

**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	v2 (current)
This version publication date	26 April 2023
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Correction of full data set and alignment between registries.

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
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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	Australia: 229
Country: Number of subjects enrolled	Belgium: 61
Country: Number of subjects enrolled	Spain: 110
Country: Number of subjects enrolled	Sweden: 110

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 2 - Year 5 (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 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 1^[1]	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5
Started	139	137
Completed	139	137

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide enrollment is from the Primary study 208127/120 and the number of subjects reported in the baseline period is from follow-up phase studies (208127/132 TO 208127/137) which started and completed the Study.

Baseline characteristics

Reporting groups

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).	

Reporting group values	Twinrix Adult Y2-Y5	Twinrix Junior Y2-Y5	Total
Number of subjects	139	137	276
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	11.6	11.2	
standard deviation	± 2.97	± 3.11	-
Gender categorical Units: Subjects			
Female	59	64	123
Male	80	73	153

End points

End points reporting groups

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)	998.6 (845.8 to 1178.9)	1347.1 (1145.1 to 1584.8)		
At year 4 (n=115; 105)	737.5 (623.6 to 872.3)	915.9 (774 to 1084)		
At year 5 (n=103; 101)	576.8 (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
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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]
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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
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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

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
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
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
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.
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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	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				
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).
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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 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

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 previously 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 previously 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	0 / 139 (0.00%)	0 / 137 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	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	7 / 139 (5.04%)	0 / 137 (0.00%)	
Nervous system disorders			
Syncope vasovagal (FU)			
subjects affected / exposed ^[1]	1 / 11 (9.09%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Redness at the injection site (FU) subjects affected / exposed ^[2] occurrences (all)	1 / 11 (9.09%) 1	0 / 5 (0.00%) 0	
Pain at the injection site (FU) subjects affected / exposed ^[3] occurrences (all)	6 / 11 (54.55%) 6	0 / 5 (0.00%) 0	
Fatigue (FU) subjects affected / exposed ^[4] occurrences (all)	3 / 11 (27.27%) 3	0 / 5 (0.00%) 0	
Gastrointestinal disorder (FU) subjects affected / exposed ^[5] occurrences (all)	2 / 11 (18.18%) 2	0 / 5 (0.00%) 0	
Headache (FU) subjects affected / exposed ^[6] occurrences (all)	4 / 11 (36.36%) 4	0 / 5 (0.00%) 0	
Reproductive system and breast disorders Balanitis (FU) subjects affected / exposed ^[7] occurrences (all)	1 / 11 (9.09%) 1	0 / 5 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia (FU) subjects affected / exposed ^[8] occurrences (all)	1 / 11 (9.09%) 1	0 / 5 (0.00%) 0	

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

[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: 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