



## Clinical trial results:

An open study to evaluate the immunogenicity, safety, and reactogenicity of GlaxoSmithKline Biologicals' commercially available combined hepatitis A / hepatitis B vaccine (TWINRIX ADULT) containing 720 ELISA units of hepatitis A antigen and 20 g of hepatitis B surface antigen, administered following a two-dose (0, 6 months) schedule in healthy children between the ages of 1 and 11 years.

### Summary

EudraCT number	2015-001516-35
Trial protocol	Outside EU/EEA
Global end of trial date	15 April 2009

### Results information

Result version number	v1
This version publication date	13 May 2016
First version publication date	09 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	100561,100562,100563,100564,100565
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00289744
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	07 October 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2009
Global end of trial reached?	Yes
Global end of trial date	15 April 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To evaluate anti-HAV and anti-HBs antibody persistence at Year 6 (i.e. Month 72), Year 7 (i.e. Month 84), Year 8 (i.e. Month 96), Year 9 (i.e. Month 108) and Year 10 (i.e. Month 120) after the first vaccine dose of two-dose primary vaccination.
- To evaluate the immune memory (after a primary two-dose schedule of TWINRIX™ ADULT 720/20 vaccine) in subjects who became seronegative for anti-HAV antibodies (i.e. titres < 15 mIU/ml) or lost seroprotective titres for anti-HBs antibodies (i.e. titres < 10 mIU/ml) at Year 6, 7, 8, 9 or 10 and subjects who received an additional vaccine dose (administered between 6 to 12 months after the Year 10 time point).

Protection of trial subjects:

All subjects were observed closely for at least 30 minutes following vaccination with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2004
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: 178
Worldwide total number of subjects	178
EEA total number of subjects	178

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)	30
Children (2-11 years)	148
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:

All subjects enrolled in the primary study (208127/076) were invited to come back for the long-term follow-up visits at Year 6 to 10. The enrollment in the protocol section reflects the amount of subjects who came back at year 10. At earlier timepoints more subjects came back and therefore this number is greater than in the protocol section.

### Pre-assignment

Screening details:

25 subjects lost seroprotective concentrations for anti-HBs antibodies at blood sampling time-points Years 6 to 10 and were offered an additional dose of Engerix™-B after Year 10 (additional dose phase). These subjects are presented in separate sub-groups for analysis purposes while as per study protocol, the single experimental group is Twinrix.

### 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

Arm title	Twinrix Group
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Arm description:

Subjects who received 2 doses (at Day 0 and Month 6) of Twinrix in the primary study (208127/076)

Arm type	Experimental
Investigational medicinal product name	TWINRIX™ ADULT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly (IM) in primary study

<b>Number of subjects in period 1</b>	Twinrix Group
Started	178
Completed	178

## Baseline characteristics

### Reporting groups

Reporting group title	Twinrix Group
Reporting group description:	
Subjects who received 2 doses (at Day 0 and Month 6) of Twinrix in the primary study (208127/076)	

Reporting group values	Twinrix Group	Total	
Number of subjects	178	178	
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	13.1		
standard deviation	± 2.82	-	
Gender categorical			
Units: Subjects			
Female	91	91	
Male	87	87	

### Subject analysis sets

Subject analysis set title	Engerix-B Additional Dose (Adult)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects aged 16 years and above who received an additional dose of EngerixTM-B (adult dose), administered intramuscularly in the deltoid region of the non-dominant arm.

Subject analysis set title	Engerix-B Additional Dose (Pediatric)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects under the age of 16 years who received an additional dose of EngerixTM-B (pediatric dose), administered intramuscularly in the deltoid region of the non-dominant arm.

Reporting group values	Engerix-B Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)	
Number of subjects	19	6	
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	17.8 ± 2.22	12.7 ± 1.03	
Gender categorical Units: Subjects			
Female	10	4	
Male	9	2	

## End points

### End points reporting groups

Reporting group title	Twinrix Group
Reporting group description:	
Subjects who received 2 doses (at Day 0 and Month 6) of Twinrix in the primary study (208127/076)	
Subject analysis set title	Engerix-B Additional Dose (Adult)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects aged 16 years and above who received an additional dose of EngerixTM-B (adult dose), administered intramuscularly in the deltoid region of the non-dominant arm.	
Subject analysis set title	Engerix-B Additional Dose (Pediatric)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects under the age of 16 years who received an additional dose of EngerixTM-B (pediatric dose), administered intramuscularly in the deltoid region of the non-dominant arm.	

### Primary: Anti-hepatitis A virus (anti-HAV) antibody concentration

End point title	Anti-hepatitis A virus (anti-HAV) antibody concentration <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe:	
At Years 6, 7, 8, 9, and 10.	

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	Twinrix Group			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: milli-international units per milliliter				
geometric mean (confidence interval 95%)				
Year 6 (n=142)	692.3 (600.9 to 797.5)			
Year 7 (n=136)	753.6 (650.2 to 873.5)			
Year 8 (n=132)	544.4 (476.9 to 621.4)			
Year 9 (n=121)	479.5 (413.3 to 556.3)			
Year 10 (n=120)	601.6 (510.6 to 708.8)			

### Statistical analyses

No statistical analyses for this end point

**Primary: Anti-hepatitis B surface antigen (anti-HBs) antibody concentration**

End point title	Anti-hepatitis B surface antigen (anti-HBs) antibody concentration <sup>[2]</sup>
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End point description:

End point type	Primary
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End point timeframe:

At Years 6, 7, 8, 9 and 10

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 analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Twinrix Group			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: milli-international units per milliliter				
geometric mean (confidence interval 95%)				
Year 6 (n= 142)	206.2 (149.3 to 284.8)			
Year 7 (n= 136)	157.5 (113.7 to 218.4)			
Year 8 (n= 132)	102.7 (74.7 to 141.1)			
Year 9 (n = 121)	89.1 (64.9 to 122.5)			
Year 10 (n= 120)	80.7 (58.1 to 112)			

**Statistical analyses**

No statistical analyses for this end point

**Primary: Anti-hepatitis B surface antigen (anti-HBs) antibody concentration**

End point title	Anti-hepatitis B surface antigen (anti-HBs) antibody concentration <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Before and 1 month after the additional dose administration

Notes:

[3] - 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 Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: milli-international units per milliliter				
geometric mean (confidence interval 95%)				
Pre-vaccination	10.4 (8 to 13.5)	8.7 (3.3 to 23)		
1 month after vaccination	1431.9 (730.2 to 2807.9)	565.9 (163.9 to 1953.5)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with immune response to the additional dose of Engerix™-B

End point title	Number of subjects with immune response to the additional dose of Engerix™-B <sup>[4]</sup>
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End point description:

Immune response was defined as: - anti-hepatitis B surface antigen (anti-HBs) antibody concentration equal or above to 10 milli-international units per milliliter (mIU/mL) at 1 month post-challenge dose in subjects seronegative at the pre-challenge time-points - at least a 4-fold increase in anti-HBs antibody concentrations at 1 month post-challenge dose in subjects seropositive at the pre-challenge time-points.

End point type	Primary
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End point timeframe:

One month after the additional dose administration

Notes:

[4] - 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 Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: Subjects				
Engerix™-B dose	19	6		

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects reporting serious adverse events (SAEs) assessed by the investigator as causally related to primary vaccination, study procedures or lack of vaccine efficacy

End point title	Number of subjects reporting serious adverse events (SAEs)
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, is 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.

End point type Primary

End point timeframe:

At Years 6, 7, 8, 9 and 10

Notes:

[5] - 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	Twinrix Group			
Subject group type	Reporting group			
Number of subjects analysed	178			
Units: Subjects				
Year 6 (n= 178)	0			
Year 7 (n= 175)	0			
Year 8 (n= 174)	0			
Year 9 (n= 173)	0			
Year 10 (n= 171)	0			

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects reporting solicited local and general symptoms

End point title Number of subjects reporting solicited local and general symptoms<sup>[6]</sup>

End point description:

Solicited local symptoms assessed include pain, redness and swelling. Solicited general symptoms assessed include fatigue, fever, gastrointestinal symptoms and headache.

