



Clinical trial results:

An open single centre study to evaluate the long-term antibody persistence and immune memory between 16 and 20 years after the primary study HAB-032 (208127/022) in which healthy adults were vaccinated with Twinrix Adult following a three-dose schedule.

Summary

EudraCT number	2009-014853-33
Trial protocol	BE
Global end of trial date	28 February 2014

Results information

Result version number	v2 (current)
This version publication date	16 September 2018
First version publication date	23 May 2015
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Data for secondary endpoints have been added.

Trial information

Trial identification

Sponsor protocol code	112266
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01037114
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, B-1330, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2014
Global end of trial reached?	Yes
Global end of trial date	28 February 2014
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 Years 16, 17, 18, 19 and 20 after a three-dose primary vaccination course with Twinrix Adult.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of the vaccine. Vaccines/products were administered by qualified and trained personnel.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2010
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: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	49
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Y16, 1 subject was administered a challenge dose of Engerix-B vaccine and at Y18 and Y20, 2 subjects were administered a challenge dose of Havrix vaccine. None of the subjects received a challenge dose at Y17 and Y19.

Period 1

Period 1 title	Year 16 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Twinrix Group_Y16
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Arm description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

Arm title	Twinrix Group_Y17
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Arm description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

Arm title	Twinrix Group_Y18
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Arm description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV

antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

Arm title	Twinrix Group_Y19
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Arm description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Arm type	Experimental
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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

Arm title	Twinrix Group_Y20
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Arm description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

Arm type	Experimental
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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

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:

If a subject became seronegative for antibodies against hepatitis A virus (anti-HAV), i.e. anti-HAV antibody concentrations < 15 mIU/mL or had anti-hepatitis B surface antigen (anti-HBs) antibody concentrations < 10 mIU/mL during the LTFU period, the immune memory to the antigens was evaluated by administering a challenge dose of the Havrix™ or Engerix™-B vaccines at the next planned visit.

Number of subjects in period 1	Twinrix Group_Y16	Twinrix Group_Y17	Twinrix Group_Y18
Started	49	48	44
Completed	49	48	44
Not completed	0	0	0
Other	-	-	-

Number of subjects in period 1	Twinrix Group_Y19	Twinrix Group_Y20
Started	45	45
Completed	45	44
Not completed	0	1
Other	-	1

Baseline characteristics

Reporting groups

Reporting group title	Twinrix Group_Y16
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y17
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y18
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y19
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y20
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

Reporting group values	Twinrix Group_Y16	Twinrix Group_Y17	Twinrix Group_Y18
Number of subjects	49	48	44
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	37.4 ± 5.66	38.6 ± 5.73	39.7 ± 5.89
Gender categorical Units: Subjects			
Female	40	38	35
Male	9	10	9

Reporting group values	Twinrix Group_Y19	Twinrix Group_Y20	Total
Number of subjects	45	45	186
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	40.7 ± 5.88	41.7 ± 5.9	-
Gender categorical Units: Subjects			
Female	36	36	149
Male	9	9	37

End points

End points reporting groups

Reporting group title	Twinrix Group_Y16
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y17
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y18
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y19
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y20
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study.

As lot to lot consistency was assessed during the primary study, the 3 groups (lot A, B or C) were pooled into the Twinrix Group for data analyses during the first long-term follow-up NCT00289718 and this long-term follow-up.

Primary: Number of subjects seropositive for anti-hepatitis A virus antibodies (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibodies and with anti-HBs antibody concentrations ≥ 10 milliinternational units per milliliter (mIU/mL)

End point title	Number of subjects seropositive for anti-hepatitis A virus antibodies (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibodies and with anti-HBs antibody concentrations ≥ 10 milliinternational units per milliliter (mIU/mL) ^[1]
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End point description:

Seropositivity for anti-HAV antibodies is defined as antibody concentrations ≥ 15 milliinternational units per milliliter (mIU/mL). Seropositivity for anti-HBs antibodies is defined as antibody concentrations ≥ 6.2 mIU/mL.

End point type	Primary
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End point timeframe:

At Years 16, 17, 18 and 19 and 20.

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_Y16	Twinrix Group_Y17	Twinrix Group_Y18	Twinrix Group_Y19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	27	25	25
Units: Subjects				
anti-HAV ≥ 15 mIU/mL	28	26	25	24
anti-HBs ≥ 6.2 mIU/mL	27	25	23	23
anti-HBs ≥ 10 mIU/mL	27	25	23	23

End point values	Twinrix Group_Y20			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Subjects				
anti-HAV ≥ 15 mIU/mL	24			
anti-HBs ≥ 6.2 mIU/mL	23			
anti-HBs ≥ 10 mIU/mL	23			

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HAV and anti-HBs Geometric Mean Concentrations (GMCs)

End point title	Anti-HAV and anti-HBs Geometric Mean Concentrations
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End point description:

Concentrations were expressed as GMCs in mIU/mL.

End point type	Primary
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End point timeframe:

At Years 16, 17, 18, 19 and 20.

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_Y16	Twinrix Group_Y17	Twinrix Group_Y18	Twinrix Group_Y19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	27	25	25
Units: mIU/mL				
geometric mean (confidence interval 95%)				
anti-HAV	262.5 (189.9 to 362.9)	369.4 (257.9 to 529.1)	237.7 (163.7 to 345.4)	234.3 (159 to 345.5)
anti-HBs	79.9 (45.2 to 141)	71.7 (39.6 to 129.8)	61.3 (36.8 to 102.3)	59.7 (35.1 to 101.4)

End point values	Twinrix Group_Y20			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
anti-HAV	229.3 (157.1 to 334.6)			
anti-HBs	57.7 (33.6 to 99.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs Concentrations After the Challenge Dose of Engerix-B

End point title	Anti-HBs Concentrations After the Challenge Dose of Engerix-
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End point description:

Concentration was given in mIU/mL. Only 1 subject was eligible for the challenge dose of Engerix-B at the Year 16 time point. Therefore the values for this subject are given without a measure of dispersion.

End point type	Secondary
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End point timeframe:

Before, 14 days and one month (30 days) after the challenge dose of Engerix-B at Year 16.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 1 subject was eligible for the challenge dose of Engerix-B at the Year 16 time point. This outcome measure therefore is applicable only to Twinrix Group_Y16.

End point values	Twinrix Group_Y16			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: mIU/mL				
number (not applicable)				
before challenge dose at Year 16	7.86			
14 days after challenge dose at Year 16	50640.0			

1 month (Day 30) after challenge dose at Year 16	31442.0			
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Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HAV Concentrations After the Challenge Dose of Havrix

End point title	Anti-HAV Concentrations After the Challenge Dose of Havrix ^[4]
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End point description:

Concentration was given in mIU/mL. Only 2 subjects were eligible for the challenge dose of Havrix, one at Year 18 and another at Year 20 time point. Therefore the values for these subject are given without a measure of dispersion.

End point type	Secondary
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End point timeframe:

Before, 14 days and one month (30 days) after the challenge dose of Havrix at Year 18.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: 2 subjects were eligible for the challenge dose of Havrix at the Years 18 & 20 time points.

This outcome measure therefore is applicable only to Twinrix Group_Y18 & Twinrix Group_Y20.

End point values	Twinrix Group_Y18	Twinrix Group_Y20		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: mIU/mL				
number (not applicable)				
Anti-HAV concentrations before challenge dose	25	19		
Anti-HAV concentration 14-days post-challenge dose	3421	1096		
Anti-HAV concentration 1-month post-challenge dose	3389	1060		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anamnestic Response to the Challenge Dose of Engerix-B

End point title	Number of Subjects With Anamnestic Response to the Challenge Dose of Engerix-B ^[5]
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End point description:

At Year 16 only 1 subject was eligible for the challenge dose of Engerix-B.

Anti-HBs anamnestic response to the challenge dose was defined as:

Anti-HBs antibody concentrations ≥ 10 mIU/mL at one month post-challenge dose in subjects seronegative at the pre-challenge time point.

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 point.

End point type	Secondary
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End point timeframe:

30 days after the challenge dose of Engerix-B at Year 16.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: At Year 16 only 1 subject was eligible for the challenge dose of Engerix-B. This outcome measure therefore is applicable only to Twinrix Group_Y16.

End point values	Twinrix Group_Y16			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Number of Subjects With Anamnestic Response	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anamnestic Response to the Challenge Dose of Havrix

End point title	Number of Subjects With Anamnestic Response to the Challenge Dose of Havrix ^[6]
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End point description:

2 subjects received a challenge dose of Havrix at Year 18 & Year 20.

Anti-HAV anamnestic response to the challenge dose was defined as:

Anti-HAV antibody concentrations ≥ 15 mIU/mL at one month post-challenge dose, in subjects seronegative at the pre-challenge time point.

At least a 2-fold increase in anti-HAV antibody concentrations one month after the challenge dose, in subjects having anti-HAV antibody concentrations ≥ 100 mIU/mL at the pre-challenge time point.

Or at least a 4-fold increase in anti-HAV antibody concentrations one month after the challenge dose, in seropositive subjects having anti-HAV antibody concentrations < 100 mIU/mL at the pre-challenge time-point.

End point type	Secondary
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End point timeframe:

30 days after the challenge dose of Havrix.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: 2 subjects received a challenge dose of Havrix at Year 18 and Year 20. This outcome measure therefore is applicable only to Twinrix Group_Y18 and Twinrix Group_Y20.

End point values	Twinrix Group_Y18	Twinrix Group_Y20		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: Subjects				
Number of Subjects With Anamnestic Response	1	1		

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
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End point description:

At Year 16, 1 subject was administered a challenge dose of Engerix-B and at Y18 and Y20, 2 subjects were administered a challenge dose of Havrix. An AE is 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.

End point type	Secondary
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End point timeframe:

31 days (Days 0-30) after the challenge dose of Engerix-B and Havrix.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: At Year 16, 1 subject was administered a challenge dose of Engerix-B and at Y18 and Y20, 2 subjects were administered a challenge dose of Havrix. This outcome measure therefore is applicable to Twinrix Group_Y16, Twinrix Group_Y18 and Twinrix Group_Y20.

End point values	Twinrix Group_Y16	Twinrix Group_Y18	Twinrix Group_Y20	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	1	
Units: Subjects				
Number of Subjects Reporting Unsolicited AEs	1	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) ^[8]
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End point description:

Only 1 subject received a challenge dose at Year 16 of Engerix-B.

An 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
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End point timeframe:

During the 31-day (Days 0-30) follow-up period after the Engerix-B challenge dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 2 subjects were eligible for the challenge dose of Havrix, one at Year 18 and another at Year 20 time point. This outcome measure therefore is applicable only to Twinrix Group_Y18 and Twinrix Group_Y20.

End point values	Twinrix Group_Y16			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Number of Subjects With SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting SAEs Related to Study Participation or a Concurrent GSK Medication

End point title	Number of Subjects Reporting SAEs Related to Study Participation or a Concurrent GSK Medication
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End point description:

An 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
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End point timeframe:

Up to Year 20.

End point values	Twinrix Group_Y16	Twinrix Group_Y17	Twinrix Group_Y18	Twinrix Group_Y19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	48	44	45
Units: Subjects				
Number of Subjects Reporting SAEs	0	0	0	0

End point values	Twinrix Group_Y20			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Subjects				
Number of Subjects Reporting SAEs	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) ^[9]
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End point description:

One subject received a challenge dose of Havrix at Year 18 and another at Year 20. Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity

End point type	Secondary
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End point timeframe:

During the 31-day (Days 0-30) follow-up period after the Havrix challenge dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only 1 subject received a challenge dose at Year 16 of Engerix-B. This outcome measure therefore is applicable only to Twinrix Group_Y16.

End point values	Twinrix Group_Y18	Twinrix Group_Y20		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: Subjects				
Number of Subjects With SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: During the 31-day (Days 0 to 30) follow-up period after the challenge dose and from the beginning of the long term follow-up to Year 20; Unsolicited symptoms: During the 31-day (Days 0 to 30) follow-up period after the challenge dose.

Adverse event reporting additional description:

As no challenge dose was administered during Y 17 & 19, SAEs & other AEs were not assessed. At Y16, 1 subject was administered challenge dose of Engerix-B & at Y 18 & 20, 2 subjects were administered challenge dose of Havrix, for whom the SAEs and other AEs were assessed during 31 day period post challenge dose.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Twinrix Group_Y16
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Reporting group description:

Subjects who received 3 doses of Twinrix (lot A, B or C) in the primary study. A challenge dose of the Havrix or Engerix-B vaccines can be administered in this study based on serology results at each time point.

Reporting group title	Twinrix Group_Y18
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Reporting group description: -

Reporting group title	Twinrix Group_Y20
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Reporting group description: -

Serious adverse events	Twinrix Group_Y16	Twinrix Group_Y18	Twinrix Group_Y20
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Twinrix Group_Y16	Twinrix Group_Y18	Twinrix Group_Y20
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

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