

**Clinical trial results:**

A phase III, open, randomized, multicentre, multicountry study to compare the reactogenicity and evaluate the safety and immunogenicity of GSK Bio's combined hepatitis A / hepatitis B vaccine (at least 720 EL.U of hepatitis A antigen and 20 µg of hepatitis B surface antigen per dose of 1 ml) administered according to a 0, 6 month schedule by intramuscular injection versus Twinrix™ Junior (at least 360 EL.U of hepatitis A antigen and 10 µg of hepatitis B surface antigen per dose of 0.5 ml) administered according to a 0, 1, 6 month schedule by intramuscular injection in healthy children between 1 to 11 years old.

Summary

EudraCT number	2015-001515-12
Trial protocol	Outside EU/EEA
Global end of trial date	25 February 2008

Results information

Result version number	v1
This version publication date	13 May 2016
First version publication date	26 July 2015

Trial information**Trial identification**

Sponsor protocol code	208127/120,/132,/133,/134,/137
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, 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	10 December 2004
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For the primary study:

To demonstrate that the combined hepatitis A / hepatitis B (720/20) vaccine is not more reactogenic than Twinrix™ Junior.

For the long term follow up (LTFU):

To evaluate anti-HAV and anti-HBs antibody persistence at Year 2, Year 3, Year 4 and Year 5 after the first vaccine dose of the primary vaccination course (a two-dose schedule of Twinrix Adult 720/20 vaccine or a three-dose schedule of Twinrix Junior 360/10 vaccine).

To evaluate the immune memory in the subjects who became seronegative for anti-HAV antibodies (i.e. anti-HAV antibody concentrations < 15 mIU/ml) or had anti-HBs antibody concentrations < 10 mIU/ml at the long-term blood sampling time-point (i.e. Year 2, 3, 4 or 5) and who received the challenge dose (administered 6 to 12 months after the Year 5 time-point).

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 30 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2001
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, 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	Spain: 110
Country: Number of subjects enrolled	Sweden: 110
Country: Number of subjects enrolled	Australia: 229
Country: Number of subjects enrolled	Belgium: 61
Worldwide total number of subjects	510
EEA total number of subjects	281

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)	100
Children (2-11 years)	410
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult

Arm description:

Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

Arm type	Active comparator
Investigational medicinal product name	Twinrix™ Adult
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in the left deltoid, 2 doses, Adult formulation in primary study.

Arm title	Twinrix Junior
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Arm description:

Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

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

Dosage and administration details:

Intramuscular injection in the left deltoid, 3 doses, junior formulation in primary study.

Number of subjects in period 1	Twinrix Adult	Twinrix Junior
Started	254	256
Completed	249	250
Not completed	5	6
Consent withdrawn by subject	4	1
Migrated/moved from study area	-	2

Lost to follow-up	-	2
Protocol deviation	1	1

Period 2

Period 2 title	Year 2 - Year 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Twinrix Adult Y2-Y5

Arm description:

Subjects previously received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

Arm type	Active comparator
Investigational medicinal product name	Twinrix™ Adult
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in the left deltoid, 2 doses, Adult formulation in primary study.

Arm title	Twinrix Junior Y2-Y5
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Arm description:

Subjects previously received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

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

Dosage and administration details:

Intramuscular injection in the left deltoid, 3 doses, junior formulation in primary study.

Number of subjects in period 2^[1]	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5
Started	139	137
Completed	139	137

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: Not all subjects returned for the follow-up phase.

Baseline characteristics

Reporting groups

Reporting group title	Twinrix Adult
Reporting group description:	
Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).	
Reporting group title	Twinrix Junior
Reporting group description:	
Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).	

Reporting group values	Twinrix Adult	Twinrix Junior	Total
Number of subjects	254	256	510
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			
median	6.2	5.8	
standard deviation	± 3.11	± 3.17	-
Gender categorical Units: Subjects			
Female	112	117	229
Male	142	139	281

End points

End points reporting groups

Reporting group title	Twinrix Adult
Reporting group description:	
Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).	
Reporting group title	Twinrix Junior
Reporting group description:	
Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).	
Reporting group title	Twinrix Adult Y2-Y5
Reporting group description:	
Subjects previously received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).	
Reporting group title	Twinrix Junior Y2-Y5
Reporting group description:	
Subjects previously received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).	

Primary: Anti-hepatitis A (HAV) antibody concentrations

End point title	Anti-hepatitis A (HAV) antibody concentrations ^[1]
End point description:	
Geometric mean concentration for anti-HAV antibodies expressed as Milli-International Units per milliliter (mIU/mL)	
End point type	Primary
End point timeframe:	
Year 2 (Month 24), Year 3 (Month 36), Year 4 (Month 48) and Year 5 (Month 60)	
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 Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	119		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
At year 2 (n=107; 94)	1122.2 (937.7 to 1343)	1377.8 (1114 to 1704.2)		
At year 3 (n=129; 119)	737.5 (845.8 to 1178.9)	1347.1 (1145.1 to 1584.8)		
At year 4 (n=115; 105)	576.8 (623.6 to 872.3)	915.9 (774 to 1084)		
At year 5 (n=103; 101)	998.6 (473.6 to 702.5)	698.4 (585.1 to 833.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-hepatitis B (HBs) antibody concentrations

End point title	Anti-hepatitis B (HBs) antibody concentrations ^[2]
End point description: Geometric mean concentration for anti-HBs antibodies expressed as Milli-International Units per milliliter (mIU/mL).	
End point type	Primary
End point timeframe: Year 2 (Month 24), Year 3 (Month 36), Year 4 (Month 48) and Year 5 (Month 60)	

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 Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	119		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
At year 2 (n=107; 94)	479.9 (356.6 to 646)	830.6 (609.5 to 1131.9)		
At year 3 (n=129; 119)	325.1 (244.7 to 431.8)	695.1 (516.5 to 935.5)		
At year 4 (n=115; 105)	270.2 (201 to 363.3)	519.7 (378.5 to 713.6)		
At year 5 (n=102; 100)	150.2 (110.5 to 204.3)	283.7 (208.6 to 386)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HAV antibody concentrations in subjects receiving the additional vaccine dose.

End point title	Anti-HAV antibody concentrations in subjects receiving the additional vaccine dose. ^[3]
End point description: Any subjects becoming seronegative for anti-HAV antibodies (i.e. titres < 15 mIU/ml) at any long term time point, were to receive an additional vaccine dose administered between 6 to 12 months after Year 5 time point.	
End point type	Primary
End point timeframe: Before and one month after additional 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	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: mIU/mL				
geometric mean (confidence interval 95%)	(to)	(to)		

Notes:

[4] - No subjects became seronegative for anti-HAV antibodies.

[5] - No subjects became seronegative for anti-HAV antibodies.

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HBs antibody concentrations in subjects receiving the additional vaccine dose.

End point title	Anti-HBs antibody concentrations in subjects receiving the additional vaccine dose. ^[6]
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End point description:

Subjects losing seroprotective anti-HBs antibody titres (i.e. titres < 10 mIU/ml) at any long term time point, received an Engerix™ challenge dose. The table presents the geometric mean concentrations for anti-HBs antibodies, expressed as Milli-International Units per milliliter (mIU/mL).

End point type	Primary
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End point timeframe:

Before and One month after additional vaccination

Notes:

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

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

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Before vaccination (n= 6; 1)	4.9 (2.1 to 11.1)	2.4 (0.9 to 6.5)		
Post vaccination (n= 11; 5)	521.3 (158.2 to 1718.1)	509.7 (173.5 to 1497.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 1 to 5 years.