End point type Primary

End point timeframe:

During the 4-day follow-up period after additional dose

Notes:

[6] - 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 Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: Subjects				
Pain	6	3		
Redness	2	1		
Swelling	1	0		

Fatigue	2	3		
Fever	0	1		
Gastrointestinal symptoms	2	1		
Headache	3	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects reporting unsolicited adverse events (AEs)

End point title	Number of subjects reporting unsolicited adverse events
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End point description:

Unsolicited adverse event (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.

End point type	Primary
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End point timeframe:

During the 30-day follow-up period after additional dose

Notes:

[7] - 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 Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: Subjects				
AEs	1	1		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects reporting serious adverse events (SAEs)

End point title	Number of subjects reporting serious adverse events (SAEs) <sup>[8]</sup>
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, is 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.

End point type	Primary
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End point timeframe:

During the 30-day follow-up period after additional dose

Notes:

[8] - 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.

<b>End point values</b>	Engerix-B Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	6		
Units: Subjects				
SAEs	0	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs: At each time-point of the long-term follow-up period & during the 30-day follow-up period after the additional dose. Other AEs: During the 4-day (solicited AEs) or the 30-day (unsolicited AEs) follow-up period after the additional dose.

Adverse event reporting additional description:

Safety results were only collected for those subjects receiving an additional vaccine dose (adult or pediatric).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	Engerix-B Additional Dose (Adult)
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Reporting group description:

Subjects who received 2 doses (at Day 0 and Month 6) of Twinrix™ in the primary study (study 208127/076). Subjects were now 16 years and above and received an additional dose of Engerix™-B (adult dose).

Reporting group title	Engerix-B Additional Dose (Pediatric)
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Reporting group description:

Subjects who received 2 doses (at Day 0 and Month 6) of Twinrix™ in the primary study (study 208127/076)

Serious adverse events	Engerix-B Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Engerix-B Additional Dose (Adult)	Engerix-B Additional Dose (Pediatric)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	3 / 6 (50.00%)	
Nervous system disorders			
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	6 / 19 (31.58%)	3 / 6 (50.00%)	
occurrences (all)	6	3	
Redness			
subjects affected / exposed	2 / 19 (10.53%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 19 (10.53%)	3 / 6 (50.00%)	
occurrences (all)	2	3	
Fever			
subjects affected / exposed	0 / 19 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal symptoms			
subjects affected / exposed	2 / 19 (10.53%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	3 / 19 (15.79%)	0 / 6 (0.00%)	
occurrences (all)	3	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2000	<p>The clinical study protocol 2018127/076 (HAB-076) was designed to evaluate TWINRIX™ ADULT (720/20) vaccine administered according to a 0, 6 month schedule to healthy children aged 1 to 11 years. The protocol was previously amended to evaluate the persistence of humoral immune response up to five years after the first vaccine dose of the primary vaccination. Results from the primary study have shown the vaccine to be safe with a good immune response (anti-HAV seropositivity rate of 100% and anti-HBs seroprotection rate of 98.5%, one month after the primary vaccination course i.e. at Month 7). Long-term data of subjects who returned for a blood sampling visit five years after the first vaccine dose of the primary vaccination course have shown that, anti-HAV seropositivity persisted in all subjects (100%) and anti-HBs seroprotection persisted in 85.8% of subjects. The protocol is currently being amended to evaluate the persistence of humoral immune response 6 years (72 months), 7 years (84 months), 8 years (96 months), 9 years (108 months) and 10 years (120 months) after the first vaccine dose of the primary vaccination. To evaluate the long-term antibody persistence, subjects will be bled at Years 6, 7, 8, 9 and 10 (intervals to be respected at <math>\pm</math> 2 months) after the first vaccine dose of the primary vaccination course, to determine their anti-HAV and anti-HBs antibody titres.</p> <p>If a subject becomes seronegative for anti-HAV antibodies or loses seroprotective titres for anti-HBs antibodies (i.e. titres &lt; 10 mIU/ml) at the long-term blood sampling time point, he/ she will be offered an additional vaccine dose, in order to assess the immune memory after a primary two-dose schedule of TWINRIX™ ADULT (720/20) vaccine. A blood sample will be taken on the day of the additional vaccination and after one month to evaluate the immune response following this vaccination.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported