



Clinical trial results:

A Phase IIIb observer-blind, randomized, multicentre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine and Merck's Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, when administered intramuscularly according to alternative 2-dose schedules in 9-14-year-old healthy females.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-002035-26 |
| Trial protocol | FR SE |
| Global end of trial date | 27 October 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v3 (current) |
| This version publication date | 12 April 2020 |
| First version publication date | 21 April 2016 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 115411 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01462357 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330 |
| Public contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate sequentially if the immunogenicity (as determined by enzyme-linked immunosorbent assay [ELISA]) of GSK Biologicals' HPV-16/18 L1 Virus-like-particle (VLP) AS04 vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of Merck's HPV-6/11/16/18 L1 VLP recombinant vaccine administered according to a 2-dose schedule at 0, 6 months in 9-14 year-old females, 1 month after the last dose (Month 7).

Protection of trial subjects:

All subjects were observed closely for 30 min after vaccination/product administration, with appropriate medical treatment readily available in case of a rare anaphylactic reaction. 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 | 21 November 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Sweden: 72 |
| Country: Number of subjects enrolled | France: 231 |
| Country: Number of subjects enrolled | Hong Kong: 534 |
| Country: Number of subjects enrolled | Singapore: 242 |
| Worldwide total number of subjects | 1079 |
| EEA total number of subjects | 303 |

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) | 551 |
| Adolescents (12-17 years) | 528 |
| 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:

1079 subjects entered this study, of which 4 subjects signed an informed consent but did not receive a single dose of the vaccine and were hence not counted as starting the study.

Pre-assignment period milestones

| | |
|----------------------------|------|
| Number of subjects started | 1079 |
|----------------------------|------|

| | |
|------------------------------|------|
| Number of subjects completed | 1075 |
|------------------------------|------|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|----------------------------|
| Reason: Number of subjects | No vaccine administered: 4 |
|----------------------------|----------------------------|

Period 1

| | |
|----------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
|----------------|--------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|---------------------------------|
| Roles blinded | Subject, Investigator, Assessor |
|---------------|---------------------------------|

Blinding implementation details:

Data was collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. immunogenicity, reactogenicity, and safety) were all unaware of which vaccine was administered. To do so, vaccine preparation and administration were be done by authorised medical personnel who did not participate in any of the study clinical evaluation assays.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|-----------|-----------------------|
| Arm title | Cervarix 2 dose Group |
|-----------|-----------------------|

Arm description:

Subjects who received 2 doses of Cervarix vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------|
| Investigational medicinal product name | Cervarix |
|--|----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|--|
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
|----------------------|--|

| | |
|--------------------------|-------------------|
| Routes of administration | Intramuscular use |
|--------------------------|-------------------|

Dosage and administration details:

2 doses of 0.5 mL supplied as a liquid in individual pre-filled syringes administered intramuscularly in the deltoid muscle of the non-dominant arm at Day 0 and Month 6.

| | |
|--|---------|
| Investigational medicinal product name | Placebo |
|--|---------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|--|
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
|----------------------|--|

| | |
|--------------------------|-------------------|
| Routes of administration | Intramuscular use |
|--------------------------|-------------------|

Dosage and administration details:

2 doses of 0.5 mL supplied as a liquid in individual pre-filled syringes, administered intramuscularly in

the deltoid muscle of the non-dominant arm at Month 2 (Cervarix 2 dose Group and Gardasil 2 dose Group) to maintain blinding.

| | |
|------------------|-----------------------|
| Arm title | Gardasil 2 dose Group |
|------------------|-----------------------|

Arm description:

Subjects who received 2 doses of Gardasil vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

2 doses of 0.5 mL supplied as a liquid in individual pre-filled syringes, administered intramuscularly in the deltoid muscle of the non-dominant arm at Month 2 (Cervarix 2 dose Group and Gardasil 2 dose Group) to maintain blinding.

| | |
|--|--|
| Investigational medicinal product name | Gardasil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

2 or 3 doses of 0.5 mL supplied as a liquid in individual pre-filled syringes or vials to be administered intramuscularly in the deltoid muscle of the non-dominant arm at Day 0 and Month 6 (Gardasil 2 dose Group) or at Day 0, Month 2 and Month 6 (Gardasil 3 dose Group), respectively.

| | |
|------------------|-----------------------|
| Arm title | Gardasil 3 dose Group |
|------------------|-----------------------|

Arm description:

Subjects who received 3 doses of Gardasil vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Gardasil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

2 or 3 doses of 0.5 mL supplied as a liquid in individual pre-filled syringes or vials to be administered intramuscularly in the deltoid muscle of the non-dominant arm at Day 0 and Month 6 (Gardasil 2 dose Group) or at Day 0, Month 2 and Month 6 (Gardasil 3 dose Group), respectively.

| Number of subjects in period 1^[1] | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group |
|---|-----------------------|-----------------------|-----------------------|
| Started | 359 | 358 | 358 |
| Completed | 351 | 339 | 346 |
| Not completed | 8 | 19 | 12 |

| | | | |
|--|---|----|---|
| Consent withdrawal (not due to an adverse event) | 3 | 11 | 3 |
| Death | - | - | 1 |
| Migrated/moved from study area | 2 | 3 | 1 |
| Lost to follow-up | 3 | 5 | 7 |

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: 1079 subjects entered this study, of which 4 subjects signed an informed consent but did not receive a single dose of the vaccine and were hence not counted as starting the study.

Baseline characteristics

Reporting groups

| | |
|---|-----------------------|
| Reporting group title | Cervarix 2 dose Group |
| Reporting group description: | |
| Subjects who received 2 doses of Cervarix vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |
| Reporting group title | Gardasil 2 dose Group |
| Reporting group description: | |
| Subjects who received 2 doses of Gardasil vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |
| Reporting group title | Gardasil 3 dose Group |
| Reporting group description: | |
| Subjects who received 3 doses of Gardasil vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |

| Reporting group values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group |
|------------------------------------|-----------------------|-----------------------|-----------------------|
| Number of subjects | 359 | 358 | 358 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age Continuous Units: Years | | | |
| arithmetic mean | 11.5 | 11.5 | 11.6 |
| standard deviation | ± 1.64 | ± 1.56 | ± 1.64 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 359 | 358 | 358 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| African Heritage / African American | 4 | 6 | 4 |
| Asian - Central / South Asian Heritage | 1 | 1 | 2 |
| Asian - East Asian Heritage | 179 | 178 | 179 |
| Asian - South East Asian Heritage | 81 | 78 | 83 |
| White - Arabic / North African Heritage | 5 | 7 | 7 |
| White - Caucasian / European Heritage | 89 | 86 | 83 |
| White - Caucasian / African Heritage | 0 | 1 | 0 |
| African - White / Caucasian Heritage | 0 | 1 | 0 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 1075 | | |

| | | | |
|---|------|--|--|
| Age categorical Units: Subjects | | | |
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 1075 | | |
| Male | 0 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| African Heritage / African American | 14 | | |
| Asian - Central / South Asian Heritage | 4 | | |
| Asian - East Asian Heritage | 536 | | |
| Asian - South East Asian Heritage | 242 | | |
| White - Arabic / North African Heritage | 19 | | |
| White - Caucasian / European Heritage | 258 | | |
| White - Caucasian / African Heritage | 1 | | |
| African - White / Caucasian Heritage | 1 | | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Cervarix 2 dose Group |
| Reporting group description: Subjects who received 2 doses of Cervarix vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |
| Reporting group title | Gardasil 2 dose Group |
| Reporting group description: Subjects who received 2 doses of Gardasil vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |
| Reporting group title | Gardasil 3 dose Group |
| Reporting group description: Subjects who received 3 doses of Gardasil vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm. | |

Primary: Number of seroconverted subjects for anti-HPV-16/18 antibodies as assessed by Enzyme-Linked Immunosorbent Assay (ELISA) at Month 7 based on the ATP cohort for immunogenicity

| | |
|---|---|
| End point title | Number of seroconverted subjects for anti-HPV-16/18 antibodies as assessed by Enzyme-Linked Immunosorbent Assay (ELISA) at Month 7 based on the ATP cohort for immunogenicity |
| End point description: Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to (\geq) 19 and 18 ELISA units per milliliter (EL.U/mL), respectively), in the serum of subjects seronegative before vaccination. | |
| End point type | Primary |
| End point timeframe: At Month 7 (i.e. one month after the last dose of study vaccine) | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 334 | 331 | 333 | |
| Units: Subjects | | | | |
| Anti-HPV-16 (N=330, 327, 322) | 330 | 327 | 322 | |
| Anti-HPV-18 (N=334, 331, 333) | 334 | 331 | 333 | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Immune response to anti-HPV-16 in terms of SCR |
| Statistical analysis description: Immune response to anti-HPV-16 in terms of seroconversion rates (SCR): To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose | |

schedule at 0, 6 months is non-inferior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, 1 month after the last dose (Month 7), in initially seronegative subjects.

| | |
|---|---|
| Comparison groups | Cervarix 2 dose Group v Gardasil 2 dose Group |
| Number of subjects included in analysis | 665 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in SCR |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.16 |
| upper limit | 1.15 |

Notes:

[1] - Non-inferiority with respect to seroconversion was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the difference (Gardasil 2 dose Group minus Cervarix 2 dose Group) was below 5%.

| | |
|-----------------------------------|--|
| Statistical analysis title | Immune response to anti-HPV-18 in terms of SCR |
|-----------------------------------|--|

Statistical analysis description:

Immune response to anti-HPV-18 in terms of SCR: To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, 1 month after the last dose (Month 7), in initially seronegative subjects.

| | |
|---|---|
| Comparison groups | Gardasil 2 dose Group v Cervarix 2 dose Group |
| Number of subjects included in analysis | 665 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Difference in SCR |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.15 |
| upper limit | 1.14 |

Notes:

[2] - Non-inferiority with respect to seroconversion was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the difference (Gardasil 2 dose Group minus Cervarix 2 dose Group) was below 5%.

Primary: Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 7 based on the ATP cohort for immunogenicity

| | |
|-----------------|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 7 based on the ATP cohort for immunogenicity |
|-----------------|---|

End point description:

Anti-HPV 16/18 antibody titers were presented as Geometric Mean Titers (GMTs) and expressed in EL.U/mL.

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

End point timeframe:

At Month 7 (i.e. one month after the last dose of study vaccine)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|---------------------------|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 334 | 331 | 333 | |
| Units: EL.U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV-16 (N=330,327,322) | 8244.1 (7678.3 to 8851.7) | 5056.0 (4596.5 to 5561.5) | 4807.4 (4420.8 to 5227.7) | |
| Anti-HPV-18 (N=334,331,333) | 5277.4 (4858.6 to 5732.4) | 1207.2 (1092.9 to 1333.4) | 1653.5 (1484.4 to 1841.8) | |

Statistical analyses

| Statistical analysis title | Immune response to anti-HPV-16 in terms of GMT |
|---|--|
| Statistical analysis description: | |
| Immune response to anti-HPV-16 in terms of Geometric Mean Titers (GMT): To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, 1 month after the last dose (Month 7), in initially seronegative subjects. | |
| Comparison groups | Gardasil 2 dose Group v Cervarix 2 dose Group |
| Number of subjects included in analysis | 665 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.69 |

Notes:

[3] - Non-inferiority with respect to GMT was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% CI for the GMT ratio (Gardasil 2 dose Group divided by Cervarix 2 dose Group) was below 2.

| Statistical analysis title | Immune response to anti-HPV-18 in terms of GMT |
|---|--|
| Statistical analysis description: | |
| Immune response to anti-HPV-18 in terms of GMT: To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, 1 month after the last dose (Month 7), in initially seronegative subjects. | |
| Comparison groups | Gardasil 2 dose Group v Cervarix 2 dose Group |
| Number of subjects included in analysis | 665 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 0.23 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.26 |

Notes:

[4] - Non-inferiority with respect to GMT was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the GMT ratio (Gardasil 2 dose Group divided by Cervarix 2 dose Group) was below 2.

Primary: Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 7 based on the Total Vaccinated Cohort (TVC)

| | |
|-----------------|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 7 based on the Total Vaccinated Cohort (TVC) |
|-----------------|---|

End point description:

Anti-HPV 16/18 antibody titers were presented as Geometric Mean Titers (GMTs) and expressed in EL.U/mL.

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

End point timeframe:

At Month 7 (i.e. one month after the last dose of study vaccine)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|---------------------------|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 357 | 353 | 351 | |
| Units: EL.U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV-16 (N=357, 353, 351) | 8256.4 (7650.3 to 8910.6) | 4886.1 (4435.4 to 5382.6) | 4789.2 (4409.6 to 5201.4) | |
| Anti-HPV-18 (N=357, 353, 351) | 5267.8 (4857.1 to 5713.2) | 1166.3 (1056 to 1288.2) | 1635.8 (1470 to 1820.4) | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Anti-HPV-18 immune response |
|----------------------------|-----------------------------|

Statistical analysis description:

Anti-HPV-18 immune response: To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose schedule at 0, 6 months is superior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7) regardless of serostatus.

| | |
|---|---|
| Comparison groups | Cervarix 2 dose Group v Gardasil 2 dose Group |
| Number of subjects included in analysis | 710 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 4.52 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.97 |
| upper limit | 5.13 |

Notes:

[5] - Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs (Cervarix 2 dose Group divided by Gardasil 2 dose Group) was above 1 for anti-HPV-18 antibodies.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Anti-HPV-16 immune response |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Anti-HPV-16 immune response: To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix vaccine administered according to a 2-dose schedule at 0, 6 months is superior to that of Gardasil vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7) regardless of serostatus.

| | |
|---|---|
| Comparison groups | Cervarix 2 dose Group v Gardasil 2 dose Group |
| Number of subjects included in analysis | 710 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.49 |
| upper limit | 1.91 |

Notes:

[6] - Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs (Cervarix 2 dose Group divided by Gardasil 2 dose Group) was above 1 for anti-HPV-16 antibodies.

Secondary: Anti-HPV-16/18 seroconversion rates as assessed by ELISA

| | |
|-----------------|--|
| End point title | Anti-HPV-16/18 seroconversion rates as assessed by ELISA |
|-----------------|--|

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers ≥ 19 and 18 EL.U/mL, respectively) in the serum of subjects seronegative before vaccination.

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

End point timeframe:

At Day 0 and Months 12, 18, 24 and 36

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|---|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 322 | 310 | 320 | |
| Units: Subjects | | | | |
| Anti-HPV-16, Day 0 (N=318, 306, 309) | 0 | 0 | 0 | |
| Anti-HPV-18, Day 0 (N=322, 310, 320) | 0 | 0 | 0 | |
| Anti-HPV-16, Month 12 (N=317, 305, 308) | 316 | 305 | 308 | |
| Anti-HPV-18, Month 12 (N=321, 309, 319) | 320 | 309 | 319 | |

| | | | | |
|---|-----|-----|-----|--|
| Anti-HPV-16, Month 18 (N=316, 305, 309) | 316 | 304 | 309 | |
| Anti-HPV-18, Month 18 (N=320, 309, 320) | 320 | 294 | 313 | |
| Anti-HPV-16, Month 24 (N=314, 304, 307) | 314 | 303 | 307 | |
| Anti-HPV-18, Month 24 (N=318, 308, 318) | 318 | 287 | 308 | |
| Anti-HPV-16, Month 36 (N=318, 306, 309) | 318 | 304 | 308 | |
| Anti-HPV-18, Month 36 (N=322, 310, 320) | 322 | 267 | 297 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers as assessed by ELISA

| | |
|--|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by ELISA |
| End point description: Anti-HPV 16/18 antibody titers were presented as GMTs and expressed in EL.U/mL based on ELISA. | |
| End point type | Secondary |
| End point timeframe: At Day 0 and Months 12, 18, 24 and 36 | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|---------------------------|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 322 | 310 | 320 | |
| Units: EL.U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV-16, Day 0 (N=318, 306, 309) | 9.5 (9.5 to 9.5) | 9.5 (9.5 to 9.5) | 9.5 (9.5 to 9.5) | |
| Anti-HPV-18, Day 0 (N=322, 310, 320) | 9.0 (9.0 to 9.0) | 9.0 (9.0 to 9.0) | 9.0 (9.0 to 9.0) | |
| Anti-HPV-16, Month 12 (N=317, 305, 308) | 2209.2 (2014 to 2423.4) | 1294.8 (1160.4 to 1444.9) | 1600.7 (1457.3 to 1758.2) | |
| Anti-HPV-18, Month 12 (N=321, 309, 319) | 1299.3 (1176.2 to 1435.6) | 266.6 (236.3 to 300.8) | 478.5 (422.8 to 541.6) | |
| Anti-HPV-16, Month 18 (N=316, 305, 309) | 1488.8 (1365.5 to 1623.3) | 684.4 (605.8 to 773.2) | 824.0 (744.4 to 912.2) | |
| Anti-HPV-18, Month 18 (N=320, 309, 320) | 754.2 (682.6 to 833.2) | 134.8 (118.1 to 154) | 231.3 (202.4 to 264.4) | |
| Anti-HPV-16, Month 24 (N=314, 304, 307) | 1285.0 (1181.1 to 1398.0) | 514.1 (455.4 to 580.3) | 637.1 (575.8 to 704.9) | |
| Anti-HPV-18, Month 24 (N=318, 308, 318) | 613.7 (555.0 to 678.6) | 106.3 (93.2 to 121.3) | 182.0 (159.3 to 208.0) | |
| Anti-HPV-16, Month 36 (N=318, 306, 309) | 1061.4 (971.8 to 1159.4) | 379.8 (333.4 to 432.7) | 472.4 (425 to 525.0) | |

| | | | | |
|---|------------------------|---------------------|------------------------|--|
| Anti-HPV-18, Month 36 (N=322, 310, 320) | 486.5 (437.8 to 540.6) | 71.0 (62.0 to 81.2) | 119.1 (103.4 to 137.1) | |
|---|------------------------|---------------------|------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 36

| | |
|--|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by ELISA at Month 36 |
| End point description: Data at Month 36 were also expressed as International Units per milliliter (IU)/mL. Conversion factor from EU/mL to IU/mL was determined to be 1/6.1 for HPV-16 and 1/5.7 for HPV-18, using the WHO International Standards (NIBSC codes 05-134 and 10-140 for HPV-16 and HPV-18, respectively). The assay cut-offs were therefore 3.1 IU/mL and 3.2 IU/mL for anti-HPV-16 and anti-HPV-18 antibodies, respectively. | |
| End point type | Secondary |
| End point timeframe: At Month 36 | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|------------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 322 | 310 | 320 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV-16 (N=318,306,309) | 174.0 (159.3 to 190.1) | 62.3 (54.7 to 71.0) | 77.4 (69.6 to 86.0) | |
| Anti-HPV-18 (N=322,310,320) | 85.3 (76.7 to 94.8) | 12.5 (10.9 to 14.3) | 20.9 (18.2 to 24.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates as assessed by pseudovirion-based neutralization assay (PBNA) in a subset of subjects, based on the Month 36 ATP cohort for immunogenicity

| | |
|---|--|
| End point title | Anti-HPV-16/18 seroconversion rates as assessed by pseudovirion-based neutralization assay (PBNA) in a subset of subjects, based on the Month 36 ATP cohort for immunogenicity |
| End point description: Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers respectively ≥ 40 ED ₅₀) in the serum of subjects seronegative before vaccination. The assay was performed on a subset of approximately 100 subjects per study group. | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Day 0 and Months 7, 12, 18, 24 and 36 | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 87 | 91 | |
| Units: Subjects | | | | |
| Anti-HPV-16, Day 0 (N=89, 85, 91) | 0 | 0 | 0 | |
| Anti-HPV-18, Day 0 (N=89, 87, 91) | 0 | 0 | 0 | |
| Anti-HPV-16, Month 7 (N=89, 85, 91) | 89 | 85 | 91 | |
| Anti-HPV-18, Month 7 (N=89, 87, 91) | 89 | 87 | 91 | |
| Anti-HPV-16, Month 12 (N=88, 85, 91) | 88 | 85 | 91 | |
| Anti-HPV-18, Month 12 (N=88, 87, 91) | 88 | 86 | 91 | |
| Anti-HPV-16, Month 18 (N=88, 85, 90) | 88 | 83 | 89 | |
| Anti-HPV-18, Month 18 (N=87, 87, 91) | 87 | 77 | 89 | |
| Anti-HPV-16, Month 24 (N=86, 83, 91) | 86 | 83 | 90 | |
| Anti-HPV-18, Month 24 (N=86, 83, 91) | 86 | 75 | 88 | |
| Anti-HPV-16, Month 36 (N=89, 85, 91) | 89 | 85 | 91 | |
| Anti-HPV-18, Month 36 (N=89, 87, 91) | 89 | 75 | 86 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers as assessed by PBNA in a subset of subjects, based on the Month 36 ATP cohort for immunogenicity

| | |
|-----------------|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by PBNA in a subset of subjects, based on the Month 36 ATP cohort for immunogenicity |
|-----------------|---|

End point description:

Anti-HPV 16/18 antibody titers were presented as GMTs and expressed in titers using the PBNA. The assay was performed on a subset of approximately 100 subjects per study group.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Day 0 and Months 7, 12, 18, 24 and 36 | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 87 | 91 | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |

| | | | | |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|--|
| Anti-HPV-16, Day 0 (N=89, 85, 91) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | |
| Anti-HPV-18, Day 0 (N=89, 87, 91) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | |
| Anti-HPV-16, Month 7 (N=89, 85, 91) | 52868.5 (44171.0 to 63278.5) | 19130.1 (15166.8 to 24129.0) | 22182.7 (17611.7 to 27940.1) | |
| Anti-HPV-18, Month 7 (N=89, 87, 91) | 24068.5 (19293.2 to 30025.8) | 4726.5 (3600.9 to 6204.0) | 8243.9 (6276.2 to 10828.4) | |
| Anti-HPV-16, Month 12 (N=88, 85, 91) | 10695.9 (8564.9 to 13357.1) | 4280.1 (3245.9 to 5643.6) | 5843.8 (4599.8 to 7424.1) | |
| Anti-HPV-18, Month 12 (N=88, 87, 91) | 3683.3 (2914.4 to 4655.2) | 689.0 (517.2 to 917.8) | 1788.6 (1308.6 to 2444.7) | |
| Anti-HPV-16, Month 18 (N=88, 85, 90) | 8436.3 (6650.6 to 10701.4) | 2129.7 (1512.8 to 2998.1) | 2987.2 (2218.5 to 4022.3) | |
| Anti-HPV-18, Month 18 (N=87, 87, 91) | 2426.3 (1885.7 to 3121.7) | 295.7 (217.0 to 402.8) | 812.1 (577.0 to 1143.0) | |
| Anti-HPV-16, Month 24 (N=86, 83, 91) | 5036.7 (4097.8 to 6190.7) | 1211.8 (893.8 to 1642.9) | 1967.2 (1507.5 to 2567.2) | |
| Anti-HPV-18, Month 24 (N=86, 83, 91) | 1763.0 (1384.5 to 2245.0) | 237.1 (177.2 to 317.1) | 573.1 (421.5 to 779.3) | |
| Anti-HPV-16, Month 36 (N=89, 85, 91) | 4357.8 (3577.8 to 5307.9) | 1128.9 (857.4 to 1486.4) | 1577.0 (1210.4 to 2054.5) | |
| Anti-HPV-18, Month 36 (N=89, 87, 91) | 1613.9 (1267.6 to 2054.7) | 185.8 (140.4 to 245.8) | 472.8 (345.8 to 646.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates as assessed by PBNA in a subset of subjects, based on the Month 36 TVC

| | |
|-----------------|--|
| End point title | Anti-HPV-16/18 seroconversion rates as assessed by PBNA in a subset of subjects, based on the Month 36 TVC |
|-----------------|--|

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers ≥ 40 ED50) in the serum of subjects seronegative before vaccination. The assay was performed on a subset of approximately 100 subjects per study group.

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

End point timeframe:

At Day 0 and Months 7, 12, 18, 24 and 36

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|---------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 99 | 92 | 98 | |
| Units: Subjects | | | | |
| Anti-HPV-16, Day 0 (N=99, 90, 98) | 0 | 0 | 0 | |
| Anti-HPV-18, Day 0 (N=99, 92, 98) | 0 | 0 | 0 | |
| Anti-HPV-16, Month 7 (N= 99, 90, 98) | 99 | 90 | 98 | |
| Anti-HPV-18, Month 7 (N= 99, 92, 98) | 99 | 92 | 98 | |
| Anti-HPV-16, Month 12 (N= 98, 90, 98) | 97 | 90 | 98 | |
| Anti-HPV-18, Month 12 (N=98, 92, 98) | 98 | 91 | 98 | |
| Anti-HPV-16, Month 18 (N=98, 90, 97) | 97 | 88 | 96 | |
| Anti-HPV-18, Month 18 (N=97, 92, 98) | 97 | 82 | 96 | |
| Anti-HPV-16, Month 24 (N=96, 87, 98) | 95 | 87 | 97 | |
| Anti-HPV-18, Month 24 (N=96, 87, 98) | 96 | 79 | 94 | |
| Anti-HPV-16, Month 36 (N=98, 90, 98) | 97 | 90 | 98 | |
| Anti-HPV-18, Month 36 (N=97, 92, 98) | 97 | 80 | 92 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers as assessed by PBNA in a subset of subjects, based on the Month 36 TVC

| | |
|-----------------|---|
| End point title | Anti-HPV-16/18 antibody titers as assessed by PBNA in a subset of subjects, based on the Month 36 TVC |
|-----------------|---|

End point description:

Anti-HPV 16/18 antibody titers were presented as GMT and expressed in titers using the PBNA. The assay was performed on a subset of approximately 100 subjects per study group.

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

End point timeframe:

At Day 0 and Months 7, 12, 18, 24 and 36

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|------------------------------|------------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 99 | 92 | 98 | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV-16, Day 0 (N=99, 90, 98) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | |
| Anti-HPV-18, Day 0 (N=99, 92, 98) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | 20.0 (20.0 to 20.0) | |
| Anti-HPV-16, Month 7 (N=99, 90, 98) | 50000.7 (39742.9 to 62906.0) | 18573.7 (14876.8 to 23189.3) | 22294.2 (17763.8 to 27980.0) | |
| Anti-HPV-18, Month 7 (N= 99, 92, 98) | 23576.9 (18922.5 to 29376.2) | 4563.7 (3519.5 to 5917.8) | 8042.1 (6186.1 to 10454.8) | |

| | | | | |
|---------------------------------------|-----------------------------|---------------------------|---------------------------|--|
| Anti-HPV-16, Month 12 (N=98, 90, 98) | 10039.6 (7884.1 to 12784.5) | 4174.9 (3207.5 to 5434.2) | 5766.0 (4573.8 to 7268.9) | |
| Anti-HPV-18, Month 12 (N= 98, 92, 98) | 3546.9 (2829.7 to 4445.8) | 670.3 (510.0 to 880.9) | 1801.4 (1333.0 to 2434.2) | |
| Anti-HPV-16, Month 18 (N= 98, 90, 97) | 7508.8 (5819.8 to 9688.0) | 2070.2 (1494.9 to 2866.9) | 2961.5 (2233.9 to 3926.2) | |
| Anti-HPV-18, Month 18 (N=97, 92, 98) | 2240.5 (1763.3 to 2846.9) | 294.5 (219.5 to 395.1) | 797.6 (576.3 to 1104.0) | |
| Anti-HPV-16, Month 24 (N=96, 87, 98) | 4609.1 (3673.5 to 5782.9) | 1193.9 (889.6 to 1602.3) | 1932.0 (1499.4 to 2489.5) | |
| Anti-HPV-18, Month 24 (N=96, 87, 98) | 1638.6 (1297.9 to 2068.8) | 239.7 (181.2 to 317.1) | 564.6 (418.1 to 762.5) | |
| Anti-HPV-16, Month 36 (N=98, 90, 98) | 4011.7 (3229.7 to 4983.0) | 1111.4 (849.1 to 1454.6) | 1517.2 (1174.7 to 1959.4) | |
| Anti-HPV-18, Month 36 (N=97, 92, 98) | 1513.7 (1197.5 to 1913.2) | 185.8 (142.2 to 242.7) | 468.6 (346.3 to 634.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for Cell-Mediated Immunity (CMI)

| | |
|-----------------|---|
| End point title | T-cell-mediated immune responses in the sub-cohort for Cell-Mediated Immunity (CMI) |
|-----------------|---|

End point description:

Among immune markers expressed were Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumor necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L). The assay was performed on a sub-cohort of approximately 100 subjects per study group.

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

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 60 | 74 | |
| Units: T-cells/million cells | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| CD4+ All doubles, Anti-HPV-16,Day 0 (N=53, 42, 53) | 10 (1 to 78) | 22 (1 to 90) | 33 (1 to 80) | |
| CD4+ All doubles, Anti-HPV-18,Day 0 (N=53, 42, 54) | 28 (1 to 83) | 47.5 (1 to 102) | 26 (1 to 92) | |
| CD4+ All doubles,Anti-HPV-16,Month 7(N=63, 58, 62) | 1662 (644 to 3221) | 872 (479 to 1275) | 1121 (694 to 1890) | |

| | | | |
|--|----------------------|-------------------------|-------------------------|
| CD4+ All doubles,Anti-HPV-18,Month 7(N=63, 58, 63) | 897 (496 to 2497) | 427 (259 to 744) | 640 (355 to 1304) |
| CD4+All doubles,Anti-HPV-16,Month 12(N=67, 58, 66) | 916 (641 to 2340) | 585.5 (316 to 1250) | 819.5 (554 to 1623) |
| CD4+All doubles,Anti-HPV-18,Month 12(N=67, 59, 66) | 789 (384 to 1492) | 327 (184 to 658) | 446 (205 to 824) |
| CD4+All doubles,Anti-HPV-16,Month 24 N=66, 60, 74) | 1068.5 (495 to 2410) | 750.5 (366.5 to 1142.5) | 968.5 (588 to 1830) |
| CD4+All doubles Anti-HPV-18,Month 24(N=65, 60, 73) | 645 (311 to 1406) | 352 (196.5 to 503) | 578 (267 to 972) |
| CD4+All doubles,Anti-HPV-16,Month 36(N=58, 55, 64) | 1012 (427 to 2373) | 685 (385 to 1321) | 842.5 (437.5 to 1624) |
| CD4+All doubles,Anti-HPV-18,Month 36(N=57, 55, 63) | 682 (313 to 1425) | 350 (196 to 665) | 516 (270 to 1029) |
| CD4-d-CD40L, Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 73) | 14 (1 to 72) | 30 (1 to 73) |
| CD4-d-CD40L, Anti-HPV-18, Day 0 (N=53, 42, 54) | 14 (1 to 83) | 39.5 (1 to 102) | 27.5 (1 to 70) |
| CD4-d-CD40L, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1515 (638 to 3098) | 779 (456 to 1211) | 1025.5 (670 to 1848) |
| CD4-d-CD40L, Anti-HPV-18, Month 7 (N=63, 58, 63) | 866 (496 to 2483) | 386.5 (237 to 708) | 574 (328 to 1224) |
| CD4-d-CD40L, Anti-HPV-16, Month 12 (N=67, 58, 66) | 889 (591 to 2236) | 524 (280 to 1135) | 761.5 (484 to 1425) |
| CD4-d-CD40L, Anti-HPV-18, Month 12 (N=67, 59, 66) | 688 (344 to 1435) | 317 (147 to 633) | 383.5 (214 to 729) |
| CD4-d-CD40L, Anti-HPV-16, Month 24 (N=66, 60, 74) | 1045.5 (518 to 2269) | 736 (348 to 1101.5) | 937 (588 to 1801) |
| CD4-d-CD40L, Anti-HPV-18, Month 24 (N=65, 60, 73) | 639 (310 to 1374) | 332 (204 to 510.5) | 564 (289 to 940) |
| CD4-d-CD40L, Anti-HPV-16, Month 36 (N=58, 55, 64) | 957 (465 to 2303) | 685 (349 to 1321) | 778.5 (416.5 to 1560.5) |
| CD4-d-CD40L, Anti-HPV-18, Month 36 (N=57, 55, 63) | 671 (290 to 1435) | 337 (204 to 648) | 499 (264 to 1020) |
| CD4-d- IFN γ , Anti-HPV-16, Day 0 (N=53, 42, 53) | 12 (1 to 30) | 19 (1 to 42) | 1 (1 to 28) |
| CD4-d- IFN γ , Anti-HPV-18, Day 0 (N=53, 42, 54) | 14 (1 to 33) | 13.5 (1 to 36) | 3.5 (1 to 30) |
| CD4-d- IFN γ , Anti-HPV-16, Month 7 (N=63, 58, 62) | 365 (161 to 881) | 320 (157 to 533) | 422.5 (206 to 708) |
| CD4-d- IFN γ , Anti-HPV-18, Month 7 (N=63, 58, 63) | 242 (111 to 712) | 133.5 (83 to 240) | 181 (78 to 409) |
| CD4-d- IFN γ , Anti-HPV-16, Month 12 (N=67, 58, 66) | 326 (110 to 644) | 235 (108 to 501) | 356 (135 to 734) |
| CD4-d- IFN γ , Anti-HPV-18, Month 12 (N=67, 59, 66) | 175 (87 to 444) | 112 (55 to 240) | 164 (57 to 315) |
| CD4-d- IFN γ , Anti-HPV-16, Month 24 (N=66, 60, 74) | 300.5 (119 to 781) | 317.5 (146.5 to 514) | 421 (157 to 767) |
| CD4-d- IFN γ , Anti-HPV-18, Month 24 (N=65, 60, 73) | 171 (68 to 462) | 112 (49.5 to 229.5) | 220 (65 to 348) |
| CD4-d-IFN γ , Anti-HPV-16, Month 36 (N=58, 55, 64) | 253.5 (81 to 667) | 301 (134 to 571) | 270.5 (129 to 666.5) |
| CD4-d-IFN γ , Anti-HPV-18, Month 36 (N=57, 55, 63) | 193 (51 to 376) | 109 (27 to 230) | 155 (45 to 314) |
| CD4-d-IL-2, Anti-HPV-16, Day 0 (N=53, 42, 53) | 14 (1 to 52) | 25 (1 to 72) | 33 (1 to 56) |
| CD4-d-IL-2, Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 49) | 36.5 (1 to 76) | 22 (1 to 60) |
| CD4-d-IL-2, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1357 (537 to 2660) | 712.5 (378 to 1037) | 866 (561 to 1420) |
| CD4-d-IL-2, Anti-HPV-18, Month 7 (N=63, 58, 63) | 737 (420 to 2185) | 304 (206 to 573) | 486 (281 to 959) |

| | | | |
|---|---------------------|------------------------|---------------------|
| CD4-d-IL-2, Anti-HPV-16, Month 12 (N=67, 58, 66) | 832 (493 to 2050) | 479 (283 to 946) | 674.5 (450 to 1316) |
| CD4-d-IL-2, Anti-HPV-18, Month 12 (N=67, 59, 66) | 620 (304 to 1157) | 259 (144 to 547) | 354 (155 to 622) |
| CD4-d-IL-2, Anti-HPV-16, Month 24 (N=66, 60, 74) | 855 (390 to 1711) | 579.5 (270.5 to 934.5) | 700 (479 to 1459) |
| CD4-d-IL-2, Anti-HPV-18, Month 24 (N=65, 60, 73) | 494 (252 to 994) | 240 (125.5 to 387.5) | 426 (216 to 695) |
| CD4-d-IL-2, Anti-HPV-16, Month 36 (N=58,55, 64) | 784 (331 to 1673) | 517 (295 to 1014) | 680 (308 to 1245.5) |
| CD4-d-IL-2, Anti-HPV-18, Month 36 (N=57, 55, 63) | 507 (213 to 1069) | 274 (137 to 467) | 341 (168 to 798) |
| CD4-d-TNFa, Anti-HPV-16, Day 0 (N=53, 42, 53) | 6 (1 to 50) | 33 (1 to 82) | 16 (1 to 69) |
| CD4-d-TNFa, Anti-HPV-18, Day 0 (N=53, 42, 54) | 27 (1 to 75) | 22.5 (1 to 82) | 23 (1 to 60) |
| CD4-d-TNFa, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1111 (430 to 2386) | 625 (292 to 899) | 796 (458 to 1448) |
| CD4-d-TNFa, Anti-HPV-18, Month 7 (N=63, 58, 63) | 647 (336 to 1415) | 283.5 (168 to 594) | 457 (266 to 978) |
| CD4-d-TNFa, Anti-HPV-16, Month 12 (N=67, 58, 66) | 790 (488 to 1924) | 482 (210 to 932) | 716 (457 to 1445) |
| CD4-d-TNFa, Anti-HPV-18, Month 12 (N=67, 59, 66) | 674 (288 to 1272) | 266 (133 to 588) | 384.5 (175 to 714) |
| CD4-d-TNFa, Anti-HPV-16, Month 24 (N=66, 60, 74) | 795.5 (343 to 1668) | 563.5 (241.5 to 895) | 760.5 (443 to 1494) |
| CD4-d-TNFa, Anti-HPV-18, Month 24 (N=65, 60, 73) | 510 (183 to 1164) | 239 (127.5 to 440.5) | 522 (228 to 710) |
| CD4-d-TNFa, Anti-HPV-16, Month 36 (N=58, 55, 64) | 786.5 (343 to 1930) | 547 (282 to 1005) | 724.5 (368 to 1338) |
| CD4-d-TNFa, Anti-HPV-18, Month 36 (N=57, 55, 63) | 588 (250 to 1138) | 301 (120 to 453) | 479 (200 to 808) |
| CD8-All Doubles, Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 14) | 4 (1 to 49) | 1 (1 to 25) |
| CD8-All Doubles, Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 16) | 1 (1 to 29) | 1 (1 to 22) |
| CD8-All Doubles, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1 (1 to 34) | 1 (1 to 41) | 1 (1 to 30) |
| CD8-All Doubles, Anti-HPV-18, Month 7 (N=63, 58, 63) | 1 (1 to 19) | 1 (1 to 40) | 1 (1 to 40) |
| CD8-All Doubles, Anti-HPV-16, Month 12 (N=67, 58, 66) | 1 (1 to 31) | 1 (1 to 29) | 1 (1 to 29) |
| CD8-All Doubles, Anti-HPV-18, Month 12 (N=67, 59, 66) | 1 (1 to 27) | 1 (1 to 27) | 1 (1 to 20) |
| CD8-All Doubles, Anti-HPV-16, Month 24 (N=66, 60, 74) | 1 (1 to 25) | 1 (1 to 1) | 1 (1 to 1) |
| CD8-All Doubles, Anti-HPV-18, Month 24 (N=65, 60, 73) | 1 (1 to 32) | 1 (1 to 23) | 1 (1 to 28) |
| CD8-All doubles, Anti-HPV-16, Month 36 (N=58, 55, 64) | 1 (1 to 48) | 1 (1 to 28) | 1 (1 to 38.5) |
| CD8-All doubles, Anti-HPV-18, Month 36 (N=57, 55, 63) | 4 (1 to 40) | 2 (1 to 41) | 1 (1 to 28) |
| CD8-d-CD40L, Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 1) | 1 (1 to 26) | 1 (1 to 1) |
| CD8-d-CD40L, Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) |
| CD8-d-CD40L, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1 (1 to 1) | 1 (1 to 29) | 1 (1 to 24) |
| CD8-d-CD40L, Anti-HPV-18, Month 7 (N=63, 58, 63) | 1 (1 to 1) | 1 (1 to 24) | 1 (1 to 23) |
| CD8-d-CD40L, Anti-HPV-16, Month 12 (N=67, 58, 66) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 3) |

| | | | | |
|---|-------------|-------------|-------------|--|
| CD8-d-CD40L, Anti-HPV-18, Month 12 (N=67, 59, 66) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-CD40L, Anti-HPV-16, Month 24 (N=66, 60, 74) | 1 (1 to 16) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-CD40L, Anti-HPV-18, Month 24 (N=65, 60, 73) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 18) | |
| CD8-d-CD40L, Anti-HPV-16, Month 36 (N=58, 55, 64) | 1 (1 to 31) | 1 (1 to 24) | 1 (1 to 29) | |
| CD8-d-CD40L, Anti-HPV-18, Month 36 (N=57, 55, 63) | 1 (1 to 6) | 1 (1 to 27) | 1 (1 to 28) | |
| CD8-d-IFN γ , Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 1) | 1 (1 to 39) | 1 (1 to 26) | |
| CD8-d-IFN γ , Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 2) | 1 (1 to 23) | 1 (1 to 18) | |
| CD8-d-IFN γ , Anti-HPV-16, Month 7 (N=63, 58, 62) | 1 (1 to 32) | 1 (1 to 40) | 1 (1 to 30) | |
| CD8-d-IFN γ , Anti-HPV-18, Month 7 (N=63, 58, 63) | 1 (1 to 1) | 1 (1 to 28) | 1 (1 to 28) | |
| CD8-d-IFN γ , Anti-HPV-16, Month 12 (N=67, 58, 66) | 1 (1 to 28) | 1 (1 to 26) | 1 (1 to 27) | |
| CD8-d-IFN γ , Anti-HPV-18, Month 12 (N=67, 59, 66) | 1 (1 to 22) | 1 (1 to 26) | 1 (1 to 10) | |
| CD8-d-IFN γ , Anti-HPV-16, Month 24 (N=66, 60, 74) | 1 (1 to 16) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IFN γ , Anti-HPV-18, Month 24 (N=65, 60, 73) | 1 (1 to 18) | 1 (1 to 23) | 1 (1 to 1) | |
| CD8-d-IFN γ , Anti-HPV-16, Month 36 (N=58, 55, 64) | 1 (1 to 47) | 1 (1 to 25) | 1 (1 to 33) | |
| CD8-d-IFN γ , Anti-HPV-18, Month 36 (N=57, 55, 63) | 1 (1 to 31) | 2 (1 to 40) | 1 (1 to 25) | |
| CD8-d-IL-2, Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-16, Month 7 (N=63, 58, 62) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-18, Month 7 (N=63, 58, 63) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-16, Month 12 (N=67, 58, 66) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-18, Month 12 (N=67, 59, 66) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-16, Month 24 (N=66, 60, 74) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-18, Month 24 (N=65, 60, 73) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-16, Month 36 (N=58, 55, 64) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-IL-2, Anti-HPV-18, Month 36 (N=57, 55, 63) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-TNF α , Anti-HPV-16, Day 0 (N=53, 42, 53) | 1 (1 to 1) | 1 (1 to 36) | 1 (1 to 16) | |
| CD8-d-TNF α , Anti-HPV-18, Day 0 (N=53, 42, 54) | 1 (1 to 27) | 1 (1 to 29) | 1 (1 to 26) | |
| CD8-d-TNF α , Anti-HPV-16, Month 7 (N=63, 58, 62) | 1 (1 to 28) | 1 (1 to 26) | 1 (1 to 18) | |
| CD8-d-TNF α , Anti-HPV-18, Month 7 (N=63, 58, 63) | 1 (1 to 1) | 1 (1 to 2) | 1 (1 to 24) | |
| CD8-d-TNF α , Anti-HPV-16, Month 12 (N=67, 58, 66) | 1 (1 to 1) | 1 (1 to 25) | 1 (1 to 28) | |
| CD8-d-TNF α , Anti-HPV-18, Month 12 (N=67, 59, 66) | 1 (1 to 8) | 1 (1 to 21) | 1 (1 to 24) | |

| | | | | |
|---|-------------|-------------|-------------|--|
| CD8-d-TNF α , Anti-HPV-16, Month 24 (N=66, 60, 74) | 1 (1 to 20) | 1 (1 to 1) | 1 (1 to 1) | |
| CD8-d-TNF α , Anti-HPV-18, Month 24 (N=65, 60, 73) | 1 (1 to 28) | 1 (1 to 7) | 1 (1 to 18) | |
| CD8-d-TNF α , Anti-HPV-16, Month 36 (N=58, 55, 64) | 1 (1 to 24) | 1 (1 to 1) | 1 (1 to 26) | |
| CD8-d-TNF α , Anti-HPV-18, Month 36 (N=57, 55, 63) | 1 (1 to 31) | 1 (1 to 21) | 1 (1 to 12) | |

Statistical analyses

No statistical analyses for this end point

Secondary: B-cell-mediated immune responses in the sub-cohort for CMI

| | |
|-----------------|--|
| End point title | B-cell-mediated immune responses in the sub-cohort for CMI |
|-----------------|--|

End point description:

The frequency of B-cell Elispot response to HPV-16/18 by overall status was presented. The assay was performed on a sub-cohort of 100 subjects per study group.

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

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|---------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 65 | 76 | |
| Units: B-cells/million cells | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| HPV-16, Day 0 (N=69, 55, 70) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| HPV-18, Day 0 (N=69, 55, 70) | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | |
| HPV-16, Month 7 (N=71, 65, 76) | 1733 (577 to 3733) | 1254 (495 to 2173) | 733 (106.5 to 1966.5) | |
| HPV-18, Month 7 (N=71, 65, 76) | 558 (106 to 1847) | 155 (1 to 379) | 111 (1 to 343.5) | |
| HPV-16, Month 12 (N=51, 51, 53) | 408 (90 to 1186) | 278 (66 to 794) | 289 (66 to 982) | |
| HPV-18, Month 12 (N=51, 51, 53) | 249 (73 to 658) | 69 (1 to 184) | 69 (1 to 250) | |
| HPV-16, Month 24 (N=54, 46, 63) | 270 (49 to 724) | 218.5 (28 to 651) | 249 (37 to 601) | |
| HPV-18, Month 24 (N=54, 46, 63) | 128.5 (35 to 402) | 57.5 (1 to 203) | 111 (1 to 317) | |
| HPV-16, Month 36 (N=59, 54, 53) | 353 (91 to 927) | 382.5 (166 to 614) | 246 (21 to 565) | |
| HPV-18, Month 36 (N=59, 54, 53) | 116 (1 to 329) | 25 (1 to 228) | 63 (1 to 150) | |

Statistical analyses

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

| | |
|---|--|
| End point title | Number of subjects with any and grade 3 solicited local symptoms |
| End point description: Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimetres (mm) of injection site. | |
| End point type | Secondary |
| End point timeframe: During the 7-day period (from the day of vaccination up to 6 subsequent days) following vaccination after each dose and across doses | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 357 | 356 | |
| Units: Subjects | | | | |
| Any Pain - Dose 1 (N=359, 357, 356) | 311 | 235 | 231 | |
| Any Pain - Dose 2 (N=357, 353, 354) | 193 | 183 | 215 | |
| Any Pain - Dose 3 (N=356, 348, 350) | 280 | 194 | 222 | |
| Any Pain - Across doses (N=359, 357, 356) | 329 | 276 | 295 | |
| Grade 3 Pain - Dose 1 (N=359, 357, 356) | 22 | 4 | 6 | |
| Grade 3 Pain - Dose 2 (N=357, 353, 354) | 8 | 8 | 8 | |
| Grade 3 Pain - Dose 3 (N=356, 348, 350) | 23 | 11 | 10 | |
| Grade 3 Pain - Across doses (N=359, 357, 356) | 42 | 17 | 18 | |
| Any Redness - Dose 1 (N=359, 357, 356) | 137 | 84 | 87 | |
| Any Redness - Dose 2 (N=357, 353, 354) | 100 | 84 | 99 | |
| Any Redness - Dose 3 (N=356, 348, 350) | 133 | 92 | 102 | |
| Any Redness - Across doses (N=359, 357, 356) | 191 | 134 | 157 | |
| Grade 3 Redness - Dose 1 (N=359, 357, 356) | 0 | 0 | 1 | |
| Grade 3 Redness - Dose 2 (N=357, 353, 354) | 0 | 0 | 0 | |
| Grade 3 Redness - Dose 3 (N=356, 348, 350) | 0 | 0 | 1 | |
| Grade 3 Redness - Across doses (N=359, 357, 356) | 0 | 0 | 2 | |
| Any Swelling - Dose 1 (N=359, 357, 356) | 112 | 44 | 39 | |
| Any Swelling - Dose 2 (N=357, 353, 354) | 63 | 35 | 76 | |
| Any Swelling - Dose 3 (N=356, 348, 350) | 113 | 67 | 85 | |

| | | | | |
|---|-----|----|-----|--|
| Any Swelling - Across doses (N=359, 357, 356) | 163 | 98 | 118 | |
| Grade 3 Swelling - Dose 1 (N=359, 357, 356) | 3 | 0 | 0 | |
| Grade 3 Swelling - Dose 2 (N=357, 353, 354) | 0 | 0 | 0 | |
| Grade 3 Swelling - Dose 3 (N=356, 348, 350) | 2 | 0 | 2 | |
| Grade 3 Swelling - Across doses (N=359, 357, 356) | 5 | 0 | 2 | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Assessed solicited general symptoms were arthralgia, fatigue, gastrointestinal symptoms, headache, myalgia, rash, temperature [defined as oral temperature equal to or above (\geq) 37.5 degrees Celsius ($^{\circ}$ C)] and urticaria. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever above ($>$) 39.0 $^{\circ}$ C. Related = symptom assessed by the investigator as related to the vaccination.

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

End point timeframe:

During the 7-day period (from the day of vaccination up to 6 subsequent days) following vaccination after each dose and across doses

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 357 | 356 | |
| Units: Subjects | | | | |
| Any Arthralgia - Dose 1 (N=359, 357, 355) | 44 | 50 | 39 | |
| Any Arthralgia - Dose 2 (N=357, 353, 354) | 23 | 30 | 34 | |
| Any Arthralgia - Dose 3 (N=354, 347, 351) | 31 | 38 | 35 | |
| Any Arthralgia - Across doses (N=359, 357, 356) | 68 | 81 | 67 | |
| Grade 3 Arthralgia - Dose 1 (N=359, 357, 355) | 5 | 1 | 1 | |
| Grade 3 Arthralgia - Dose 2 (N=357, 353, 354) | 1 | 2 | 1 | |
| Grade 3 Arthralgia - Dose 3 (N=354, 347, 351) | 2 | 3 | 1 | |
| Grade 3 Arthralgia -Across doses (N=359, 357, 356) | 6 | 4 | 1 | |
| Related Arthralgia - Dose 1 (N=359, 357, 355) | 29 | 32 | 28 | |

| | | | | |
|--|-----|-----|-----|--|
| Related Arthralgia - Dose 2 (N=357, 353, 354) | 17 | 17 | 18 | |
| Related Arthralgia - Dose 3 (N=354, 347, 351) | 20 | 27 | 27 | |
| Related Arthralgia -Across doses (N=359, 357, 356) | 51 | 55 | 51 | |
| Any Fatigue - Dose 1 (N=359, 357, 355) | 163 | 157 | 168 | |
| Any Fatigue - Dose 2 (N=357, 353, 354) | 103 | 104 | 119 | |
| Any Fatigue - Dose 3 (N=354, 347, 351) | 108 | 97 | 103 | |
| Any Fatigue - Across doses (N=359, 357, 356) | 192 | 199 | 193 | |
| Grade 3 Fatigue - Dose 1 (N=359, 357, 355) | 7 | 10 | 5 | |
| Grade 3 Fatigue - Dose 2 (N=357, 353, 354) | 12 | 3 | 2 | |
| Grade 3 Fatigue - Dose 3 (N=354, 347, 351) | 7 | 3 | 3 | |
| Grade 3 Fatigue - Across doses (N=359, 357, 356) | 18 | 15 | 7 | |
| Related Fatigue - Dose 1 (N=359, 357, 355) | 103 | 102 | 98 | |
| Related Fatigue - Dose 2 (N=357, 353, 354) | 68 | 66 | 67 | |
| Related Fatigue - Dose 3 (N=354, 347, 351) | 70 | 67 | 67 | |
| Related Fatigue -Across doses (N=359, 357, 356) | 152 | 151 | 143 | |
| Any Gastrointestinal - Dose 1 (N=359, 357, 355) | 34 | 52 | 44 | |
| Any Gastrointestinal - Dose 2 (N=357, 353, 354) | 19 | 22 | 23 | |
| Any Gastrointestinal - Dose 3 (N=354, 347, 351) | 16 | 29 | 24 | |
| Any Gastrointestinal -Across doses (N=359,357,356) | 55 | 74 | 70 | |
| Grade 3 Gastrointestinal -Dose 1 (N=359, 357, 355) | 3 | 2 | 2 | |
| Grade 3 Gastrointestinal -Dose 2 (N=357, 353, 354) | 2 | 1 | 0 | |
| Grade 3 Gastrointestinal -Dose 3 (N=354, 347, 351) | 1 | 4 | 2 | |
| Grade 3 Gastro -Across doses (N=359, 357, 356) | 5 | 6 | 3 | |
| Related Gastrointestinal -Dose 1 (N=359, 357, 355) | 21 | 26 | 22 | |
| Related Gastrointestinal -Dose 2 (N=357, 353, 354) | 8 | 17 | 6 | |
| Related Gastrointestinal -Dose 3 (N=354, 347, 351) | 10 | 20 | 17 | |
| Related Gastro - Across doses (N=359, 357, 356) | 32 | 49 | 40 | |
| Any Headache - Dose 1 (N=359, 357, 355) | 102 | 87 | 90 | |
| Any Headache - Dose 2 (N=357, 353, 354) | 62 | 64 | 73 | |
| Any Headache - Dose 3 (N=354, 347, 351) | 63 | 54 | 65 | |
| Any Headache -Across doses (N=359, 357, 356) | 147 | 133 | 151 | |

| | | | | |
|--|-----|-----|-----|--|
| Grade 3 Headache - Dose 1 (N=359, 357, 355) | 7 | 6 | 1 | |
| Grade 3 Headache - Dose 2 (N=357, 353, 354) | 6 | 2 | 4 | |
| Grade 3 Headache - Dose 3 (N=354, 347, 351) | 7 | 1 | 1 | |
| Grade 3 Headache -Across doses (N=359, 357, 356) | 17 | 7 | 4 | |
| Related Headache - Dose 1 (N=359, 357, 355) | 61 | 51 | 48 | |
| Related Headache - Dose 2 (N=357, 353, 354) | 39 | 37 | 41 | |
| Related Headache - Dose 3 (N=354, 347, 351) | 45 | 33 | 42 | |
| Related Headache -Across doses (N=359, 357, 356) | 107 | 88 | 100 | |
| Any Myalgia - Dose 1 (N=359, 357, 355) | 131 | 101 | 101 | |
| Any Myalgia - Dose 2 (N=357, 353, 354) | 59 | 60 | 80 | |
| Any Myalgia - Dose 3 (N=354, 347, 351) | 77 | 68 | 72 | |
| Any Myalgia - Across doses (N=359, 357, 356) | 166 | 143 | 136 | |
| Grade 3 Myalgia - Dose 1 (N=359, 357, 355) | 5 | 3 | 2 | |
| Grade 3 Myalgia - Dose 2 (N=357, 353, 354) | 2 | 3 | 2 | |
| Grade 3 Myalgia - Dose 3 (N=354, 347, 351) | 3 | 4 | 5 | |
| Grade 3 Myalgia -Across doses (N=359, 357, 356) | 8 | 8 | 6 | |
| Related Myalgia - Dose 1 (N=359, 357, 355) | 91 | 70 | 67 | |
| Related Myalgia - Dose 2 (N=357, 353, 354) | 36 | 40 | 51 | |
| Related Myalgia - Dose 3 (N=354, 347, 351) | 50 | 49 | 46 | |
| Related Myalgia -Across doses (N=359, 357, 356) | 128 | 111 | 100 | |
| Any Rash - Dose 1 (N=359, 357, 355) | 14 | 7 | 10 | |
| Any Rash - Dose 2 (N=357, 353, 354) | 10 | 5 | 8 | |
| Any Rash - Dose 3 (N=354, 347, 351) | 7 | 5 | 4 | |
| Any Rash - Across doses (N=359, 357, 356) | 25 | 16 | 18 | |
| Grade 3 Rash - Dose 1 (N=359, 357, 356) | 0 | 0 | 0 | |
| Grade 3 Rash - Dose 2 (N=357, 353, 354) | 0 | 0 | 0 | |
| Grade 3 Rash - Dose 3 (N=354, 347, 351) | 0 | 0 | 0 | |
| Grade 3 Rash -Across doses (N=359, 357, 356) | 0 | 0 | 0 | |
| Related Rash - Dose 1 (N=359, 357, 355) | 6 | 5 | 6 | |
| Related Rash - Dose 2 (N=357, 353, 354) | 6 | 3 | 4 | |
| Related Rash - Dose 3 (N=354, 347, 351) | 6 | 3 | 3 | |
| Related Rash - Across doses (N=359, 357, 356) | 16 | 10 | 12 | |

| | | | | |
|---|----|----|----|--|
| Any Temperature($\geq 37.5^{\circ}\text{C}$) -Dose 1(N=359, 357, 355) | 19 | 23 | 18 | |
| Any Temperature($\geq 37.5^{\circ}\text{C}$) -Dose 2(N=357, 353, 354) | 13 | 21 | 19 | |
| Any Temperature($\geq 37.5^{\circ}\text{C}$) -Dose 3(N=354, 347, 351) | 32 | 22 | 22 | |
| Any Temp ($\geq 37.5^{\circ}\text{C}$) -Across doses(N=359, 357, 356) | 53 | 59 | 47 | |
| Grade 3 Temp ($> 39.0^{\circ}\text{C}$) - Dose 1 (N=359, 357, 355) | 2 | 2 | 2 | |
| Grade 3 Temp ($> 39.0^{\circ}\text{C}$) - Dose 2 (N=357, 353, 354) | 0 | 0 | 2 | |
| Grade 3 Temp ($> 39.0^{\circ}\text{C}$) - Dose 3 (N=354, 347, 351) | 6 | 0 | 0 | |
| Grade 3 Temp($>39.0^{\circ}\text{C}$) -Across doses(N=359,357,356) | 7 | 2 | 4 | |
| Related Temperature - Dose 1 (N=359, 357, 355) | 13 | 11 | 7 | |
| Related Temperature - Dose 2 (N=357, 353, 354) | 8 | 9 | 11 | |
| Related Temperature - Dose 3 (N=354, 347, 351) | 19 | 12 | 15 | |
| Related Temperature -Across doses(N=359, 357, 356) | 35 | 31 | 30 | |
| Any Urticaria - Dose 1 (N=359, 357, 355) | 15 | 7 | 12 | |
| Any Urticaria - Dose 2 (N=357, 353, 354) | 8 | 5 | 12 | |
| Any Urticaria - Dose 3 (N=354, 347, 351) | 11 | 4 | 9 | |
| Any Urticaria - Across doses (N=359, 357, 356) | 28 | 13 | 25 | |
| Grade 3 Urticaria - Dose 1 (N=359, 357, 355) | 2 | 0 | 0 | |
| Grade 3 Urticaria - Dose 2 (N=357, 353, 354) | 0 | 1 | 0 | |
| Grade 3 Urticaria - Dose 3 (N=354, 347, 351) | 2 | 0 | 0 | |
| Grade 3 Urticaria -Across doses (N=359, 357, 356) | 4 | 1 | 0 | |
| Related Urticaria - Dose 1 (N=359, 357, 355) | 7 | 6 | 7 | |
| Related Urticaria - Dose 2 (N=357, 353, 354) | 5 | 4 | 4 | |
| Related Urticaria - Dose 3 (N=354, 347, 351) | 6 | 4 | 2 | |
| Related Urticaria -Across doses (N=359, 357, 356) | 15 | 11 | 9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related unsolicited adverse events (AEs)

| | |
|-----------------|---|
| End point title | Number of subjects with any, grade 3 and related unsolicited adverse events (AEs) |
|-----------------|---|

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and 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. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related to the vaccination.

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

End point timeframe:

During the 30-day (from the day of vaccination up to 29 subsequent days) post-vaccination period

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|---|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | | | | |
| Subjects with any AE(s) (N=359, 358, 358) | 91 | 96 | 101 | |
| Subjects with any Grade 3 AE(s) (N=359, 358, 358) | 18 | 8 | 20 | |
| Subjects with any Related AE(s) (N=359, 358, 358) | 8 | 14 | 15 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with potentially immune mediated diseases (pIMDs)

| | |
|-----------------|--|
| End point title | Number of subjects with potentially immune mediated diseases (pIMDs) |
|-----------------|--|

End point description:

pIMDs are defined as a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.

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

End point timeframe:

From Day 0 up to Month 12

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | | | | |
| pIMD(s) | 3 | 3 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with medically significant conditions (MSCs)

| | |
|-----------------|---|
| End point title | Number of subjects with medically significant conditions (MSCs) |
|-----------------|---|

End point description:

MSCs are defined as AEs prompting emergency room (ER) or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

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

End point timeframe:

From Day 0 up to Month 36 (throughout the study period)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | 77 | 79 | 63 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events (SAEs)

| | |
|-----------------|---|
| End point title | Number of subjects with serious adverse events (SAEs) |
|-----------------|---|

End point description:

SAEs assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity.

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

End point timeframe:

From Day 0 up to Month 36 (throughout the study period)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | 21 | 11 | 14 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with SAEs related to the investigational product, to study participation, to GSK concomitant products or any fatal SAE

| | |
|-----------------|---|
| End point title | Number of subjects with SAEs related to the investigational product, to study participation, to GSK concomitant products or any fatal SAE |
|-----------------|---|

End point description:

SAEs assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity. Related = an event assessed by the investigator as causally related to the investigational product, to study participation or to GSK concomitant products.

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

End point timeframe:

From Day 0 up to Month 36 (throughout the study period)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|----------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | | | | |
| Related SAE(s) (N=359, 358, 358) | 0 | 0 | 0 | |
| Fatal SAE(s) (N=359, 358, 358) | 0 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting pregnancies and outcomes of reported pregnancies

| | |
|-----------------|---|
| End point title | Number of subjects reporting pregnancies and outcomes of reported pregnancies |
|-----------------|---|

End point description:

Outcomes of pregnancies were: Live infant NO apparent congenital anomaly (ACA), Live infant congenital anomaly (CA), Elective termination NO ACA, Elective termination CA, Ectopic pregnancy, Spontaneous abortion NO ACA, Stillbirth NO ACA, Stillbirth CA, Lost to follow up and Pregnancy ongoing.

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

End point timeframe:

From Day 0 up to Month 36 (throughout the study period)

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | 1 | |
| Units: Subjects | | | | |
| Live infant NO ACA | | | 0 | |
| Live infant CA | | | 0 | |
| Elective termination NO ACA | | | 1 | |
| Elective termination CA | | | 0 | |
| Ectopic pregnancy | | | 0 | |
| Spontaneous abortion NO ACA | | | 0 | |
| Stillbirth NO ACA | | | 0 | |
| Stillbirth CA | | | 0 | |
| Lost to follow up | | | 0 | |
| Pregnancy ongoing | | | 0 | |
| Missing | | | 0 | |

Notes:

[7] - No pregnancies were reported for this group.

[8] - No pregnancies were reported for this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects using a concomitant medication throughout the study period

| | |
|---|---|
| End point title | Number of subjects using a concomitant medication throughout the study period |
| End point description: The number of subjects who have used any concomitant medication, as well as any antipyretic, any prophylactic antipyretic and any antibiotic. | |
| End point type | Secondary |
| End point timeframe: From Day 0 up to Month 36 (throughout the study period) following vaccination after each dose and across doses | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | | | | |
| Any, Dose 1 (N=359, 358, 358) | 85 | 87 | 93 | |
| Any antipyretic, Dose 1 (N=359, 358, 358) | 51 | 53 | 47 | |
| Prophylactic antipyretic, Dose 1 (N=359, 358, 358) | 4 | 0 | 0 | |
| Any antibiotic, Dose 1 (N=359, 358, 358) | 15 | 13 | 23 | |
| Prophylactic antibiotic, Dose 1 (N=359, 358, 358) | 0 | 0 | 0 | |
| Any, Dose 2 (N=358, 356, 356) | 52 | 55 | 47 | |

| | | | | |
|--|-----|-----|-----|--|
| Any antipyretic, Dose 2 (N=358, 356, 356) | 32 | 26 | 29 | |
| Prophylactic antipyretic, Dose 2 (N=358, 356, 356) | 0 | 1 | 2 | |
| Any antibiotic, Dose 2 (N=358, 356, 356) | 8 | 13 | 12 | |
| Prophylactic antibiotic, Dose 2 (N=358, 356, 356) | 0 | 0 | 0 | |
| Any, Dose 3 (N=357, 352, 354) | 90 | 83 | 81 | |
| Any antipyretic, Dose 3 (N=357, 352, 354) | 48 | 45 | 38 | |
| Prophylactic antipyretic, Dose 3 (N=357, 352, 354) | 3 | 1 | 0 | |
| Any antibiotic, Dose 3 (N=357, 352, 354) | 28 | 21 | 24 | |
| Prophylactic antibiotic, Dose 3 (N=357, 352, 354) | 0 | 0 | 0 | |
| Any, Across doses (N=359, 358, 358) | 171 | 157 | 161 | |
| Any antipyretic, Across doses (N=359, 358, 358) | 110 | 102 | 95 | |
| Prophylactic antipyretic, Across doses N=359, 358, 358 | 5 | 2 | 2 | |
| Any antibiotic, Across doses (N=359, 358, 358) | 48 | 42 | 50 | |
| Prophylactic antibiotic, Across doses N=359, 358, 358 | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects completing the vaccination schedule

| | |
|--|--|
| End point title | Number of subjects completing the vaccination schedule |
| End point description: The number of subjects who have completed the three-dose vaccination schedule in all groups. | |
| End point type | Secondary |
| End point timeframe: From Day 0 up to Month 36 (throughout the study period) | |

| End point values | Cervarix 2 dose Group | Gardasil 2 dose Group | Gardasil 3 dose Group | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 359 | 358 | 358 | |
| Units: Subjects | 351 | 339 | 346 | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local and general symptoms: during the 7-day period after vaccination. Unsolicited AEs: during the 30-day period after vaccination. SAEs: throughout the study period (from Day 0 up to Month 36).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Cervarix 2 dose Group |
|-----------------------|-----------------------|

Reporting group description:

Subjects who received 2 doses of Cervarix vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| | |
|-----------------------|-----------------------|
| Reporting group title | Gardasil 3 dose Group |
|-----------------------|-----------------------|

Reporting group description:

Subjects who received 3 doses of Gardasil vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| | |
|-----------------------|-----------------------|
| Reporting group title | Gardasil 2 dose Group |
|-----------------------|-----------------------|

Reporting group description:

Subjects who received 2 doses of Gardasil vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

| Serious adverse events | Cervarix 2 dose Group | Gardasil 3 dose Group | Gardasil 2 dose Group |
|---|-----------------------|-----------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 359 (5.85%) | 14 / 358 (3.91%) | 11 / 358 (3.07%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Teratoma | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Abortion spontaneous incomplete subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Vulval ulceration | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 359 (0.56%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Depression | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 2 / 359 (0.56%) | 0 / 358 (0.00%) | 0 / 358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Contusion | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Foreign body | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Tendon injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Mouth cyst | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema nodosum | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Juvenile idiopathic arthritis | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Infections and infestations | | | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 359 (0.84%) | 0 / 358 (0.00%) | 0 / 358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 359 (0.56%) | 1 / 358 (0.28%) | 0 / 358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 1 / 358 (0.28%) | 0 / 358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 358 (0.28%) | 0 / 358 (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 |
| Lung abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 358 (0.00%) | 0 / 358 (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 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 0 / 358 (0.00%) | 1 / 358 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 2 dose Group | Gardasil 3 dose Group | Gardasil 2 dose Group |
|---|-----------------------|-----------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 343 / 359 (95.54%) | 324 / 358 (90.50%) | 321 / 358 (89.66%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 149 / 359 (41.50%) | 152 / 358 (42.46%) | 134 / 358 (37.43%) |
| occurrences (all) | 241 | 232 | 213 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 192 / 359 (53.48%) | 193 / 358 (53.91%) | 199 / 358 (55.59%) |
| occurrences (all) | 374 | 390 | 359 |
| Pain | | | |

| | | | |
|---|---------------------------|---------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 329 / 359 (91.64%) 784 | 295 / 358 (82.40%) 669 | 277 / 358 (77.37%) 613 |
| Pyrexia subjects affected / exposed occurrences (all) | 59 / 359 (16.43%) 70 | 53 / 358 (14.80%) 65 | 64 / 358 (17.88%) 71 |
| Swelling subjects affected / exposed occurrences (all) | 163 / 359 (45.40%) 288 | 118 / 358 (32.96%) 200 | 98 / 358 (27.37%) 146 |
| Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all) | 55 / 359 (15.32%) 69 | 70 / 358 (19.55%) 91 | 74 / 358 (20.67%) 103 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 191 / 359 (53.20%) 370 | 157 / 358 (43.85%) 288 | 135 / 358 (37.71%) 261 |
| Rash subjects affected / exposed occurrences (all) | 26 / 359 (7.24%) 32 | 18 / 358 (5.03%) 23 | 16 / 358 (4.47%) 17 |
| Urticaria subjects affected / exposed occurrences (all) | 28 / 359 (7.80%) 36 | 25 / 358 (6.98%) 33 | 13 / 358 (3.63%) 16 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 68 / 359 (18.94%) 98 | 67 / 358 (18.72%) 108 | 82 / 358 (22.91%) 119 |
| Myalgia subjects affected / exposed occurrences (all) | 166 / 359 (46.24%) 267 | 136 / 358 (37.99%) 254 | 144 / 358 (40.22%) 230 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 359 (2.23%) 10 | 20 / 358 (5.59%) 22 | 11 / 358 (3.07%) 12 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 27 / 359 (7.52%) 31 | 31 / 358 (8.66%) 34 | 29 / 358 (8.10%) 33 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 July 2012 | Amendment 1: At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator had full authority to break the treatment code. |
| 28 November 2013 | Amendment 2: The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. This change in the assay was implemented for the testing of samples at all time points. |
| 24 June 2014 | Amendment 3: At the time of study initiation, Cervarix was approved to be administered according to a 3-dose vaccination course. Subjects belonging to the Cervarix 2 dose Group and Gardasil 2 dose Group received two doses of either Cervarix or Gardasil during the primary study epoch. These subjects were to be offered a third dose of the vaccine that they received at the end of the study, at Month 36. Recently, the 2-dose schedule of Cervarix and Gardasil has been approved in some countries, and hence the protocol is being amended to reflect that a third dose of the vaccine that they received was offered to the subjects in the two 2-dose groups (Cervarix 2 dose Group and Gardasil 2 dose Group) only if required based on local prescribing recommendations. In addition, the indication for Cervarix and the list of contributing authors have been updated. The number of countries in which Cervarix and Gardasil are licensed has been updated. Minor changes have been made in a few sections to correct typographical errors. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported