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	v2 (current)
This version publication date	16 September 2018
First version publication date	30 October 2014
Version creation reason	• Correction of full data set Minor corrections of the full study results.

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	26 November 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 (≥) 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 (≥) 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 scope of this primary end point was descriptive, 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 ≥ 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 (≥) 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 ≥/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 ≥ the 6.2 mIU/mLcut-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 temparature 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	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

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			
alternative assessment type: Non-systematic			
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	48 / 95 (50.53%)	43 / 90 (47.78%)	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	30 / 95 (31.58%)	24 / 90 (26.67%)	
occurrences (all)	30	24	
Redness			
subjects affected / exposed	25 / 95 (26.32%)	22 / 90 (24.44%)	
occurrences (all)	25	22	
Swelling			
subjects affected / exposed	15 / 95 (15.79%)	8 / 90 (8.89%)	
occurrences (all)	15	8	
Fatigue			
subjects affected / exposed	23 / 95 (24.21%)	22 / 90 (24.44%)	
occurrences (all)	23	22	
Gastrointestinal			
subjects affected / exposed	9 / 95 (9.47%)	9 / 90 (10.00%)	
occurrences (all)	9	9	
Headache			
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