Clinical trial results:
A phase IV, open-label, non-randomised, multicentre study to assess the long-term persistence of immunity to hepatitis B in adults vaccinated 20 to 30 years ago with 3 or 4 doses of GSK Biologicals' hepatitis B vaccine, Engerix-B

Summary

EudraCT number	2015-004099-31
Trial protocol	BE
Global end of trial date	01 May 2017

Results information

Result version number	v1
This version publication date	11 May 2018
First version publication date	11 May 2018

Trial information

Trial identification

Sponsor protocol code	116811

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02901951
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)2089 904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, (44)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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2017
Global end of trial reached?	Yes
Global end of trial date	01 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the persistence of immunity to hepatitis B in terms of anti-hepatitis B surface antigen (anti-HBs) anamnestic response to an Engerix-B (HBV vaccine) challenge dose, in adult subjects vaccinated with three or four doses of HBV vaccine 20 to 30 years ago.

Protection of trial subjects:

All vaccinated 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	11 October 2016
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	Belgium: 53
Country: Number of subjects enrolled	Canada: 50
Worldwide total number of subjects	103
EEA total number of subjects	53

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)	0
Adults (18-64 years)	103
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

103 subjects aged between and including 40 to 60 years were enrolled in this study, in compliance with the inclusion criteria, which required the documented evidence of previous vaccination with three or four consecutive doses of Engerix-B administered in adulthood (i.e. at least 18 years of age).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	103
Number of subjects completed	103

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 aged 40 to 60 years old who received 3 or 4 doses of Engerix-B (HBV vaccine) 20 to 30 years ago and were administered with a single challenge dose of HBV vaccine in this study at Day 0 (Visit 1).

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

Dosage and administration details:

Intramuscular administration of single challenge dose of Engerix-B vaccine in the deltoid region of the non-dominant arm.

Number of subjects in period 1	HBV Group
Started	103
Completed	103

Baseline characteristics

Reporting groups	
Reporting group title	HBV Group

Reporting group description:

Subjects aged 40 to 60 years old who received 3 or 4 doses of Engerix-B (HBV vaccine) 20 to 30 years ago and were administered with a single challenge dose of HBV vaccine in this study at Day 0 (Visit 1).

Reporting group values	HBV Group	Total	
Number of subjects	103	103	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.6		
standard deviation	± 5.9	-	
Gender categorical Units: Subjects			
Female	87	87	
Male	16	16	
Race/Ethnicity, Customized Units: Subjects			
White - Caucasian / European Heritage	103	103	

End points

End points reporting groups

Reporting group title	HBV Group

Reporting group description:

Subjects aged 40 to 60 years old who received 3 or 4 doses of Engerix-B (HBV vaccine) 20 to 30 years ago and were administered with a single challenge dose of HBV vaccine in this study at Day 0 (Visit 1).

Primary: Percentage of subjects with an anamnestic response to the HBV challenge dose, based on the last available time point before the challenge dose

End point title	Percentage of subjects with an anamnestic response to the HBV challenge dose, based on the last available time point before the challenge dose[1]

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 one month post-vaccination anti-hepatitis B surface antigen (anti-HBs) antibody concentrations in previously seropositive subjects (Subjects with anti-HBs antibody concentration ≥ 6.2 milli International Unit/Milliliter (mIU/mL) at the pre-challenge dose time point); In previously seronegative subjects (Subjects with anti-HBs antibody concentration < 6.2 mIU/mL at the pre-challenge dose time point), anti-HBs antibody concentrations ≥10 mIU/mL at one month post-challenge dose time-point.

End point type	Primary

End point timeframe:

7 days after the challenge dose (Day 7)

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	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of subjects				
number (confidence interval 95%)				
< 6.2 mIU/mL (N=6)	66.7 (22.3 to 95.7)			
≥ 6.2 mIU/mL (N=95)	85.3 (76.5 to 91.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with an anamnestic response to the HBV challenge dose, based on the last available time point before the challenge dose

End point title	Percentage of subjects with an anamnestic response to the HBV challenge dose, based on the last available time point before the challenge dose[2]

End point description:

Anamnestic response to the challenge dose was defined as: At least (i.e. ≥ 4-fold rise in one month post-vaccination anti-HBs antibody concentrations in previously seropositive subjects (Subjects with anti-HBs antibody concentration ≥ 6.2 mIU/mL at the pre-challenge dose time point); In previously seronegative subjects (Subjects with anti-HBs antibody concentration < 6.2 mIU/mL at the pre-challenge dose time point), anti-HBs antibody concentrations ≥10 mIU/mL at one month post-challenge dose time-point.

End point type	Primary

End point timeframe:

30 days after the challenge dose (Day 30)

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 scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of subjects				
number (confidence interval 95%)				
< 6.2 mIU/mL (N=6)	100 (54.1 to 100)			
≥ 6.2 mIU/mL (N=95)	100 (96.2 to 100)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/mL, ≥ 10 mIU/mL and ≥ 100 mIU/mL.

End point type	Secondary

End point timeframe:

At the pre-challenge dose time-point (Day 0), at 7 days post-challenge time-point (Day 7) and at 30 days post-challenge time-point (Day 30)

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of subjects				
number (confidence interval 95%)				
≥ 6.2 mIU/mL [Day 0]	94.1 (87.5 to 97.8)			

≥ 10 mIU/mL [Day 0]	90.1 (82.5 to 95.1)			
≥ 100 mIU/mL [Day 0]	61.4 (51.2 to 70.9)			
≥ 6.2 mIU/mL [Day 7]	98.0 (93.0 to 99.8)			
≥ 10 mIU/mL [Day 7]	97.0 (91.6 to 99.4)			
≥ 100 mIU/mL [Day 7]	92.1 (85.0 to 96.5)			
≥ 6.2 mIU/mL [Day 30]	100 (96.4 to 100)			
≥ 10 mIU/mL [Day 30]	100 (96.4 to 100)			
≥ 100 mIU/mL [Day 30]	98.0 (93.0 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations

End point description:

Anti-HBs antibody concentrations were expressed as Geometric Mean Concentrations (GMCs) in mIU/mL.

End point type	Secondary

End point timeframe:

At the pre-challenge dose time-point (Day 0), at 7 days post-challenge dose time-point (Day 7) and at 30 days post-challenge dose time-point (Day 30)

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
At Day 0	184.6 (121.5 to 280.3)			
At Day 7	3840.0 (2330.0 to 6328.6)			
At Day 30	48999.1 (33572.7 to 71513.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited local adverse events (AEs)

End point title	Number of subjects with any solicited local adverse events (AEs)

End point description:

Assessed solicited local symptoms were injection site pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

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	103			
Units: Participants				
Any Pain	40			
Any Redness (mm)	4			
Any Swelling (mm)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited general AEs

End point title	Number of subjects with any solicited general AEs

End point description:

Assessed solicited general symptoms were fatigue, fever (defined as axillary temperature ≥ 37.5 degrees Celsius [°C]) , gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain) and headache. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

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	103			
Units: Participants				
Any Fatigue	27			
Any Gastrointestinal symptoms	10			
Any Headache	20			
Any Fever	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited AEs

End point title	Number of subjects with any unsolicited AEs

End point description:

An 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 = occurrence of the 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	103			
Units: Participants				
Participants	41			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with any serious adverse events (SAEs)

End point description:

SAEs assessed included any untoward medical occurrences that resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or congenital anomaly/birth defect in the offspring of a study subject. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary

End point timeframe:

During the entire study period (Day 0 to Day 30)

End point values	HBV Group			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Participants				
Participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local & general AEs: during 4-day (Days 0-3) follow-up period after challenge dose; Unsolicited AEs: during 31-day (Days 0-30) follow-up period after challenge dose; SAEs: during the entire study period (Day 0 to Day 30).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	HBV Group

Reporting group description:

Subjects aged 40 to 60 years old who received 3 or 4 doses of HBV vaccine 20 to 30 years ago and were administered with a single challenge dose of HBV vaccine in this study at Day 0 (Visit 1).

Serious adverse events	HBV Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 103 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HBV Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 103 (72.82%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 103 (28.16%)		
occurrences (all)	30		
Injection site erythema			

subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		
Injection site pain			
subjects affected / exposed	40 / 103 (38.83%)		
occurrences (all)	40		
Injection site pruritus			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Pharyngeal erythema			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	3		
Sinus pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Meniscus injury			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 103 (24.27%)		
occurrences (all)	26		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		

Eye disorders			
Eye pruritus			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Frequent bowel movements			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	10 / 103 (9.71%)		
occurrences (all)	10		
Lip swelling			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		
Joint warmth			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Sinusitis			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		

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