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 (Engerix-B™ Kinder) vaccine challenge in children aged 7–8 years, previously primed and boosted in the first two years of life with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa™) vaccine

Summary

EudraCT number	2010-022538-10
Trial protocol	DE
Global end of trial date	28 September 2011

Results information

Result version number	v2 (current)
This version publication date	14 May 2018
First version publication date	20 February 2015
Version creation reason	• Correction of full data set Minor corrections of the full study results.

Trial information

Trial identification

Sponsor protocol code	112688

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01333813
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	30 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2011
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 7–8 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.

Protection of trial subjects:

In order to ensure proper IM injection of the study vaccine, a needle of at least 1 inch (2.54 cm) length, 25 gauge was used.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2011
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: 297
Worldwide total number of subjects	297
EEA total number of subjects	297

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)	297
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:

A total of 300 subjects were enrolled in the study. Among them 297 subjects were included in the Total Vaccinated cohort. Remaining 3 subjects were not included as they failed to meet protocol specified criteria and as such they are not included in the Participant Flow as Started.

Period 1

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

Arms

Arm title	Engerix-B Kinder Group

Arm description:

Subjects previously primed and boosted with 4 doses of Infanrix hexa vaccine in the first 2 years of life.

Arm type	Experimental
Investigational medicinal product name	Engerix-B™ Kinder
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	Engerix-B Kinder Group
Started	297
Completed	297

Baseline characteristics

Reporting groups	
Reporting group title	Engerix-B Kinder Group
Reporting group description:	
Subjects previously primed and boosted with 4 doses of Infanrix hexa vaccine in the first 2 years of life.	

Reporting group values	Engerix-B Kinder Group	Total	
Number of subjects	297	297	
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			
median	7.5		
standard deviation	± 0.52	-	
Gender categorical Units: Subjects			
Female	144	144	
Male	153	153	

End points

End points reporting groups

Reporting group title	Engerix-B Kinder Group

Reporting group description:

Subjects previously primed and boosted with 4 doses of Infanrix hexa vaccine in the first 2 years of life.

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-HBs enzyme-linked immunosorbent assay (ELISA) had been observed in some studies for low levels of anti-HBs antibodies (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:

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

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 Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: subjects				
≥ 100 mIU/mL	251			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations after previous vaccination with Infanrix hexa vaccine.

End point title	Anti-HBs antibody concentrations after previous vaccination with Infanrix hexa vaccine.

End point description:

Antibody concentrations are expressed as Geometric mean antibody concentrations (GMCs) in mIU/mL. A decrease in the specificity of the anti-HBs ELISA had been observed in some studies for low levels of anti-HBs antibodies (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 (Day 0) a challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	287			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs GMCs	36.6 (29.7 to 45.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentrations equal to or above the protocol specified cut-off values after previous vaccination with Infanrix hexa vaccine

End point title	Number of subjects with anti-HBs antibody concentrations equal to or above the protocol specified cut-off values after previous vaccination with Infanrix hexa vaccine

End point description:

Anti-HBs antibody concentrations cut-off values assessed were ≥ 6.2 mIU/mL (previously 3.3 mIU/mL), ≥ 10 mIU/mL, ≥ 10 mIU/mL to <100 mIU/mL and ≥ 100 mIU/mL. A decrease in the specificity of the anti-HBs ELISA had been observed in some studies for low levels of anti-HBs antibodies (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 (Day 0) a challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	287			
Units: subjects				
Anti-HBs antibody ≥ 6.2 mIU/mL	225			
Anti-HBs antibody ≥ 10 mIU/mL	207			
Anti-HBs antibody between ≥ 10 and < 100 mIU/mL	118			
Anti-HBs antibody ≥ 100 mIU/mL	89			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentrations equal to or above protocol specified cut-off values

End point title	Number of subjects with anti-HBs antibody concentrations equal to or above protocol specified cut-off values

End point description:

Anti-HBs antibody concentrations cut-off values assessed were ≥ 6.2 mIU/mL (previously 3.3 mIU/mL) and ≥ 10 mIU/mL. A decrease in the specificity of the anti-HBs ELISA had been observed in some studies for low levels of anti-HBs antibodies (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:

One month (Month 1) after a challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: subjects				
Anti-HBs antibody ≥ 6.2 mIU/mL	259			
Anti-HBs antibody ≥ 10 mIU/mL	259			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations

End point description:

Antibody concentrations are expressed as Geometric mean antibody concentrations (GMCs) in mIU/mL. A decrease in the specificity of the anti-HBs 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:

One month (Month 1) after a challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	282			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs GMCs	4819.1 (3749.7 to 6193.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects demonstrating an anamnestic response to the Engerix-B Kinder challenge dose

End point title	Number of subjects demonstrating an anamnestic response to the Engerix-B Kinder challenge dose

End point description:

The anamnestic response is defined as an antibody concentration ≥ 10 mIU/mL at post Engerix-B Kinder challenge dose time point for initially seronegative subjects ,and as an antibody concentration at post Engerix-B Kinder challenge dose time point ≥ 4 fold the pre-vaccination antibody concentration for initially seropositive subjects. A seropositive/seronegative subject was defined as subject with HBs antibody concentration below/greater than or equal to the seropositivity cut-off of 6.2 mIU/mL. A decrease in the specificity of the anti-HBs 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:

After Engerix-B Kinder challenge dose (Month 1)

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: subjects				
Anamnestic response	253			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local Adverse Events (AEs)

End point title	Number of subjects reporting any and grade 3 solicited local Adverse Events (AEs)

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was occurrence of any local symptom regardless of their intensity grade. Grade 3 pain was considerable pain at rest that prevented normal everyday activities. Grade 3 redness and swelling was > 50 millimeter (mm).

End point type	Secondary

End point timeframe:

Number of subjects reporting any and grade 3 solicited local Adverse Events (AEs)

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	297			
Units: subjects				
Any pain	91			
Grade 3 pain	2			
Any redness	84			
Grade 3 redness	0			
Any swelling	49			
Grade 3 swelling	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general AEs

End point title	Number of subjects reporting any, grade 3 and related solicited general AEs

End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache and temeperature. Any temperature was defined as axillary temperature ≥ 37.5 degree centigrade (°C), grade 3 temperature was axillary temperature > 39.0°C. For other symptoms, any was defined as occurrence of any general symptom regardless of intensity grade or relation to vaccination and grade 3 was defined as a general symptom that prevented normal activity. Related was a general symptom assessed by the investigator as causally related to the study vaccination.

End point type	Secondary

End point timeframe:

During the 4-day (Day 0-3) follow-up period after the challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	297			
Units: subjects				
Any fatigue	37			
Grade 3 fatigue	1			
Related fatigue	21			
Any gastrointestinal symptoms	27			
Grade 3 gastrointestinal symptoms	5			
Related gastrointestinal symptoms	5			
Any headache	36			
Grade 3 headache	2			
Related headache	15			
Any temperature	14			
Grade 3 temperature	0			
Related temperature	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any unsolicited AEs

End point title	Number of subjects reporting any unsolicited 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. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary

End point timeframe:

During the 31-day (Day 0-30) follow-up period after the challenge dose of Engerix-B Kinder vaccine

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	297			
Units: subjects				
Any unsolicited AE	42			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects reporting any 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. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary

End point timeframe:

After the challenge dose of Engerix-B Kinder vaccine up to the study end (Day 0 to Month 1)

End point values	Engerix-B Kinder Group			
Subject group type	Reporting group			
Number of subjects analysed	297			
Units: subjects				
Any SAE(s)	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events were assessed from Day 0 to Month 1. Systematically assessed frequent adverse events were assessed during the 4-day post vaccination period.

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	9.0

Reporting groups

Reporting group title	Engerix-B Kinder Group

Reporting group description:

Subjects previously primed and boosted with 4 doses of Infanrix hexa vaccine in the first 2 years of life received a single dose of Engerix-B Kinder vaccine as an intramuscular (IM) injection into the deltoid region of the non-dominant arm at 7-8 years of age.

Serious adverse events	Engerix-B Kinder Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 297 (0.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
VIIth nerve paralysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 297 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 297 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lyme disease			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 297 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Engerix-B Kinder Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 297 (55.22%)		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	91 / 297 (30.64%)		
occurrences (all)	91		
Redness			
subjects affected / exposed	84 / 297 (28.28%)		
occurrences (all)	84		
Swelling			
subjects affected / exposed	49 / 297 (16.50%)		
occurrences (all)	49		
Fatigue			
subjects affected / exposed	37 / 297 (12.46%)		
occurrences (all)	37		
Gastrointestinal symptoms			
subjects affected / exposed	27 / 297 (9.09%)		
occurrences (all)	27		
Gastrointestinal disorders			
Headache			
subjects affected / exposed	36 / 297 (12.12%)		
occurrences (all)	36		

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