU/mL). All the available blood samples initially tested with ELISA were re-tested using the Chemi Luminescence Immuno Assay (CLIA) approved by the US Food and Drug Administration (FDA). The table shows updated results following partial or complete retesting/reanalysis.

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

End point timeframe:

Before the challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 89 | | |
| Units: Subjects | | | | |
| ≥ 100 mIU/mL [pre-challenge dose] | 14 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local symptoms

End point title Number of subjects reporting solicited local symptoms

End point description:

Solicited local symptoms assessed were pain, redness and swelling.

End point type Secondary

End point timeframe:

During the 4-day (Days 0-3) follow-up period after a challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Subjects | | | | |
| Pain | 30 | 24 | | |
| Redness | 25 | 22 | | |
| Swelling | 15 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited general symptoms

End point title Number of subjects reporting solicited general symptoms

End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal, headache and temperature (Temperature is defined as axillary temperature equal to or above 37.5 degrees Celsius (°C)).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| During the 4-day (Days 0-3) follow-up period after a challenge dose of Engerix™-B vaccine | |

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Subjects | | | | |
| Fatigue | 23 | 22 | | |
| Gastrointestinal | 9 | 9 | | |
| Headache | 19 | 14 | | |
| Temperature ≥ 37.5°C | 1 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events (AEs)

| | |
|-----------------|---|
| End point title | Number of subjects reporting unsolicited adverse events (AEs) |
|-----------------|---|

End point description:

An unsolicited adverse event is any adverse event (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) 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 (Days 0-30) follow-up period after a challenge dose of Engerix™-B vaccine

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Subjects | | | | |
| Unsolicited AEs | 5 | 7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

| | |
|-----------------|--|
| End point title | Number of subjects reporting serious adverse events (SAEs) |
|-----------------|--|

End point description:

SAEs assessed include medical occurrences that results in death, are life threatening, require hospitalization or prolongation of hospitalization, results in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subjects.

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

End point timeframe:

After the challenge dose of Engerix™-B vaccine up to the study end

| End point values | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | | |
|-----------------------------|-------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Subjects | | | | |
| SAEs | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: During the 4-day (Days 0-3) follow-up period after the challenge dose of Engerix-B vaccine. SAEs: after the challenge dose of Engerix-B vaccine up to the study end

Adverse event reporting additional description:

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 | 13.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Infanrix-hexa/Engerix-B Group |
|-----------------------|-------------------------------|

Reporting group description:

Subjects aged 11-12 year old received 3 doses of Infanrix-hexa vaccine in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Infanrix-IPV+Hib/Engerix-B Group |
|-----------------------|----------------------------------|

Reporting group description:

Subjects aged 11-12 year old received 3 doses of Infanrix-IPV+Hib and Engerix-B vaccines in the primary study (NCT01457495) and a challenge dose of Engerix-B vaccine in this study. Engerix-B was administered as a single dose intramuscularly into the deltoid region of the non-dominant arm.

| Serious adverse events | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | |
|---|-------------------------------|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (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 | Infanrix-hexa/Engerix-B Group | Infanrix-IPV+Hib/Engerix-B Group | |
|---|--------------------------------------|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 95 (31.58%) | 24 / 90 (26.67%) | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 30 / 95 (31.58%) | 24 / 90 (26.67%) | |
| occurrences (all) | 30 | 24 | |
| Redness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 25 / 95 (26.32%) | 22 / 90 (24.44%) | |
| occurrences (all) | 25 | 22 | |
| Swelling | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 15 / 95 (15.79%) | 8 / 90 (8.89%) | |
| occurrences (all) | 15 | 8 | |
| Fatigue | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 23 / 95 (24.21%) | 22 / 90 (24.44%) | |
| occurrences (all) | 23 | 22 | |
| Gastrointestinal | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 9 / 95 (9.47%) | 9 / 90 (10.00%) | |
| occurrences (all) | 9 | 9 | |
| Headache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 19 / 95 (20.00%) | 14 / 90 (15.56%) | |
| occurrences (all) | 19 | 14 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported