Clinical trial results:
An open, phase IV, single-group, multicenter study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a challenge dose of Engerix™-B Kinder in adolescents 15-16 years of age who were vaccinated in infancy with three doses of Engerix™-B Kinder.

Summary

EudraCT number	2012-003950-10
Trial protocol	DE
Global end of trial date	21 February 2014

Results information

Result version number	v2
This version publication date	28 April 2016
First version publication date	29 May 2015
Version creation reason	• New data added to full data set Data for secondary endpoints have been added.

Trial information

Trial identification

Sponsor protocol code	116722

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01847430
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 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	14 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2014
Global end of trial reached?	Yes
Global end of trial date	21 February 2014
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 Engerix-B Kinder in subjects 15-16 years of age vaccinated with three doses of Engerix-B Kinder in infancy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2013
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: 303
Worldwide total number of subjects	303
EEA total number of subjects	303

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)	303
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One subject from the total planned number of 303 subjects was not enrolled and therefore not included in "Started".

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	Not applicable
Blinding used	Not blinded

Arms

Arm title	HBV Group

Arm description:

Subjects received a single dose of Engerix™-B Kinder vaccine (HBV). The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.

Arm type	Experimental
Investigational medicinal product name	Engerix™-B Kinder
Investigational medicinal product code	SB103860
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Single dose of HBV administered intramuscularly in the deltoid region of the non-dominant arm

Number of subjects in period 1[1]	HBV Group
Started	302
Completed	302

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject from the total number of 303 subjects enrolled did not qualify to start the study due to a protocol violation.

Baseline characteristics

Reporting groups	
Reporting group title	HBV Group
Reporting group description:	
Subjects received a single dose of Engerix™-B Kinder vaccine (HBV). The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.	

Reporting group values	HBV Group	Total	
Number of subjects	302	302	
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	15.3		
standard deviation	± 0.5	-	
Gender categorical Units: Subjects			
Female	139	139	
Male	163	163	

End points

End points reporting groups

Reporting group title	HBV Group

Reporting group description:

Subjects received a single dose of Engerix™-B Kinder vaccine (HBV). The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.

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

End point title	Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut off value[1]

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 scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	292			
Units: Subjects				
anti-HBs ≥ 100 mIU/mL	265			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Any and Grade 3 Solicited Local Symptoms.

End point title	Number of Subjects Reporting Any and Grade 3 Solicited Local Symptoms.

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was defined as any solicited local symptom reported irrespective of intensity. Grade 3 pain was defined as significant pain at rest that prevented normal everyday activities. Grade 3 redness and swelling was greater than 50 millimeters (mm) i.e. >50 mm.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) follow-up period after the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	302			
Units: Subjects				
Any Pain	81			
Grade 3 Pain	1			
Any Redness	48			
Grade 3 Redness	0			
Any Swelling	16			
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 Symptoms

End point title	Number of Subjects Reporting Any, Grade 3 and Related Solicited General Symptoms

End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache and fever [axillary temperature above 37.5 degrees Celsius (°C)]. Gastrointestinal symptoms included nausea, vomiting, diarrhoea and/or abdominal pain. Any = any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related = symptoms considered by the investigator to have a causal relationship to vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Grade 3 fever = axillary temperature above 39.0°C

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) follow-up period after the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	302			
Units: Subjects				
Any Fatigue	84			
Grade 3 Fatigue	8			
Related Fatigue	47			
Any Gastrointestinal symptoms	41			
Grade 3 Gastrointestinal symptoms	1			
Related Gastrointestinal symptoms	21			
Any Headache	67			
Grade 3 Headache	4			
Related Headache	41			
Any Fever (≥ 37.5°C)	7			

Grade 3 Fever (> 39.0°C)	0			
Related Fever	4			

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:

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 (Days 0-30) follow-up period after the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	302			
Units: Subjects				
Subjects with any AE(s)	46			

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:

Serious adverse event was any untoward medical occurrence that: resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or was 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:

During the entire study period (Day 0 to Month 1)

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	302			
Units: Subjects				
Subjects with any SAE(s)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with an anamnestic response to the challenge dose in relation to their pre-vaccination status

End point title	Number of subjects with an anamnestic response to the challenge dose in relation to their pre-vaccination status

End point description:

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

End point type	Secondary

End point timeframe:

Prior to vaccination with the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	291			
Units: Subjects				
Day 0 < 6.2 mIU/mL [N= 84]	78			
Day 0 ≥ 6.2 mIU/mL [N= 207]	204			
Total [N=291]	282			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut off value.

End point title	Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut off value.

End point description:

The cut-off values defined were ≥ 6.2 mIU/mL, ≥ 10 mIU/mL and ≥ 100 mIU/mL.

End point type	Secondary

End point timeframe:

Prior to (Day 0) and one month after (Month 1) the administration of the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	292			
Units: Subjects				
Day 0, ≥ 6.2 mIU/mL [N=292]	208			
Day 0, ≥ 10 mIU/mL [N=292]	191			
Day 0, ≥ 100 mIU/mL [N=292]	68			
Month 1, ≥ 6.2 mIU/mL [N=292]	287			
Month 1, ≥ 10 mIU/mL [N=292]	286			
Month 1, ≥ 100 mIU/mL [N=292]	265			

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:

Prior to (Day 0) and one month after (Month 1) the administration of the challenge dose

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	292			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs, Day 0 [N=292]	26.5 (21.4 to 32.8)			
Anti-HBs, Month 1 [N=292]	4134.9 (3114.2 to 5490.1)			

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 (Day 0 to Month 1), Solicited local and general symptoms: During the 4-day (Days 0-3) follow-up period after the HBV challenge dose.

Adverse event reporting additional description:

The number of occurrences reported for solicited symptoms, adverse events, and serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	HBV Group

Reporting group description:

Subjects received a single dose of Engerix™-B Kinder vaccine (HBV). The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.

Serious adverse events	HBV Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 302 (0.66%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Lower limb fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 302 (0.33%)		
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	HBV Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 302 (27.81%)		
Nervous system disorders			
Headache			
subjects affected / exposed	67 / 302 (22.19%)		
occurrences (all)	67		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	81 / 302 (26.82%)		
occurrences (all)	81		
Swelling			
subjects affected / exposed	16 / 302 (5.30%)		
occurrences (all)	16		
Fatigue			
subjects affected / exposed	84 / 302 (27.81%)		
occurrences (all)	84		
Redness			
subjects affected / exposed	48 / 302 (15.89%)		
occurrences (all)	48		
Gastrointestinal disorders			
Gastrointestinal symptoms			
subjects affected / exposed	41 / 302 (13.58%)		
occurrences (all)	41		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	• GSK has discontinued the use of its in-house Enzyme-Linked ImmunoSorbent Assay (ELISA) that was used to measure anti-HBs (antibodies to Hepatitis B surface antigen) antibody concentrations. This assay is being replaced by ChemiLuminescence ImmunoAssay (CLIA). The new assay cut-off is 6.2 mIU/ml and is updated throughout the protocol. • The threshold level of prednisone in this study has been modified from 0.5 mg/kg/day to 20 mg/day, in order to align the dosage with that prescribed for adolescents. • The primary objective was not stated correctly in the sample size section. This has been amended to state that despite the primary objective being descriptive, the sample size has been computed, on the assumption that 90% antibody persistence would be observed. • The intensity of local injection site redness/swelling has been corrected to indicate the scale reflective for adolescents and adults. Several typos in the table for the maximum intensity of fever have also been rectified in the same section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported