



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 ^[1] |

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 |
| Arm title | 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.

| | |
|------------------|-----------------|
| Arm title | 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.

| | |
|------------------|----------------|
| Arm title | 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.

| Number of subjects in period 1 | 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^[1]

| | |
|---|----------------------------|
| 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 ^{[1][2]} |
| 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. ^{[3][4]} |
| 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 ^{[5][6]} | | | |
| 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 ^{[7][8]} |
|-----------------|---|

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 ^{[9][10]} |
|-----------------|--|

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.

| End point values | 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 ^[11] |
| 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.

| End point values | 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 ^[12] |
|-----------------|--|

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 ^[13] |
|-----------------|--|

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 ^[14] |
|-----------------|--|

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.

| End point values | 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 ^[15] |
| 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.

| End point values | 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 ^[16] |
| 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.

| End point values | 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 ^[17] |
|-----------------|--|

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.

| End point values | 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 ^[18] |
|-----------------|---|

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.

| End point values | 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 ^[19] |
|-----------------|---|

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.

| End point values | 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

| 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 | | | | |
| 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)

| End point values | 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) | |

| End point values | 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 | |

| End point values | 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) |
|-----------------|---|

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

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

End point timeframe:

Throughout the study (up to Month 12)

| End point values | 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 | 4 | 4 | |

Statistical analyses

No statistical analyses for this end point

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).

| Serious adverse events | Cervarix™ & Twinrix™ Group | Cervarix™ Group | Twinrix™ Group |
|---|----------------------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| 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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| 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 |
| Concussion | | | |
| 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 |
| Head 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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| 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 %

| Non-serious adverse events | 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