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 1 to 5 years. ^[7]
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End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

End point type	Primary
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End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	122		
Units: subjects				
Pain, any	53	56		
Pain, Grade 3	2	1		
Redness, any	31	45		
Redness, >25 mm	1	2		
Swelling, any	26	29		
Swelling, >25 mm	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 6 to 11 years.

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 6 to 11 years. ^[8]
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End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

End point type	Primary
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End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	125		
Units: subjects				
Pain, any	82	72		
Pain, Grade 3	3	2		

Redness, any	32	31		
Redness, >25mm	0	1		
Swelling, any	13	23		
Swelling, >25mm	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 1 to 5 years.

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 1 to 5 years. ^[9]
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End point description:

Solicited general symptoms assessed include drowsiness, irritability/fussiness, loss of appetite and fever. Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity; Related= considered by the investigator to be causally related to the vaccination

End point type	Primary
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End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

[9] - 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 Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	122		
Units: subjects				
Drowsiness, Any	24	39		
Drowsiness, Grade 3	2	3		
Drowsiness, Related	23	36		
Irritability/Fussiness, Any	36	52		
Irritability/Fussiness, Grade 3	0	1		
Irritability/Fussiness, Related	29	48		
Loss of appetite, Any	20	37		
Loss of appetite, Grade 3	2	0		
Loss of appetite, Related	16	33		
Fever (axillary), $\geq 37^{\circ}\text{C}$	13	19		
Fever (axillary), $> 39.5^{\circ}\text{C}$	0	1		
Fever (axillary), Related	13	16		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 6 to 11 years.

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 6 to 11 years. ^[10]
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End point description:

Solicited general symptoms assessed include fatigue, fever, gastrointestinal symptoms and headache. Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity; Related= considered by the investigator to be causally related to the vaccination

End point type	Primary
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End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

[10] - 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 Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	125		
Units: subjects				
Fatigue, Any	30	36		
Fatigue, Grade 3	1	3		
Fatigue, Related	28	30		
Gastrointestinal, Any	21	26		
Gastrointestinal, Grade 3	1	4		
Gastrointestinal, Related	14	17		
Headache, Any	25	40		
Headache, Grade 3	1	1		
Headache, Related	20	30		
Fever (axillary), $\geq 37^{\circ}\text{C}$	8	16		
Fever (axillary), $> 39.5^{\circ}\text{C}$	0	1		
Fever (axillary), Related	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Serious Adverse Events (SAEs) determined by the investigator to have a causal relationship to primary vaccination or due to lack of vaccine efficacy.

End point title	Number of subjects reporting Serious Adverse Events (SAEs) determined by the investigator to have a causal relationship to primary vaccination or due to lack of vaccine efficacy.
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End point description:

A serious adverse event (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:

From last study visit of the primary study up to Year 5 long term follow-up

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	137		
Units: subjects				
SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms
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End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

End point type	Secondary
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End point timeframe:

during the 4-day follow-up period after additional vaccination

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: subjects				
Pain, any	6	0		
Pain, grade 3	0	0		
Redness, any	1	0		
Redness, >20mm	0	0		
Swelling, any	0	0		
Swelling, >20mm	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms.

End point title	Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms.
End point description: Solicited general symptoms assessed include fatigue, fever, gastrointestinal symptoms and headache. Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity; Related= considered by the investigator to be causally related to the vaccination	
End point type	Secondary
End point timeframe: During the 4-day follow-up period after additional vaccination	

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: subjects				
Fatigue, any	3	0		
Fatigue, grade 3	0	0		
Fatigue, related	3	0		
Fever (axillary), $\geq 37^{\circ}\text{C}$	0	0		
Fever (axillary), $> 39.5^{\circ}\text{C}$	0	0		
Fever (axillary), related	0	0		
Gastrointestinal, any	2	0		
Gastrointestinal, grade 3	0	0		
Gastrointestinal, related	2	0		
Headache, any	4	0		
Headache, grade 3	0	0		
Headache, related	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).

End point title	Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).
End point description: An Adverse Event 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
End point timeframe: During the 30-day follow-up period after additional vaccination.	

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: subjects				
AEs	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events

End point title	Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events
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End point description:

A serious adverse event (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:

At least one month after vaccination

End point values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: subjects				
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).

End point title	Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).
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End point description:

An Adverse Event 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:

During the 30-day follow-up period after additional vaccination.

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	254 ^[11]		
Units: subjects				
AEs	139	169		

Notes:

[11] - Safety data were not available for 2 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events

End point title	Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events
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End point description:

A serious adverse event (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:

At least one month after vaccination

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	254 ^[12]		
Units: subjects				
SAEs	5	5		

Notes:

[12] - Safety data were not available for 2 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis A (HAV) antibody concentrations

End point title	Anti-hepatitis A (HAV) antibody concentrations
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End point description:

Geometric mean concentration for anti-HAV antibodies expressed as Milli-International Units per milliliter (mIU/mL)

End point type	Secondary
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End point timeframe:

Before (PRE) and 7 Months after vaccination (POST)

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	188		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
PRE (N=154;138)	7.5 (7.5 to 7.5)	7.5 (7.5 to 7.5)		
POST (N=201;188)	8412.1 (7483 to 9456.5)	9256.8 (8160 to 10501.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis B (HBs) antibody concentrations

End point title	Anti-hepatitis B (HBs) antibody concentrations
End point description: Geometric mean concentration for anti-HBs antibodies expressed as Milli-International Units per milliliter (mIU/mL).	
End point type	Secondary
End point timeframe: Before (PRE) and 7 Months after vaccination (POST)	

End point values	Twinrix Adult	Twinrix Junior		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	188		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
PRE (N=154;138)	7894.4 (1.7 to 1.7)	1.7 (1.7 to 1.7)		
POST (N=201;188)	1.7 (6130.9 to 10165.1)	13683.1 (11314.5 to 16547.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: During the 4-day (Day 0-3) follow-up period after the additional vaccination.

Unsolicited AEs: During the 31-day (Day 0-30) period after the additional vaccination; SAEs: During the entire study period

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	7.1

Reporting groups

Reporting group title	Twinrix Adult
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Reporting group description:

Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

Reporting group title	Twinrix Junior
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Reporting group description:

Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

Serious adverse events	Twinrix Adult	Twinrix Junior	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 254 (1.97%)	5 / 254 (1.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 254 (1.57%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 254 (0.39%)	0 / 254 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 254 (0.39%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 254 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
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	Twinrix Junior	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 254 (53.15%)	128 / 254 (50.39%)	
Nervous system disorders			
Syncope vasovagal (FU)			
subjects affected / exposed ^[1]	1 / 11 (9.09%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Headache (AEs) (Primary)			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 254 (5.12%)	18 / 254 (7.09%)	
occurrences (all)	13	18	
General disorders and administration site conditions			
Redness at the injection site (FU)			
subjects affected / exposed ^[2]	1 / 11 (9.09%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Pain at the injection site (FU)			
subjects affected / exposed ^[3]	6 / 11 (54.55%)	0 / 5 (0.00%)	
occurrences (all)	6	0	
Fatigue (FU)			
subjects affected / exposed ^[4]	3 / 11 (27.27%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorder (FU)			

subjects affected / exposed ^[5]	2 / 11 (18.18%)	0 / 5 (0.00%)
occurrences (all)	2	0
Headache (FU)		
subjects affected / exposed ^[6]	4 / 11 (36.36%)	0 / 5 (0.00%)
occurrences (all)	4	0
Pain (Primary)		
subjects affected / exposed ^[7]	135 / 250 (54.00%)	128 / 247 (51.82%)
occurrences (all)	135	128
Redness (Primary)		
subjects affected / exposed ^[8]	63 / 250 (25.20%)	76 / 247 (30.77%)
occurrences (all)	63	76
Swelling (Primary)		
subjects affected / exposed ^[9]	39 / 250 (15.60%)	52 / 247 (21.05%)
occurrences (all)	39	52
Drowsiness (Primary)		
subjects affected / exposed ^[10]	24 / 112 (21.43%)	39 / 122 (31.97%)
occurrences (all)	24	39
Irritability/Fussiness (Primary)		
subjects affected / exposed ^[11]	36 / 112 (32.14%)	52 / 122 (42.62%)
occurrences (all)	36	52
Loss of appetite (Primary)		
subjects affected / exposed ^[12]	20 / 112 (17.86%)	37 / 122 (30.33%)
occurrences (all)	20	37
Fever (Primary)		
subjects affected / exposed	21 / 254 (8.27%)	35 / 254 (13.78%)
occurrences (all)	21	35
Fatigue (Primary)		
subjects affected / exposed ^[13]	30 / 138 (21.74%)	36 / 125 (28.80%)
occurrences (all)	30	36
Gastrointestinal (Primary)		
subjects affected / exposed ^[14]	21 / 138 (15.22%)	26 / 125 (20.80%)
occurrences (all)	21	26
Headache (Primary)		
subjects affected / exposed ^[15]	25 / 138 (18.12%)	40 / 125 (32.00%)
occurrences (all)	25	40
Fever (AEs) (Primary)		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	14 / 254 (5.51%) 14	26 / 254 (10.24%) 26	
Injection site reaction (Primary) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	17 / 254 (6.69%) 17	21 / 254 (8.27%) 21	
Blood and lymphatic system disorders Pharyngitis (Primary) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	21 / 254 (8.27%) 21	31 / 254 (12.20%) 31	
Reproductive system and breast disorders Balanitis (FU) subjects affected / exposed ^[16] occurrences (all)	1 / 11 (9.09%) 1	0 / 5 (0.00%) 0	
Gastrointestinal disorders Vomiting (Primary) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	15 / 254 (5.91%) 15	16 / 254 (6.30%) 16	
Diarrhea (Primary) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	10 / 254 (3.94%) 10	13 / 254 (5.12%) 13	
Respiratory, thoracic and mediastinal disorders Coughing (Primary) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	11 / 254 (4.33%) 11	34 / 254 (13.39%) 34	
Musculoskeletal and connective tissue disorders Arthralgia (FU) subjects affected / exposed ^[17] occurrences (all)	1 / 11 (9.09%) 1	0 / 5 (0.00%) 0	
Infections and infestations			

Upper respiratory tract infection (Primary)			
alternative assessment type: Non-systematic			
subjects affected / exposed	35 / 254 (13.78%)	54 / 254 (21.26%)	
occurrences (all)	35	54	
Rhinitis (Primary)			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 254 (5.12%)	27 / 254 (10.63%)	
occurrences (all)	13	27	
Otitis media (Primary)			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 254 (4.33%)	15 / 254 (5.91%)	
occurrences (all)	11	15	

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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[11] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[12] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[13] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[14] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[15] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[16] - 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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[17] - 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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2001	<ul style="list-style-type: none">• To account for the competitive enrolment that is to be used for this study, extra randomization numbers and vaccine supplies will be needed at the study centres.• The study site in The Netherlands under Professor R.A. Coutinho and the study site in Croatia under Professor Berislav Borčić will now not be used and, in consequence, can be deleted from the study protocol. To replace these two sites, a new study site in Belgium has been incorporated (UCL, Brussels under Dr Etienne Sokal).• Anne Howard has been appointed as the Australian Study Monitor for this project, replacing Serge De Bartolo, therefore, her contact details are now included.• Inmaculada Nuñez Arias has been appointed as one of the Spanish Study Monitors for this project, replacing Sandra Sistiaga, therefore, her contact details are now included.• The section of the title pages requiring the signatures of the Principal Investigators has been deleted due to its redundancy in the modified protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported