



## Clinical trial results:

**A phase IIIb, randomized, open, multicentre study to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine co-administered with GlaxoSmithKline Biologicals' inactivated hepatitis A and hepatitis B vaccine adsorbed (Twinrix® Paediatric) in healthy female subjects aged 9–15 years.**

### Summary

EudraCT number	2007-004347-30
Trial protocol	SE HU DK
Global end of trial date	28 April 2009

### Results information

Result version number	v1
This version publication date	11 May 2016
First version publication date	22 November 2014

### Trial information

#### Trial identification

Sponsor protocol code	110886
-----------------------	--------

#### 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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2009
Global end of trial reached?	Yes
Global end of trial date	28 April 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To demonstrate non-inferiority of the hepatitis A immune response when HAB is co-administered with HPV-16/18 vaccine at Month 0, 1 and 6 compared to when HAB is administered alone at Month 0, 1 and 6.
- To demonstrate non-inferiority of the hepatitis B immune response in terms of proportion of subjects who are seroprotected for anti-HBs at Month 7 when HAB is co-administered with HPV-16/18 vaccine at Month 0, 1 and 6 compared to when HAB is administered alone at Month 0, 1 and 6.
- To demonstrate non-inferiority of the HPV-16/18 immune response at Month 7 when the HPV-16/18 vaccine is co-administered with HAB compared to when the HPV-16/18 vaccine is administered alone.

Protection of trial subjects:

As with all injectable vaccines, appropriate medical treatment was always readily available in case of anaphylactic reactions following the administration of the vaccine.  
For this reason, the vaccinee remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 220
Country: Number of subjects enrolled	Denmark: 213
Country: Number of subjects enrolled	Hungary: 268
Country: Number of subjects enrolled	Canada: 113
Worldwide total number of subjects	814
EEA total number of subjects	701

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)	814
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:

Although the total number of enrolled subjects for this study was 814, one subject did not receive any study vaccine and was therefore not considered as started in the 'Participant Flow' section.

### Pre-assignment period milestones

Number of subjects started	814
Number of subjects completed	813 <sup>[1]</sup>

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	No vaccination received: 1
----------------------------	----------------------------

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.

Justification: Although the total number of enrolled subjects for this study was 814, 1 subject did not receive any study vaccine and was therefore not considered as having started the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Cervarix™ & Twinrix™ Group

Arm description:

Subjects received 3 doses of Human Papilloma Virus (HPV) vaccine co-administered with combined Hepatitis A & Hepatitis B (HAB) vaccine (Months 0, 1 & 6).

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered at Day 0, Month 1 and Month 6. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm when administered alone or in both arms when co-administered.

Investigational medicinal product name	Twinrix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered at Day 0, at Month 1 and Month 6. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm when administered alone or in both arms when co-administered.

<b>Arm title</b>	Cervarix™ Group
------------------	-----------------

Arm description:

Subjects received 3 doses of HPV vaccine (Months 0, 1 & 6).

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered at Day 0, Month 1 and Month 6. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm when administered alone or in both arms when co-administered.

<b>Arm title</b>	Twinrix™ Group
------------------	----------------

Arm description:

Subjects received 3 doses of HAB vaccine (Months 0, 1 & 6).

Arm type	Active comparator
Investigational medicinal product name	Twinrix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered at Day 0, at Month 1 and Month 6. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm when administered alone or in both arms when co-administered.

<b>Number of subjects in period 1</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group
Started	272	270	271
Completed	267	268	267
Not completed	5	2	4
Consent withdrawn by subject	5	1	3
Lost to follow-up	-	1	1

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

Reporting group title	Cervarix™ & Twinrix™ Group
-----------------------	----------------------------

Reporting group description:

Subjects received 3 doses of Human Papilloma Virus (HPV) vaccine co-administered with combined Hepatitis A & Hepatitis B (HAB) vaccine (Months 0, 1 & 6).

Reporting group title	Cervarix™ Group
-----------------------	-----------------

Reporting group description:

Subjects received 3 doses of HPV vaccine (Months 0, 1 & 6).

Reporting group title	Twinrix™ Group
-----------------------	----------------

Reporting group description:

Subjects received 3 doses of HAB vaccine (Months 0, 1 & 6).

Notes:

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

Justification: Although the total number of enrolled subjects for this study was 814, 1 subject did not receive any study vaccine and was therefore not considered as having started the study.

Reporting group values	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group
Number of subjects	272	270	271
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
geometric mean	11.2	11.2	11.2
standard deviation	± 2.04	± 2.02	± 1.99
Gender categorical Units: Subjects			
Female	272	270	271
Male	0	0	0

Reporting group values	Total		
Number of subjects	813		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years geometric mean standard deviation	-		
Gender categorical Units: Subjects			
Female	813		
Male	0		

## End points

### End points reporting groups

Reporting group title	Cervarix™ & Twinrix™ Group
Reporting group description:	
Subjects received 3 doses of Human Papilloma Virus (HPV) vaccine co-administered with combined Hepatitis A & Hepatitis B (HAB) vaccine (Months 0, 1 & 6).	
Reporting group title	Cervarix™ Group
Reporting group description:	
Subjects received 3 doses of HPV vaccine (Months 0, 1 & 6).	
Reporting group title	Twinrix™ Group
Reporting group description:	
Subjects received 3 doses of HAB vaccine (Months 0, 1 & 6).	

### Primary: Number of subjects seroconverted for anti-hepatitis A (anti-HAV) antibodies

End point title	Number of subjects seroconverted for anti-hepatitis A (anti-HAV) antibodies <sup>[1][2]</sup>
End point description:	
Seroconversion is defined as the appearance of anti-HAV antibodies [i.e., antibody titer greater than or equal to 15 milli-international units/milliliter (mIU/mL)] in the sera of subjects seronegative (antibody titer below 15 mIU/mL) before vaccination.	
End point type	Primary
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	
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis was only performed on subjects who had received HAB vaccination.	

End point values	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	242		
Units: Subjects	240	242		

### Statistical analyses

No statistical analyses for this end point

### Primary: Anti-Heptatis A (HAV) antibody titers.

End point title	Anti-Heptatis A (HAV) antibody titers. <sup>[3][4]</sup>
End point description:	
Titers are given as Geometric Mean Titers (GMTs) expressed as mIU/mL.	

End point type	Primary
----------------	---------

End point timeframe:

At Month 7

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.

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

End point values	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	242		
Units: mIU/mL				
geometric mean (confidence interval 95%)	4504.2 (3993 to 5080.8)	5288.4 (4713.3 to 5933.7)		

## 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 <sup>[5][6]</sup>
-----------------	---

End point description:

A subject seroprotected against HBs is a subject with antibody titers greater than or equal to 10 mIU/mL.

End point type	Primary
----------------	---------

End point timeframe:

At Month 7

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

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

End point values	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	161		
Units: Subjects	175	161		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies

End point title	Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies <sup>[7][8]</sup>
-----------------	---

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values = 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies.

End point type	Primary
----------------	---------

End point timeframe:

At Month 7

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

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

Justification: The analysis was only performed on subjects who had received HPV vaccination.

End point values	Cervarix™ & Twinrix™ Group	Cervarix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	241		
Units: Subjects				
Anti-HPV-16 (n= 229, 233)	228	223		
Anti-HPV-18 (n= 239, 241)	238	241		

## Statistical analyses

No statistical analyses for this end point

### Primary: Anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibody titers

End point title	Anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibody titers <sup>[9][10]</sup>
-----------------	--

End point description:

Titers are given as Geometric Mean Titers (GMTs) expressed as Enzyme-linked Immunosorbent Assay Units Per Milliliter (EL.U/mL).

End point type	Primary
----------------	---------

End point timeframe:

At Month 7

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

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

Justification: The analysis was only performed on subjects who had received HPV vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	241		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 GMTs (n= 229, 233)	22993.5 (20093.4 to 26312)	26981.9 (23909.5 to 30449.1)		
Anti-HPV-18 GMTs (n= 239, 241)	8671.2 (7651.7 to 9826.6)	11182.7 (9924.8 to 12600.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-HBs antibody Titers

End point title	Anti-HBs antibody Titers <sup>[11]</sup>
End point description:	Titers are given as Geometric Mean Titers (GMTs) expressed as mIU/mL.
End point type	Secondary
End point timeframe:	At Month 7

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	161		
Units: mIU/mL				
geometric mean (confidence interval 95%)	3136.5 (2436 to 4038.4)	5646.5 (4481.3 to 7114.6)		

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seroconverted for anti-HBs antibodies

End point title | Number of subjects seroconverted for anti-HBs antibodies<sup>[12]</sup>

End point description:

Seroconversion is defined as the appearance of anti-HBs antibodies (i.e., antibody titer greater than or equal to 3.3 mIU/mL) in the sera of subjects seronegative (with antibody titers below 3.3 mIU/mL) before vaccination.

End point type | Secondary

End point timeframe:

At month 7

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

End point values	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	161		
Units: Subjects	175	161		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies in vaccine recipients aged 9 years

End point title | Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies in vaccine recipients aged 9 years<sup>[13]</sup>

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values = 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies.

End point type | Secondary

End point timeframe:

At Month 7

Notes:

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

Justification: The analysis was only performed on subjects who had received HPV vaccination.

End point values	Cervarix™ Group			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Subjects				
Anti-HPV-16 (n= 156)	156			
Anti-HPV-18 (n= 161)	161			

## Statistical analyses

No statistical analyses for this end point

---

### Secondary: Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibody Titers in vaccine recipients aged 9 years

End point title	Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-human Papilloma Virus 18 (Anti-HPV-18) Antibody Titers in vaccine recipients aged 9 years
-----------------	--

End point description:

Titers are given as Geometric Mean Titers (GMTs) expressed as Enzyme-linked Immunosorbent Assay Units Per Milliliter (EL.U/mL).

End point type	Secondary
----------------	-----------

End point timeframe:

At Month 7

---

## Statistical analyses

No statistical analyses for this end point

---

### Secondary: Number of subjects seroconverted for anti-HAV antibodies

End point title	Number of subjects seroconverted for anti-HAV antibodies <sup>[14]</sup>
-----------------	--

End point description:

Seroconversion is defined as the appearance of anti-HAV antibodies (i.e., antibody titer greater than or equal to 15 mIU/mL) in the sera of subjects seronegative (antibody titer below 15 mIU/mL) before vaccination.

End point type	Secondary
----------------	-----------

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Subjects	112	112		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-HAV antibody titers

End point title	Anti-HAV antibody titers <sup>[15]</sup>
-----------------	--

End point description:

Titers are given as geometric mean titers (GMTs) expressed as mIU/mL.

End point type	Secondary
----------------	-----------

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: mIU/mL				
geometric mean (confidence interval 95%)	467 (374.4 to 582.5)	513.9 (418.7 to 630.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seroconverted and number of subjects seroprotected for anti-HBs antibodies

End point title	Number of subjects seroconverted and number of subjects seroprotected for anti-HBs antibodies <sup>[16]</sup>
-----------------	---

End point description:

Seroconversion is defined as the appearance of anti-HBs antibodies (i.e., antibody titer greater than or equal to 3.3 mIU/mL) in the sera of subjects seronegative (with antibody titers below 3.3 mIU/mL) before vaccination. A seroprotected subject against HBs is a subject with antibody titers greater than or equal to 10 mIU/mL.

End point type	Secondary
----------------	-----------

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	58		
Units: Subjects				
Seroconverted	68	56		
Seroprotected	60	53		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-HBs antibody titers

End point title | Anti-HBs antibody titers<sup>[17]</sup>

End point description:

Titers are given as geometric mean titers (GMTs) expressed as mIU/mL.

End point type | Secondary

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HAB vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Twinrix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	58		
Units: mIU/mL				
geometric mean (confidence interval 95%)	33.7 (24.9 to 45.8)	43 (30.1 to 61.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies

End point title | Number of subjects seroconverted for anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies<sup>[18]</sup>

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values assessed include 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies.

End point type Secondary

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HPV vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Subjects				
Anti-HPV-16 (n=105, 107)	105	106		
Anti-HPV-18 (n= 112, 112)	112	111		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibody titers

End point title Anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibody titers<sup>[19]</sup>

End point description:

Titers are given as Geometric Mean Titers (GMTs) expressed as EL.U/mL.

End point type Secondary

End point timeframe:

One month after the second dose of vaccine

Notes:

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

Justification: The analysis was only performed on subjects who had received HPV vaccination.

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 GMTs (n= 105, 107)	5215.2 (4598.2 to 5915)	4967.2 (4142.5 to 5956.1)		

Anti-HPV-18 GMTs (n= 112, 112)	4496.8 (3899.4 to 5185.8)	4266.5 (3562.9 to 5109)		
--------------------------------	---------------------------	-------------------------	--	--

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Reporting Solicited Local Symptoms

End point title	Number of Subjects Reporting Solicited Local Symptoms
-----------------	---

End point description:

Solicited local symptoms assessed include injection site pain, redness and swelling. Data are presented across doses.

End point type	Secondary
----------------	-----------

End point timeframe:

During the 7-day period (Day 0-6) following vaccination

End point values	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	270	271	
Units: Subjects				
Pain	252	250	202	
Redness	155	170	74	
Swelling	146	137	56	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Reporting Solicited General Symptoms

End point title	Number of Subjects Reporting Solicited General Symptoms
-----------------	---

End point description:

Solicited general symptoms assessed include arthralgia, fatigue, gastrointestinal symptoms, headache, myalgia, rash, temperature [axillary route, greater than or equal to 37.5 degree Celsius (°C)] and urticaria.

End point type	Secondary
----------------	-----------

End point timeframe:

During the 7-day period following vaccination

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	270	271	
Units: Subjects				
Arthralgia	50	45	40	
Fatigue	122	133	119	
Fever	24	28	14	
Gastrointestinal	70	65	72	
Headache	125	124	110	
Myalgia	103	99	75	
Rash	18	21	12	
Urticaria	6	11	9	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting medically significant conditions

End point title	Number of subjects reporting medically significant conditions
-----------------	---

End point description:

Medically significant conditions include adverse events (AEs) prompting emergency room or physician visits that are not related to common diseases or routine visits for physical examination or vaccination, or serious adverse events (SAEs) that are not related to common diseases. Common diseases include upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervico-vaginal yeast infections, menstrual cycle abnormalities and injury.

End point type	Secondary
----------------	-----------

End point timeframe:

Throughout the active phase of the study (up to Month 7)

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	272	270	271	
Units: Subjects	22	23	31	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Reporting Medically Significant Conditions

End point title	Number of Subjects Reporting Medically Significant Conditions
-----------------	---

End point description:

Medically significant conditions include adverse events (AEs) prompting emergency room or physician

visits that are not related to common diseases or routine visits for physical examination or vaccination, or serious adverse events (SAEs) that are not related to common diseases. Common diseases include upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervico-vaginal yeast infections, menstrual cycle abnormalities and injury.

End point type	Secondary
End point timeframe:	
Throughout the safety follow-up (from Month 7 up to Month 12)	

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	272	270	271	
Units: Subjects	2	2	1	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Reporting Unsolicited Adverse Events

End point title	Number of Subjects Reporting Unsolicited Adverse Events
End point description:	
Unsolicited adverse events include any adverse event reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.	
End point type	Secondary
End point timeframe:	
During the 30-day period following any vaccination	

<b>End point values</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	272	270	271	
Units: Subjects	83	96	83	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Reporting Serious Adverse Events (SAE)

End point title	Number of Subjects Reporting Serious Adverse Events (SAE)
-----------------	---



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 0 up to Month 12.

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	10.0
--------------------	------

### Reporting groups

Reporting group title	Cervarix™ & Twinrix™ Group
-----------------------	----------------------------

Reporting group description:

Subjects received 3 doses of Human Papilloma Virus (HPV) vaccine co-administered with combined Hepatitis A & Hepatitis B (HAB) vaccine (Months 0, 1 & 6).

Reporting group title	Cervarix™ Group
-----------------------	-----------------

Reporting group description:

Subjects received 3 doses of HPV vaccine (Months 0, 1 & 6).

Reporting group title	Twinrix™ Group
-----------------------	----------------

Reporting group description:

Subjects received 3 doses of HAB vaccine (Months 0, 1 & 6).

<b>Serious adverse events</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	2 / 272 (0.74%)	3 / 270 (1.11%)	4 / 271 (1.48%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
<b>Injury, poisoning and procedural complications</b>			
<b>Ankle fracture</b>			
subjects affected / exposed	0 / 272 (0.00%)	1 / 270 (0.37%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Concussion</b>			
subjects affected / exposed	1 / 272 (0.37%)	0 / 270 (0.00%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Head injury</b>			
subjects affected / exposed	0 / 272 (0.00%)	0 / 270 (0.00%)	1 / 271 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tibia fracture			
subjects affected / exposed	0 / 272 (0.00%)	0 / 270 (0.00%)	1 / 271 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous injury			
subjects affected / exposed	0 / 272 (0.00%)	0 / 270 (0.00%)	1 / 271 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 272 (0.37%)	0 / 270 (0.00%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 272 (0.00%)	1 / 270 (0.37%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 272 (0.00%)	0 / 270 (0.00%)	1 / 271 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 272 (0.00%)	0 / 270 (0.00%)	1 / 271 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 272 (0.00%)	1 / 270 (0.37%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	0 / 272 (0.00%)	1 / 270 (0.37%)	0 / 271 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Cervarix™ & Twinrix™ Group	Cervarix™ Group	Twinrix™ Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	251 / 272 (92.28%)	250 / 270 (92.59%)	202 / 271 (74.54%)
General disorders and administration site conditions			
Pain at injection site			
alternative assessment type: Systematic			
subjects affected / exposed	251 / 272 (92.28%)	250 / 270 (92.59%)	202 / 271 (74.54%)
occurrences (all)	251	250	202
Redness at injection site			
alternative assessment type: Systematic			
subjects affected / exposed	155 / 272 (56.99%)	170 / 270 (62.96%)	74 / 271 (27.31%)
occurrences (all)	155	170	74
Swelling at injection site			
alternative assessment type: Systematic			
subjects affected / exposed	146 / 272 (53.68%)	137 / 270 (50.74%)	56 / 271 (20.66%)
occurrences (all)	146	137	56
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	50 / 272 (18.38%)	45 / 270 (16.67%)	40 / 271 (14.76%)
occurrences (all)	50	45	40
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 272 (8.82%)	28 / 270 (10.37%)	14 / 271 (5.17%)
occurrences (all)	24	28	14
Gastrointestinal symptoms			
alternative assessment type: Systematic			
subjects affected / exposed	70 / 272 (25.74%)	65 / 270 (24.07%)	72 / 271 (26.57%)
occurrences (all)	70	65	72

Headache			
alternative assessment type: Systematic			
subjects affected / exposed	125 / 272 (45.96%)	124 / 270 (45.93%)	110 / 271 (40.59%)
occurrences (all)	125	124	110
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	103 / 272 (37.87%)	99 / 270 (36.67%)	75 / 271 (27.68%)
occurrences (all)	103	99	75
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	18 / 272 (6.62%)	21 / 270 (7.78%)	12 / 271 (4.43%)
occurrences (all)	18	21	12
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	122 / 272 (44.85%)	133 / 270 (49.26%)	119 / 271 (43.91%)
occurrences (all)	122	133	119
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 272 (2.21%)	21 / 270 (7.78%)	13 / 271 (4.80%)
occurrences (all)	6	21	13

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported