



Clinical trial results:

An open multicentre, multicountry study to evaluate long-term anti-body 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.

Summary

EudraCT number	2015-001517-27
Trial protocol	Outside EU/EEA
Global end of trial date	18 July 2008

Results information

Result version number	v1 (current)
This version publication date	13 May 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	208127/084,100566/567/568/569/570
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00197119
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	22 December 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2008
Global end of trial reached?	Yes
Global end of trial date	18 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For primary study:

To demonstrate, that the immunogenicity elicited by the combined hepatitis A / hepatitis B vaccine Twinrix™ is at least equivalent to that of Twinrix™ Junior vaccine, by measuring the anti-hepatitis A virus (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibody levels reached at month 7.

For the long term follow-up (LTFU):

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 the two-dose or three-dose primary vaccination.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes after administration of additional vaccine dose, 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	03 April 1998
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 155
Country: Number of subjects enrolled	Czech Republic: 145
Worldwide total number of subjects	300
EEA total number of subjects	300

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)	300
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At the time of initiation of the long-term follow-up study, the investigators contacted the subjects who had consented to participate in the long-term follow-up studies. At each subsequent visit, subjects who were present at the previous long-term blood sampling time points were contacted again.

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

Period 1 title	Primary Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Junior Group

Arm description:

Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.

Arm type	Experimental
Investigational medicinal product name	Twinrix Paediatric
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered intramuscularly in the deltoid region.

Arm title	Twinrix Adult Group
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Arm description:

Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study.

Arm type	Experimental
Investigational medicinal product name	Twinrix Adult
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly in the deltoid region.

Number of subjects in period 1	Twinrix Junior Group	Twinrix Adult Group
Started	150	150
Completed	148	149
Not completed	2	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups

Reporting group title	Twinrix Junior Group
Reporting group description:	
Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description:	
Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study.	

Reporting group values	Twinrix Junior Group	Twinrix Adult Group	Total
Number of subjects	150	150	300
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	13.4	13.4	
standard deviation	± 1.01	± 1.07	-
Gender categorical			
Units: Subjects			
Female	72	78	150
Male	78	72	150

End points

End points reporting groups

Reporting group title	Twinrix Junior Group
Reporting group description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.	
Reporting group title	Twinrix Adult Group
Reporting group description: Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study.	
Subject analysis set title	Year 6 Twinrix Junior Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.	
Subject analysis set title	Year 6 Twinrix Adult Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study.	
Subject analysis set title	Year 7 Twinrix Junior Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study. 4 subjects who participated in the Year 6 follow-up time point did not return for this time point.	
Subject analysis set title	Year 7 Twinrix Adult Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study. 4 subjects who participated in the Year 6 follow-up time point did not return for this time point.	
Subject analysis set title	Year 8 Twinrix Junior Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.	
Subject analysis set title	Year 8 Twinrix Adult Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study. One additional subject (compared to Year 7) participated in the current follow-up time point.	
Subject analysis set title	Year 9 Twinrix Junior Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study. One subject participating in the Year 8 time point did not return for the current time point.	
Subject analysis set title	Year 9 Twinrix Adult Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study. One subject participating in the Year 8 time point did not return for the current time point.	
Subject analysis set title	Year 10 Twinrix Junior Group
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study. One subject participating in the Year 9 time point did not return for the current time point.	
Subject analysis set title	Year 10 Twinrix Adult Group

Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study. Six subjects participating in the Year 9 time point did not return for the current time point.

Primary: Antibody titers against hepatitis A and B viruses

End point title	Antibody titers against hepatitis A and B viruses
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End point description:

Antibody titers were summarized by Geometric Mean Concentrations (GMCs) with their 95% CIs.

