Clinical trial results:
An open multicentre, multicountry study to evaluate long-term antibody persistence and immune memory between Years 11 and 15 after the primary study HAB-084 in which healthy adolescents were vaccinated with Twinrix™ Adult following a two-dose schedule or Twinrix™ Junior following a three-dose schedule.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2008-006083-11
Trial protocol	BE CZ
Global end of trial date	18 July 2014

Results information

Result version number	v2
This version publication date	28 April 2016
First version publication date	06 June 2015
Version creation reason	• New data added to full data set • Correction of full data set Data for secondary endpoints have been added; Data correction due to a system error in EudraCT – Results

Trial information

Trial identification

Sponsor protocol code	110699 to 110704

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00875485
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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2014
Global end of trial reached?	Yes
Global end of trial date	18 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For the long-term follow-up phase:
To evaluate anti-HAV and anti-HBs antibody persistence at Years 11, 12, 13, 14 and 15 after the first vaccine dose of a two-dose Twinrix Adult or a three-dose Twinrix Junior primary vaccination course.

For the Challenge dose phase:
To evaluate the immune memory 15 years after primary vaccination with a two-dose Twinrix Adult versus a three-dose Twinrix Junior vaccination course in subjects who became seronegative for anti-HAV antibodies (less than 15 mIU/ml) or whose anti-HBs antibody concentrations decreased below 10 mIU/ml during the long-term follow-up period.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2009
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: 72
Country: Number of subjects enrolled	Czech Republic: 138
Worldwide total number of subjects	210
EEA total number of subjects	210

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)	210
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this study, a total of 210 subjects were enrolled who participated at Year 11 (Y11) and Y12. There were a total of 8 additional subjects at Y13 and Y14 who came back from the primary study but did not participate in Y11 and Y12 as allowed by the protocol. One subject from the 210 subjects who participated in Y11 and Y12 did not return at Y15.

Period 1

Period 1 title	Year 11
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 1	Twinrix Adult Group	Twinrix Junior Group
Started	99	111
Completed	99	111

Period 2

Period 2 title	Year 12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to

a 0, 1, 6 month schedule in the primary study.

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 2	Twinrix Adult Group	Twinrix Junior Group
Started	101	109
Completed	101	109

Period 3

Period 3 title	Year 13
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 3	Twinrix Adult Group	Twinrix Junior Group
Started	101	109
Year 13, Started	102	113
Completed	102	113

Joined	1	4
Additional subjects who joined at Year 13	1	4

Period 4

Period 4 title	Year 14
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 4[1]	Twinrix Adult Group	Twinrix Junior Group
Started	100	113
Completed	100	113

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In this study, a total of 210 subjects were enrolled who participated at Year 11 (Y11) and Y12. There were a total of 8 additional subjects at Y13 and Y14 who came back from the primary study but did not participate in Y11 and Y12 as allowed by the protocol. One subject from the 210 subjects who participated in Y11 and Y12 did not return at Y15.

Period 5

Period 5 title	Year 15
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 5[2]	Twinrix Adult Group	Twinrix Junior Group
Started	98	111
Completed	98	111

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In this study, a total of 210 subjects were enrolled who participated at Year 11 (Y11) and Y12. There were a total of 8 additional subjects at Y13 and Y14 who came back from the primary study but did not participate in Y11 and Y12 as allowed by the protocol. One subject from the 210 subjects who participated in Y11 and Y12 did not return at Y15.

Period 6

Period 6 title	Challenge dose epoch
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Group

Arm description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study

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:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Arm title	Twinrix Junior Group

Arm description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.

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:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Investigational medicinal product name	Havrix 1440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly into the upper arm (deltoid muscle) region.

Number of subjects in period 6[3]	Twinrix Adult Group	Twinrix Junior Group
Started	8	11
Completed	7	11
Not completed	1	0
Pregnancy	1	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only 8 subjects in the Twinrix Adult Group and 11 subjects in the Twinrix Junior Group were eligible to receive the challenge dose.

Baseline characteristics

Reporting groups	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	

Reporting group values	Twinrix Adult Group	Twinrix Junior Group	Total
Number of subjects	99	111	210
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	24.5	24.5	
standard deviation	± 1.06	± 1.05	-
Gender categorical Units: Subjects			
Female	49	52	101
Male	50	59	109

End points

End points reporting groups

Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study	
Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.	

Primary: Number of Subjects With Anti-Hepatitis A (HAV) Antibody Concentrations Equal to or Above the Cut-Off Value.

End point title	Number of Subjects With Anti-Hepatitis A (HAV) Antibody Concentrations Equal to or Above the Cut-Off Value.[1]

End point description:

Anti-HAV antibody cut-off value assessed was >= 15 milli-International Units per milliliter (mIU/mL).

End point type	Primary

End point timeframe:

At Year 11, 12, 13, 14 and 15 after the first vaccine dose of the two-dose or three-dose primary vaccination in study HAB-084.

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	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	92		
Units: Subjects				
Year 11	78	92		
Year 12	75	90		
Year 13	76	92		
Year 14	75	91		
Year 15	74	88		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HAV antibody concentrations

End point title	Anti-HAV antibody concentrations[2]

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL. The analysis was performed on anti-HAV seropositive subjects. Seropositive subjects are subjects with anti-HAV antibody concentrations >= 15 mIU/mL.

End point type	Primary

End point timeframe:

At Year 11, 12, 13, 14 and 15 after the first vaccine dose of two-dose or three-dose primary vaccination in study HAB-084

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 endpoint was descriptive, no statistical analyses were conducted.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	92		
Units: mIU/mL				
geometric mean (confidence interval 95%)				

Year 11 (N= 78; 92)	360.5 (292 to 445.1)	257.2 (215.1 to 307.5)		
Year 12 (N= 75; 90)	450.8 (359.6 to 565.1)	335.6 (279 to 403.6)		
Year 13 (N= 77; 92)	401.5 (328.2 to 491.1)	293.6 (244.2 to 352.9)		
Year 14 (N= 75; 91)	388 (309.2 to 487)	291.4 (240.6 to 352.9)		
Year 15 (N= 74; 88)	387.5 (306.6 to 489.8)	299.4 (247.6 to 362)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Anti-Hepatitis B Surface Antigen (HBs) Antibody Concentrations Equal to or Above the Cut-Off Values

End point title	Number of Subjects With Anti-Hepatitis B Surface Antigen (HBs) Antibody Concentrations Equal to or Above the Cut-Off Values[3]

End point description:

Anti-HBs antibody cut-off values assessed were >= 6.2 mIU/mL and >= 10 mIU/mL. Note: A decrease in the specificity of the anti-HB ELISA assay had been observed in some studies for low levels of antibody (10-100 mIU/mL). The table shows updated results following complete retesting and reanalysis for years 11 to 13. Results of year 14 and year 15 were only analysed by ChemiLuminescence ImmunoAssay (CLIA).

End point type	Primary

End point timeframe:

At Year 11, 12, 13, 14 and 15 after the first vaccine dose of the two-dose or three-dose primary vaccination in study HAB-084

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

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	92		
Units: Subjects				
Year 11 [6.2 mIU/mL] (N = 78;91)	68	79		
Year 12 [6.2 mIU/mL] (N = 75;90)	64	80		
Year 13 [6.2 mIU/mL] (N = 77;92)	65	83		
Year 14 [6.2 mIU/mL] (N= 75;91)	66	80		
Year 15 [6.2 mIU/mL] (N= 74;88)	62	79		
Year 11 [10 mIU/mL] (N = 78;91)	64	75		
Year 12 [10 mIU/mL] (N = 75;90)	62	76		
Year 13 [10 mIU/mL] (N = 77;92)	62	77		
Year 14 [10 mIU/mL] (N= 75;91)	62	73		
Year 15 [10 mIU/mL] (N= 74;88)	60	72		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations[4]

End point description:

Antibodys concentrations are expressed as Geometric Mean concentrations (GMCs) in mIU/mL. The analysis was performed on anti-HBs seropositive subjects. Seropositive subjects are subjects with anti-HBs antibody concentrations >= 6.2 mIU/mL. Note: A decrease in the specificity of the anti-HB ELISA assay had been observed in some studies for low levels of antibody (10-100 mIU/mL). The table shows updated results following complete retesting and reanalysis for years 11 to 13. Results of year 14 and year 15 were only analysed by CLIA.

End point type	Primary

End point timeframe:

At Year 11, 12, 13, 14 and 15 after the first vaccine dose of a two-dose or a three-dose primary vaccination in study HAB-084.

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

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	92		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Year 11 (N = 78;91)	88 (63.2 to 122.5)	75.2 (55.6 to 101.8)		
Year 12 (N = 75;90)	93.3 (66.2 to 131.6)	77 (56.1 to 105.7)		
Year 13 (N = 77;92)	92.4 (65.9 to 129.5)	70.1 (51.2 to 96)		
Year 14 (N= 75;91)	81.8 (57.5 to 116.4)	70.2 (51 to 96.8)		
Year 15 (N= 74;88)	87.2 (61 to 124.5)	69.6 (50 to 96.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HBs anamnestic response

End point title	Anti-HBs anamnestic response[5]

End point description:

Anamnestic response was defined as: Anti-HBs antibody concentrations ≥ 10 mIU/mL at one 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 one month post-challenge dose in subjects seropositive at the pre-challenge time-points.

End point type	Primary

End point timeframe:

One month after the challenge dose

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

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
ANTI-HBS ANAMNESTIC RESPONSE	8	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point title	Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point description:

SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Since the last long-term follow-up visit up to Year 11.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	111		
Units: Subjects				
SAE (s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point title	Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point description:

SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital

anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Since the last long-term follow-up visit up to Year 12.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	109		
Units: Subjects				
SAE (s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection.

End point title	Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection.

End point description:

SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Since the last long-term follow-up visit up to Year 13.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	113		
Units: Subjects				
SAE (s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection.

End point title	Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection.

End point description:

SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Since the last long-term follow-up visit up to Year 14.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	113		
Units: Subjects				
SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point title	Number of subjects reporting Serious Adverse Events (SAEs) or Hepatitis A or B Infection

End point description:

SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Since the last long-term follow-up visit up to Year 15.

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	111		
Units: Subjects				
SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-hepatitis A (HAV) antibody concentrations equal to or above the cut-off value

End point title	Number of subjects with anti-hepatitis A (HAV) antibody concentrations equal to or above the cut-off value

End point description:

Anti-HAV antibody cut-off value assessed was >= 15 milli-International Units per milliliter (mIU/mL).
Note: Since none of the subjects were seronegative for anti-HAV antibody concentration at the pre-challenge time point, subjects received only the HBV vaccine as the challenge dose.

End point type	Secondary

End point timeframe:

Before (PRE) the challenge dose

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
PRE (N = 8;11)	8	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HAV antibody concentrations

End point title	Anti-HAV antibody concentrations

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL. The analysis was performed on anti-HAV seropositive subjects. Seropositive subjects are subjects with anti-HAV antibody concentrations >= 15 mIU/mL.

End point type	Secondary

End point timeframe:

Before (PRE) the challenge dose

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
PRE (N =8;11)	270.9 (173.8 to 422.3)	201.3 (123.1 to 329)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Anti-HBs antibody cut-off values assessed were >= 6.2 mIU/mL and >= 10 mIU/mL

End point type	Secondary

End point timeframe:

Before (PRE) and one month after (POST) the challenge dose

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
PRE [6.2 MIU/ML] (N = 8;11)	0	2		
POST [6.2 MIU/ML] (N = 8;11)	8	11		
PRE [10 MIU/ML] (N = 8;11)	0	1		
POST [10 MIU/ML] (N = 8;11)	8	10		

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 concentrations (GMCs) in mIU/mL. The analysis was performed on anti-HBs seropositive subjects. Seropositive subjects are subjects with anti-HBs antibody concentrations >= 6.2 mIU/mL.

End point type	Secondary

End point timeframe:

Before (PRE) and one month after (POST) the challenge dose

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
PRE (N= 8;11)	3.1 (3.1 to 3.1)	4.1 (2.5 to 6.9)		
POST (N= 8;11)	3022.8 (407.8 to 22405.5)	1433.1 (324.5 to 6328.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local adverse events

End point title	Number of subjects reporting any and grade 3 solicited local adverse events

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimeters (mm) of injection site.

End point type	Secondary

End point timeframe:

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

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
ANY PAIN	5	4		
GRADE 3 PAIN	0	0		
ANY REDNESS	1	2		
GRADE 3 REDNESS	0	0		
ANY SWELLING	0	0		
GRADE 3 SWELLING	0	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). Gastrointestinal symptoms included nausea, vomiting, diarrhoea and/or abdominal pain. Any = occurrence of any general symptom regardless of intensity grade or relationship to vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Grade 3 fever = axillary temperature > 39.5°C. Related = general symptoms which were assessed by the investigator as causally related to vaccination.

End point type	Secondary

End point timeframe:

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

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
ANY FATIGUE	3	3		
GRADE 3 FATIGUE	0	0		
RELATED FATIGUE	3	3		
ANY GASTROINTESTINAL SYMPTOMS	1	1		
GRADE 3 GASTROINTESTINAL SYMPTOMS	0	0		
RELATED GASTROINTESTINAL SYMPTOMS	1	1		
ANY HEADACHE	1	2		
GRADE 3 HEADACHE	0	0		
RELATED HEADACHE	1	2		
ANY TEMPERATURE	0	0		
GRADE 3 TEMPERATURE	0	0		
RELATED TEMPERATURE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related unsolicited symptoms

End point title	Number of subjects reporting any, grade 3 and related unsolicited symptoms

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any was defined as an adverse event (AE) reported in addition to those solicited during the clinical study. Any solicited symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited adverse event. Grade 3 = AE that prevented normal activity. Related = AE assessed by the investigator as causally related to the study vaccination.

End point type	Secondary

End point timeframe:

During the 31-day (Day 0 to 30) follow-up period after the challenge dose

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
ANY AE(S)	4	0		
GRADE 3 AE(S)	0	0		
RELATED AE(S)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Serious Adverse Events (SAEs)

End point title	Number of subjects with Serious Adverse Events (SAEs)

End point description:

Serious adverse events (SAEs) assessed included medical occurrences that resulted in death, were life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary

End point timeframe:

One month after the administration of the challenge dose (Month 0 to Month 1)

End point values	Twinrix Adult Group	Twinrix Junior Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
SAE(S)	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Year 15 of the long-term follow-up. SAEs: one month post challenge dose, solicited symptoms: during the 4-day (Days 0-3) post challenge dose and unsolicited AEs: within the 31-day (Days 0-30) post challenge dose.

Adverse event reporting additional description:

No Serious Adverse Events (SAEs) related to primary vaccination or to lack of vaccine efficacy were reported during this long-term follow-up study up to Year 15. Other (non-serious) adverse events were not assessed for the long-term follow-up phase as per protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Twinrix Adult Group

Reporting group description:

Subjects received 2 doses of Twinrix™ Adult intramuscularly according to a 0, 6 month schedule in the primary study.

Reporting group title	Twinrix Junior Group

Reporting group description:

Subjects received 3 doses of Twinrix™ Junior (= half dose Twinrix™ Adult) intramuscularly according to a 0, 1, 6 month schedule in the primary study.

Serious adverse events	Twinrix Adult Group	Twinrix Junior Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (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	Twinrix Adult Group	Twinrix Junior Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	4 / 11 (36.36%)	
Nervous system disorders			
HEADACHE (solicited)			
subjects affected / exposed	1 / 8 (12.50%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
HEADACHE (unsolicited)			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 8 (37.50%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
PAIN			
subjects affected / exposed	5 / 8 (62.50%)	4 / 11 (36.36%)	
occurrences (all)	5	4	
REDNESS			
subjects affected / exposed	1 / 8 (12.50%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
FATIGUE			
subjects affected / exposed	3 / 8 (37.50%)	3 / 11 (27.27%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
GASTROINTESTINAL SYMPTOMS			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	1	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