End point type	Primary
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End point timeframe:

At Month 7

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	142		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
anti-HAV	4174 (3659.5 to 4760.8)	5486.9 (4797.4 to 6275.7)		
anti-HBs	5054.3 (4129.9 to 6185.6)	4948.6 (3624.8 to 6755.8)		

Statistical analyses

Statistical analysis title	Combined response rate to anti-HAV and anti-HBs
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Statistical analysis description:

To demonstrate that the immunogenicity elicited by the Twinrix Adult vaccine is at least equivalent to that of Twinrix Junior vaccine, by measuring the anti-hepatitis A virus (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibody levels reached at Month 7. This was concluded if the lower limit of the exact 90% CI for the difference [Twinrix Adult - Twinrix Junior] in the proportion of subjects with the combined antibody response rate at Month 7 was $\geq -10\%$.

Comparison groups	Twinrix Junior Group v Twinrix Adult Group
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Number of subjects included in analysis	289
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Analysis specification	Pre-specified
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Analysis type	equivalence
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Parameter estimate	Combined response rate difference
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Point estimate	-2.11
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Confidence interval

level	90 %
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sides	2-sided
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lower limit	-7.04
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upper limit	1.92
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Primary: Number of subjects seroconverted for anti-hepatitis A virus (anti-HAV) antibodies

End point title	Number of subjects seroconverted for anti-hepatitis A virus (anti-HAV) antibodies ^[1]
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End point description:

Seroconversion was defined as evolution of antibody concentrations (anti-HAV) \geq the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood sample. An increase in antibody concentration from less than 1 mIU/mL to \geq 1 mIU/mL was considered to be a seroconversion.

End point type	Primary
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End point timeframe:

At Month 7.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	142		
Units: Subjects				
anti-HAV	147	142		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibodies

End point title	Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibodies ^[2]
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End point description:

Seroprotection was defined as anti-HBs concentration \geq 10 mIU/mL.

End point type	Primary
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End point timeframe:

At Month 7.

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 Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	142		
Units: Subjects				
anti-HBs	147	139		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-hepatitis A virus (HAV) antibody concentrations above the cut-off value

End point title	Number of subjects with anti-hepatitis A virus (HAV) antibody concentrations above the cut-off value ^[3]
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End point description:

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

End point type	Primary
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End point timeframe:

At Year 6, 7, 8, 9 and 10 after the first vaccine dose of a two-dose or three-dose primary vaccination

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	Year 6 Twinrix Junior Group	Year 6 Twinrix Adult Group	Year 7 Twinrix Junior Group	Year 7 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	113	100	105	92
Units: Subjects				
Anti-HAV ≥ 15 mIU/mL	113	100	105	92

End point values	Year 8 Twinrix Junior Group	Year 8 Twinrix Adult Group	Year 9 Twinrix Junior Group	Year 9 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104	93	103	90
Units: Subjects				
Anti-HAV ≥ 15 mIU/mL	104	93	103	90

End point values	Year 10 Twinrix Junior Group	Year 10 Twinrix Adult Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	77		
Units: Subjects				
Anti-HAV ≥ 15 mIU/mL	100	77		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Anti-Hepatitis B Surface Antigen (HBs) Antibody Concentrations Above the Cut-Off Value ^[4]
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End point description:

Anti-HBs antibody concentration cut-off value assessed was ≥ 3.3 mIU/mL.

End point type	Primary
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End point timeframe:

At Year 6, 7, 8, 9 and 10 after the first vaccine dose of a two-dose or three-dose primary vaccination.

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	Year 6 Twinrix Junior Group	Year 6 Twinrix Adult Group	Year 7 Twinrix Junior Group	Year 7 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	113	100	105	92
Units: Subjects				
anti-HBs ≥ 3.3 mIU/mL	100	93	98	85

End point values	Year 8 Twinrix Junior Group	Year 8 Twinrix Adult Group	Year 9 Twinrix Junior Group	Year 9 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104	93	103	90
Units: Subjects				
anti-HBs ≥ 3.3 mIU/mL	96	84	96	86

End point values	Year 10 Twinrix Junior Group	Year 10 Twinrix Adult Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	78		
Units: Subjects				
anti-HBs ≥ 3.3 mIU/mL	97	75		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting Serious adverse events (SAE) causally related to primary vaccination or related to hepatitis A or B infection or related to study participation (blood sampling)

End point title	Number of subjects reporting Serious adverse events (SAE) causally related to primary vaccination or related to hepatitis A or B infection or related to study participation (blood sampling) ^[5]
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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	Primary
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End point timeframe:

From Year 6 through to Year 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	Year 6 Twinrix Junior Group	Year 6 Twinrix Adult Group	Year 7 Twinrix Junior Group	Year 7 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	126	118	122	114
Units: Subjects				
SAE(s)	0	0	0	0

End point values	Year 8 Twinrix Junior Group	Year 8 Twinrix Adult Group	Year 9 Twinrix Junior Group	Year 9 Twinrix Adult Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	122	115	121	114
Units: Subjects				
SAE(s)	0	0	0	0

End point values	Year 10 Twinrix Junior Group	Year 10 Twinrix Adult Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	108		
Units: Subjects				
SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody titers against hepatitis A and hepatitis B viruses.

End point title	Antibody titers against hepatitis A and hepatitis B viruses.
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End point description:

Antibody titers were summarized by Geometric Mean Concentrations (GMCs) with their 95% CIs.

End point type	Secondary
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End point timeframe:

At months 1, 2, and 6.

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	142		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
anti-HAV, M1 (N=148,142)	227.4 (196.4 to 263.2)	348.7 (302.4 to 402.2)		
anti-HAV, M2 (N=146,142)	548.8 (472.7 to 637.2)	244.7 (213.6 to 280.5)		
anti-HAV, M6 (N=147,142)	298.8 (263.1 to 339.4)	178 (159.4 to 198.7)		
anti-HBs, M1 (N=148,142)	9.8 (7.2 to 13.3)	14.3 (10.4 to 19.7)		
anti-HBs, M2 (N=146,142)	42.1 (33.3 to 53.1)	9.9 (7.7 to 12.6)		
anti-HBs, M6 (N=147,142)	305.3 (249 to 374.1)	20.1 (16 to 25.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seroconverted for anti-hepatitis A virus (anti-HAV) antibodies

End point title	Number of subjects seroconverted for anti-hepatitis A virus (anti-HAV) antibodies
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End point description:

Seroconversion was defined as evolution of antibody concentrations (anti-HAV) \geq the lowest sensitivity limit of the serological assay in a subject who was seronegative vaccination. An increase in antibody concentration from less than 1 mIU/mL to \geq 1 mIU/mL was considered to be a seroconversion.

End point type	Secondary
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End point timeframe:

At months 1, 2, and 6.

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	142		
Units: Subjects				
anti-HAV, M1 (N=148,142)	138	141		
anti-HAV, M2 (N=146,142)	145	142		
anti-HAV, M6 (N=147,142)	146	142		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibodies.

End point title	Number of subjects seroprotected for anti-hepatitis B surface antigen (anti-HBs) antibodies.
End point description:	Seroprotections was defined as anti-HBs concentration ≥ 10 mIU/mL.
End point type	Secondary
End point timeframe:	At months 1, 2, and 6.

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	142		
Units: Subjects				
anti-HBs, M1 (N=148,142)	43	61		
anti-HBs, M2 (N=146,142)	125	54		
anti-HBs, M6 (N=147,142)	144	97		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited local symptoms.

End point title	Number of subjects with any and Grade 3 solicited local symptoms.
End point description:	Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = spontaneously painful (prevents normal activities). Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimeters (mm) of injection site.
End point type	Secondary
End point timeframe:	During the three days (days 0-4) follow-up period after each vaccine dose (Dose 1, 2 and 3)

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	149		
Units: Subjects				
Any Pain; Dose 1 (N=149,149)	53	68		
Grade 3 Pain; Dose 1 (N=149,149)	0	3		
Any Redness; Dose 1 (N=149,149)	15	24		
Grade 3 Redness; Dose 1 (N=149,149)	0	0		
Any Swelling; Dose 1 (N=149,149)	3	4		
Grade 3 Swelling; Dose 1 (N=149,149)	0	0		
Any Pain; Dose 2 (N=148,149)	56	83		
Grade 3 Pain; Dose 2 (N=148,149)	0	2		
Any Redness; Dose 2 (N=148,149)	13	24		
Grade 3 Redness; Dose 2 (N=148,149)	0	0		
Any Swelling; Dose 2 (N=148,149)	7	9		
Grade 3 Swelling; Dose 2 (N=148,149)	1	0		
Any Pain; Dose 3 (N=148,0)	65	0		
Grade 3 Pain; Dose 3 (N=148,0)	0	0		
Any Redness; Dose 3 (N=148,0)	25	0		
Grade 3 Redness; Dose 3 (N=148,0)	0	0		
Any Swelling; Dose 3 (N=148,0)	12	0		
Grade 3 Swelling; Dose 3 (N=148,0)	0	0		
Any Pain; Across Doses (N=149,149)	95	99		
Grade 3 pain; Across Doses (N=149,149)	0	5		
Any Redness; Across Doses (N=149,149)	35	34		
Grade 3 Redness; Across Doses (N=149,149)	0	0		
Any Swelling; Across Doses (N=149,149)	19	11		
Grade 3 Swelling; Across Doses (N=149,149)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited general symptoms

End point title	Number of subjects with any, grade 3 and related solicited general symptoms
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End point description:

Solicited general symptoms assessed were fatigue, fever (defined as rectal temperature $\geq 38^{\circ}\text{C}$), gastrointestinal symptoms (GS), and headache. Any was defined as incidence of the specified symptoms regardless of intensity or relationship to study vaccine. Grade 3 was defined as an event that prevented normal activity and Grade 3 fever (oral/axillary route) = temperature > 39.0 degree Celsius ($^{\circ}\text{C}$). Related was defined as an event assessed by the investigator as causally related to the study

vaccination.

End point type	Secondary
End point timeframe:	
During the three days (days 0-4) follow-up period after each vaccine dose (Dose 1, 2 and 3).	

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	149		
Units: Subjects				
Any Fatigue; Dose 1 (N=149,149)	34	48		
Grade 3 Fatigue; Dose 1 (N=149,149)	3	0		
Related Fatigue; Dose 1 (N=149,149)	16	23		
Any Temperature; Dose 1 (N=149,149)	3	2		
Grade 3 Temperature; Dose 1 (N=149,149)	0	0		
Related Temperature; Dose 1 (N=149,149)	2	1		
Any GS; Dose 1 (N=149,149)	8	11		
Grade 3 GS; Dose 1 (N=149,149)	0	0		
Related GS; Dose 1 (N=149,149)	5	6		
Any Headache; Dose 1 (N=149,149)	21	24		
Grade 3 Headache; Dose 1 (N=149,149)	0	0		
Related Headache; Dose 1 (N=149,149)	10	13		
Any Fatigue; Dose 2 (N=148,149)	25	39		
Grade 3 Fatigue; Dose 2 (N=148,149)	1	0		
Related Fatigue; Dose 2 (N=148,149)	10	19		
Any temperature; Dose 2 (N=148,149)	1	3		
Grade 3 Temperature; Dose 2 (N=148,149)	0	0		
Related Temperature (N=148,149)	1	1		
Any GS; Dose 2 (N=148,149)	5	5		
Grade 3 GS; Dose 2 (N=148,149)	0	1		
Related GS; Dose 2 (N=148,149)	0	3		
Any Headache; Dose 2 (N=148,149)	20	23		
Grade 3 Headache; Dose 2 (N=148,149)	0	0		
Related Headache; Dose 2 (N=148,149)	10	16		
Any Fatigue; Dose 3 (N=148,0)	27	0		
Grade 3 Fatigue; Dose 3 (N=148,0)	1	0		
Related Fatigue; Dose 3 (N=148,0)	16	0		
Any Temperature; Dose 3 (N=148,0)	2	0		
Grade 3 Temperature; Dose 3 (N=148,0)	0	0		
Related Temperature; Dose 3 (N=148,0)	1	0		
Any GS; Dose 3 (N=148,0)	2	0		
Grade 3 GS; Dose 3 (N=148,0)	0	0		
Related GS; Dose 3 (N=148,0)	1	0		
Any Headache; Dose 3 (N=148,0)	21	0		

Grade 3 Headache; Dose 3 (N=148,0)	1	0		
Related Headache; Dose 3 (N=148,0)	11	0		
Any Fatigue; Across Doses (N=149,149)	54	59		
Grade 3 Fatigue; Across Doses (N=149,149)	3	0		
Related Fatigue; Across Doses (N=149,149)	32	35		
Any Temperature; Across Doses (N=149,149)	5	5		
Grade 3 Temperature; Across Doses (N=149,149)	0	0		
Related Temperature; Across Doses (N=149,149)	3	2		
Any GS; Across Doses (N=149,149)	13	15		
Grade 3 GS; Across Doses (N=149,149)	0	1		
Related GS; Across Doses (N=149,149)	6	9		
Any Headache; Across Doses (N=149,149)	44	37		
Grade 3 Headache; Across Doses (N=149,149)	1	0		
Related Headache; Across Doses (N=149,149)	22	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any unsolicited Adverse Events (AEs)

End point title	Number of subjects reporting any unsolicited Adverse Events (AEs)
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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.

End point type	Secondary
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End point timeframe:

Within 31 days (days0-30) after each vaccine dose

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	149		
Units: Subjects				
any AE (s)	47	38		

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)
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End point description:

SAEs assessed included medical occurrences that were fatal, life threatening, disabling/incapacitating or resulted in hospitalization, prolonged a hospital stay or was associated with congenital abnormality in offspring, cancer or overdose (either accidental or intentional). Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

During the course of the study (7 months)

End point values	Twinrix Junior Group	Twinrix Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: Subjects				
Any SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Primary study- SAEs: During the course of the study, solicited local and general symptoms: During the 3 days (days 0-4) post each dose, unsolicited AEs: Within 31 days (days 0-30) post each dose. LFTU-SAEs: From Years 6 to 10

Adverse event reporting additional description:

The number of occurrences reported for solicited symptoms, adverse events, and serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences. Other (non-serious) adverse event data was not collected during this long-term follow-up phase of the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	7.1
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Reporting groups

Reporting group title	Twinrix Junior Group
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Reporting group description:

Subjects received Twinrix™ Junior (360/10) in a 0, 1, 6 month schedule in the primary study.

Reporting group title	Twinrix Adult Group
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Reporting group description:

Subjects received Twinrix™ Adult (720/20) in a 0, 6 month schedule in the primary study.

Serious adverse events	Twinrix Junior Group	Twinrix Adult Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 149 (0.00%)	0 / 149 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Twinrix Junior Group	Twinrix Adult Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 149 (63.76%)	99 / 149 (66.44%)	
Nervous system disorders			
Headache; Dose 1			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 149 (14.09%)	24 / 149 (16.11%)	
occurrences (all)	21	24	
Headache; Dose 3			

subjects affected / exposed ^[1]	21 / 148 (14.19%)	0 / 149 (0.00%)
occurrences (all)	21	0
Headache; Across Doses alternative assessment type: Systematic		
subjects affected / exposed	44 / 149 (29.53%)	37 / 149 (24.83%)
occurrences (all)	44	37
General disorders and administration site conditions		
Pain; Dose 1 alternative assessment type: Systematic		
subjects affected / exposed	53 / 149 (35.57%)	68 / 149 (45.64%)
occurrences (all)	53	68
Pain; Dose 2 alternative assessment type: Systematic		
subjects affected / exposed ^[2]	56 / 148 (37.84%)	83 / 149 (55.70%)
occurrences (all)	56	83
Pain; Dose 3 alternative assessment type: Systematic		
subjects affected / exposed ^[3]	65 / 148 (43.92%)	0 / 149 (0.00%)
occurrences (all)	65	0
Redness; Dose 1 alternative assessment type: Systematic		
subjects affected / exposed	15 / 149 (10.07%)	24 / 149 (16.11%)
occurrences (all)	15	24
Redness; Dose 2 alternative assessment type: Systematic		
subjects affected / exposed ^[4]	13 / 148 (8.78%)	24 / 149 (16.11%)
occurrences (all)	13	24
Redness; Dose 3 alternative assessment type: Systematic		
subjects affected / exposed ^[5]	25 / 148 (16.89%)	0 / 149 (0.00%)
occurrences (all)	25	0
Swelling; Dose 1 alternative assessment type: Systematic		

subjects affected / exposed	3 / 149 (2.01%)	4 / 149 (2.68%)
occurrences (all)	3	4
Swelling; Dose 2		
alternative assessment type: Systematic		
subjects affected / exposed ^[6]	7 / 148 (4.73%)	9 / 149 (6.04%)
occurrences (all)	7	9
Swelling; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[7]	12 / 148 (8.11%)	0 / 149 (0.00%)
occurrences (all)	12	0
Pain; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed	95 / 149 (63.76%)	99 / 149 (66.44%)
occurrences (all)	95	99
Redness; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed	35 / 149 (23.49%)	34 / 149 (22.82%)
occurrences (all)	35	34
Swelling; Across Doses		
alternative assessment type: Systematic		
subjects affected / exposed	19 / 149 (12.75%)	11 / 149 (7.38%)
occurrences (all)	19	11
Fatigue; Dose 1		
alternative assessment type: Systematic		
subjects affected / exposed	34 / 149 (22.82%)	48 / 149 (32.21%)
occurrences (all)	34	48
Fatigue; Dose 2		
alternative assessment type: Systematic		
subjects affected / exposed ^[8]	25 / 148 (16.89%)	39 / 149 (26.17%)
occurrences (all)	25	39
Fatigue; Dose 3		
alternative assessment type: Systematic		
subjects affected / exposed ^[9]	27 / 148 (18.24%)	0 / 149 (0.00%)
occurrences (all)	27	0

Headache; Dose 2 alternative assessment type: Systematic subjects affected / exposed ^[10] occurrences (all)	20 / 148 (13.51%) 20	23 / 149 (15.44%) 23	
Fatigue; Across Doses alternative assessment type: Systematic subjects affected / exposed occurrences (all)	54 / 149 (36.24%) 54	59 / 149 (39.60%) 59	
Gastrointestinal disorders Gastrointestinal symptoms; Dose 1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8	11 / 149 (7.38%) 11	
Gastrointestinal symptoms; Across Doses alternative assessment type: Systematic subjects affected / exposed occurrences (all)	13 / 149 (8.72%) 13	15 / 149 (10.07%) 15	
Respiratory, thoracic and mediastinal disorders Pharyngitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	11 / 149 (7.38%) 11	7 / 149 (4.70%) 7	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For a given subject cohort and the analysis of a given measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2008	<p>Because a high proportion of subjects returned for the long-term follow-up visits up to Year 9, the follow-up period was further extended. It was intended to prolong the follow-up until Year 15 after primary vaccination. At which time the immune memory to HAV and HBs was evaluated by the administration of a challenge dose.</p> <p>In order to describe the extended follow-up according to current standards, a new study protocol describing the additional five years (Y11-Y15) of follow-up and the challenge phase of the study was written. The protocol was consequently amended to reflect that the challenge dose was not administered at Year 10 after primary vaccination.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported