



Clinical trial results:

A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2009-011617-25 |
| Trial protocol | FI BE AT SE ES PL Outside EU/EEA |
| Global end of trial date | 22 April 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 (current) |
| This version publication date | 06 April 2023 |
| First version publication date | 08 March 2022 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | V503-002 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00943722 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000654-PIP01-09 |
| 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 April 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective was to demonstrate that the 9-valent HPV L1 VLP vaccine induces noninferior Geometric Mean Titers (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in preadolescent and adolescent boys and girls 9 to 15 years of age compared to young women 16 to 26 years of age. A protocol-specified lot consistency (Lots 1, 2, 3 separate) outcome analysis in 9 to 15 year-old girls was done in the base study only.

Extension studies (EXT 1 and 2) were conducted up to Month 36 and ~11 years respectively. No study vaccine was given and 16-26 year olds were excluded from extensions; per protocol, extensions provided data for 9- to 15-year-old girls (Lots 1, 2, 3 pooled) and 9- to 15-year-old boys.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 27 August 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Thailand: 200 |
| Country: Number of subjects enrolled | Brazil: 50 |
| Country: Number of subjects enrolled | Peru: 160 |
| Country: Number of subjects enrolled | United States: 649 |
| Country: Number of subjects enrolled | South Africa: 165 |
| Country: Number of subjects enrolled | Belgium: 122 |
| Country: Number of subjects enrolled | Costa Rica: 75 |
| Country: Number of subjects enrolled | Colombia: 303 |
| Country: Number of subjects enrolled | Austria: 46 |
| Country: Number of subjects enrolled | Spain: 209 |
| Country: Number of subjects enrolled | Taiwan: 159 |
| Country: Number of subjects enrolled | Poland: 120 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Chile: 40 |
| Country: Number of subjects enrolled | Korea, Republic of: 149 |
| Country: Number of subjects enrolled | Finland: 284 |
| Country: Number of subjects enrolled | Sweden: 118 |
| Country: Number of subjects enrolled | India: 225 |
| Worldwide total number of subjects | 3074 |
| EEA total number of subjects | 899 |

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) | 1283 |
| Adolescents (12-17 years) | 1360 |
| Adults (18-64 years) | 431 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The base study V503-002 was a 12-month study that is collecting safety and immunogenicity information for six months following the participants' third dose of study vaccine.

Pre-assignment

Screening details:

Extension study 1 (EXT1) collected data to Month 36. Extension study 2 (EXT2) collected long-term data through ~11 years. No study vaccine was administered.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Base Study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Base Study: 9- to 15-Year-Old Females (Lot 1) |

Arm description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | V503 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Multivalent human papillomavirus [HPV] L1 virus-like particle [VLP] vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

| | |
|------------------|---|
| Arm title | Base Study: 9- to 15-Year-Old Females (Lot 2) |
|------------------|---|

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | V503 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

| | |
|------------------|---|
| Arm title | Base Study: 9- to 15-Year-Old Females (Lot 3) |
|------------------|---|

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.

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

| | |
|--|-------------------|
| Investigational medicinal product name | V503 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

| | |
|------------------|---|
| Arm title | Base Study: 9- to 15-Year-Old Males (Lot 1) |
|------------------|---|

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | V503 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

| | |
|------------------|--|
| Arm title | Base Study: 16- to 26-Year-Old Females (Lot 1) |
|------------------|--|

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | V503 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

| Number of subjects in period 1 | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lot 2) | Base Study: 9- to 15-Year-Old Females (Lot 3) |
|---------------------------------------|---|---|---|
| Started | 648 | 643 | 644 |
| Vaccination 1 | 646 | 642 | 644 |
| Vaccination 2 | 637 | 633 | 638 |
| Vaccination 3 | 635 | 627 | 637 |
| Completed | 623 | 621 | 631 |
| Not completed | 25 | 22 | 13 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | 12 | 13 | 2 |
| Adverse event, non-fatal | - | - | - |
| Pregnancy | - | - | 1 |

| | | | |
|--------------------|----|---|----|
| Lost to follow-up | 12 | 8 | 10 |
| unknown status | - | - | - |
| Protocol deviation | - | 1 | - |

| Number of subjects in period 1 | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) |
|--------------------------------|---|--|
| Started | 669 | 470 |
| Vaccination 1 | 666 | 468 |
| Vaccination 2 | 658 | 462 |
| Vaccination 3 | 653 | 455 |
| Completed | 647 | 444 |
| Not completed | 22 | 26 |
| Physician decision | - | 1 |
| Consent withdrawn by subject | 13 | 8 |
| Adverse event, non-fatal | 1 | - |
| Pregnancy | - | - |
| Lost to follow-up | 8 | 11 |
| unknown status | - | 4 |
| Protocol deviation | - | 2 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Extension Study 1 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Extension Study: 9- to 15-Year-Old Females |

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|---|--|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Extension Study: 9- to 15-Year-Old Males |

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

| Number of subjects in period 2^[1] | Extension Study: 9- to 15-Year-Old Females | Extension Study: 9- to 15-Year-Old Males |
|---|--|--|
| Started | 1604 | 568 |
| Completed | 1489 | 527 |
| Not completed | 115 | 41 |
| Consent withdrawn by subject | 32 | 10 |
| Adverse event, non-fatal | 1 | - |
| Unknown | 44 | 21 |
| Lost to follow-up | 38 | 10 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Per protocol, the subject disposition for this extension study included only 2 treatment arms: 9- to 15-year-old males and 9- to 15-year-old females.

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Extension Study 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Extension Study: 9- to 15-Year-Old Females |

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|---|--|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Extension Study: 9- to 15-Year-Old Males |

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 3^[2] | Extension Study: 9- to 15-Year-Old Females | Extension Study: 9- to 15-Year-Old Males |
|---|--|--|
| Started | 971 | 301 |
| Completed | 720 | 202 |
| Not completed | 251 | 99 |
| Physician decision | 1 | 3 |
| Consent withdrawn by subject | 137 | 50 |
| Adverse event, non-fatal | 1 | - |
| Pregnancy | 1 | - |
| Lost to follow-up | 111 | 46 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Per protocol, the subject disposition for this extension study included only 2 treatment arms: 9- to 15-year-old males and 9- to 15-year-old females.

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 1) |
| Reporting group description: | |
| Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Reporting group description: | |
| Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Reporting group description: | |
| Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Males (Lot 1) |
| Reporting group description: | |
| Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |
| Reporting group title | Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Reporting group description: | |
| Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |

| Reporting group values | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lot 2) | Base Study: 9- to 15-Year-Old Females (Lot 3) |
|---|---|---|---|
| Number of subjects | 648 | 643 | 644 |
| Age Categorical | | | |
| Base Study | | | |
| Units: Years | | | |
| 9 to 12 years | 440 | 432 | 432 |
| 13 to 15 years | 208 | 211 | 212 |
| 16 to 26 years | 0 | 0 | 0 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 648 | 643 | 644 |
| Male | 0 | 0 | 0 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 0 |
| Asian | 150 | 141 | 139 |
| Black or African American | 50 | 59 | 52 |
| Multi-Racial | 81 | 91 | 86 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 366 | 351 | 367 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 176 | 191 | 193 |
| Not Hispanic or Latino | 472 | 452 | 451 |

| Reporting group values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | Total |
|---|---|--|-------|
| Number of subjects | 669 | 470 | 3074 |
| Age Categorical | | | |
| Base Study | | | |
| Units: Years | | | |
| 9 to 12 years | 450 | 0 | 1754 |
| 13 to 15 years | 219 | 0 | 850 |
| 16 to 26 years | 0 | 470 | 470 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 0 | 470 | 2405 |
| Male | 669 | 0 | 669 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 0 | 4 |
| Asian | 186 | 128 | 744 |
| Black or African American | 37 | 48 | 246 |
| Multi-Racial | 149 | 53 | 460 |
| Native Hawaiian or Other Pacific Islander | 3 | 1 | 4 |
| White | 292 | 240 | 1616 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 195 | 128 | 883 |
| Not Hispanic or Latino | 474 | 342 | 2191 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 1) |
| Reporting group description: Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Reporting group description: Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Reporting group description: Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3. | |
| Reporting group title | Base Study: 9- to 15-Year-Old Males (Lot 1) |
| Reporting group description: Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |
| Reporting group title | Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Reporting group description: Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1. | |
| Reporting group title | Extension Study: 9- to 15-Year-Old Females |
| Reporting group description: In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]). | |
| Reporting group title | Extension Study: 9- to 15-Year-Old Males |
| Reporting group description: In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]). | |
| Reporting group title | Extension Study: 9- to 15-Year-Old Females |
| Reporting group description: In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]). | |
| Reporting group title | Extension Study: 9- to 15-Year-Old Males |
| Reporting group description: In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]). | |
| Subject analysis set title | Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants received the 9-valent human papillomavirus (9vHPV) L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing | |

Lots 1, 2, or 3

| | |
|----------------------------|---|
| Subject analysis set title | Base Study: 9- to 15-Year-Old Females (Lots 1, 2, or 3) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received the multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Primary: Base Study: Geometric Mean Titers (GMTs) for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] and 16- to 26-Year-Old Females [Lot 1])

| | |
|-----------------|---|
| End point title | Base Study: Geometric Mean Titers (GMTs) for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] and 16- to 26-Year-Old Females [Lot 1]) ^[1] |
|-----------------|---|

End point description:

Serum antibody titers for HPV virus-like particles (VLPs), Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using a competitive luminex immunoassay (cLIA). Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old females and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint included only the GMTs of girls 9 to 15 years of age compared to women 16 to 26 years of age.

| End point values | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 535 | 378 | | |
| Units: milli Merck Units/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=517; 328) | 1715.4 (1595.1 to 1844.7) | 900.8 (822.3 to 986.9) | | |
| Anti-HPV 11 (n=517; 332) | 1295.1 (1204.1 to 1393.0) | 706.6 (645.2 to 773.8) | | |
| Anti-HPV 16 (n=529; 329) | 6979.8 (6508.1 to 7485.8) | 3522.6 (3223.5 to 3849.5) | | |
| Anti-HPV 18 (n=531; 345) | 2153.7 (1980.4 to 2342.1) | 882.7 (795.4 to 979.5) | | |
| Anti-HPV 31 (n=522; 340) | 1891.6 (1745.7 to 2049.7) | 753.9 (682.5 to 832.7) | | |
| Anti-HPV 33 (n=534; 354) | 980.4 (911.7 to 1054.3) | 466.8 (426.9 to 510.3) | | |
| Anti-HPV 45 (n=534; 368) | 714.4 (651.9 to 782.8) | 272.2 (243.8 to 303.9) | | |
| Anti-HPV 52 (n=533; 337) | 932.9 (864.8 to 1006.4) | 419.6 (381.4 to 461.5) | | |

| | | | | |
|--------------------------|---------------------------|------------------------|--|--|
| Anti-HPV 58 (n=531; 332) | 1286.7 (1195.7 to 1384.6) | 590.5 (538.2 to 647.9) | | |
|--------------------------|---------------------------|------------------------|--|--|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Females |
| Statistical analysis description: Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| P-value | < 0.001 ^[3] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.7 |
| upper limit | 2.14 |

Notes:

[2] - non-inferiority requires that the lower bound of two-sided 95% confidence interval (CI) of GMT ratio be greater than 0.67.

[3] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Females |
| Statistical analysis description: Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| P-value | < 0.001 ^[5] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 1.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.77 |
| upper limit | 2.22 |

Notes:

[4] - Non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[5] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Females |
| Statistical analysis description: Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| P-value | < 0.001 ^[7] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.13 |
| upper limit | 2.8 |

Notes:

[6] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[7] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Females |
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| P-value | < 0.001 ^[9] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 1.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.63 |
| upper limit | 2.06 |

Notes:

[8] - Non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[9] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Females |
| Statistical analysis description: Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[10] |
| P-value | < 0.001 ^[11] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.21 |
| upper limit | 2.85 |

Notes:

[10] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[11] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Females |
|-----------------------------------|---------------------------|

Statistical analysis description:

Anti-HPV 33

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[12] |
| P-value | < 0.001 ^[13] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.87 |
| upper limit | 2.36 |

Notes:

[12] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[13] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Females |
|-----------------------------------|---------------------------|

Statistical analysis description:

Anti-HPV 45

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[14] |
| P-value | < 0.001 ^[15] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.62 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.27 |
| upper limit | 3.03 |

Notes:

[14] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[15] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Females |
|-----------------------------------|---------------------------|

Statistical analysis description:

Anti-HPV 52

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[16] |
| P-value | < 0.001 ^[17] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.97 |
| upper limit | 2.51 |

Notes:

[16] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[17] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Females |
|-----------------------------------|---------------------------|

Statistical analysis description:

Anti-HPV 58

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[18] |
| P-value | < 0.001 ^[19] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.93 |
| upper limit | 2.45 |

Notes:

[18] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

Primary: Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] and 16- to 26-Year-Old Females [Lot 1])

| | |
|-----------------|--|
| End point title | Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] and 16- to 26-Year-Old Females [Lot 1]) ^[20] |
|-----------------|--|

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using a cLIA. Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old males and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

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

Justification: This endpoint included only the GMTs of males 9 to 15 years of age compared to females 16 to 26 years of age.

| End point values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 570 | 378 | | |
| Units: milli Merck Units/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=559; 328) | 2084.7 (1944.0 to 2235.7) | 900.8 (822.3 to 986.9) | | |
| Anti-HPV 11 (n=559; 332) | 1487.1 (1386.5 to 1595.0) | 706.6 (645.2 to 773.8) | | |
| Anti-HPV 16 (n=569; 329) | 8628.9 (8065.9 to 9231.3) | 3522.6 (3223.5 to 3849.5) | | |
| Anti-HPV 18 (n=567; 345) | 2822.8 (2602.8 to 3061.5) | 882.7 (795.4 to 979.5) | | |
| Anti-HPV 31 (n=564; 340) | 2221.2 (2056.1 to 2399.5) | 753.9 (682.5 to 832.7) | | |
| Anti-HPV 33 (n=567; 354) | 1198.7 (1117.1 to 1286.2) | 466.8 (426.9 to 510.3) | | |
| Anti-HPV 45 (n=570; 368) | 907.0 (830.2 to 991.0) | 272.2 (243.8 to 303.9) | | |
| Anti-HPV 52 (n=568; 337) | 1037.8 (964.4 to 1116.9) | 419.6 (381.4 to 461.5) | | |
| Anti-HPV 58 (n=566; 332) | 1567.7 (1460.2 to 1683.1) | 590.5 (538.2 to 647.9) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Males |
| Statistical analysis description: Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[21] |
| P-value | < 0.001 ^[22] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.07 |
| upper limit | 2.59 |

Notes:

[21] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[22] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Males |
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[23] |
| P-value | < 0.001 ^[24] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.88 |
| upper limit | 2.36 |

Notes:

[23] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[24] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Males |
| Statistical analysis description: Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[25] |
| P-value | < 0.001 ^[26] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.19 |
| upper limit | 2.74 |

Notes:

[25] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[26] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Males |
| Statistical analysis description: Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[27] |
| P-value | < 0.001 ^[28] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.8 |
| upper limit | 3.65 |

Notes:

[27] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[28] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|--|--|
| Statistical analysis title | GMTs for HPV VLPs-Males |
| Statistical analysis description: Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[29] |
| P-value | < 0.001 ^[30] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.6 |
| upper limit | 3.34 |

Notes:

[29] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[30] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Males |
|-----------------------------------|-------------------------|

Statistical analysis description:

Anti-HPV 33

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[31] |
| P-value | < 0.001 ^[32] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.29 |
| upper limit | 2.88 |

Notes:

[31] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[32] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Males |
|-----------------------------------|-------------------------|

Statistical analysis description:

Anti-HPV 45

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[33] |
| P-value | < 0.001 ^[34] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 3.33 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.89 |
| upper limit | 3.84 |

Notes:

[33] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[34] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Males |
|-----------------------------------|-------------------------|

Statistical analysis description:

Anti-HPV 52

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[35] |
| P-value | < 0.001 ^[36] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.19 |
| upper limit | 2.79 |

Notes:

[35] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[36] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Males |
|-----------------------------------|-------------------------|

Statistical analysis description:

Anti-HPV 58

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[37] |
| P-value | < 0.001 ^[38] |
| Method | ANOVA |
| Parameter estimate | GMT ratio |
| Point estimate | 2.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.37 |
| upper limit | 2.98 |

Notes:

[37] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

Primary: Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)

| | |
|-----------------|---|
| End point title | Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (Lot Consistency Study) ^[39] |
|-----------------|---|

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old females who received 3 vaccinations from Lots 1, 2, or 3 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

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

Justification: This endpoint included only the GMTs across 3 lots.

| End point values | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lot 2) | Base Study: 9- to 15-Year-Old Females (Lot 3) | |
|--|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 535 | 549 | 565 | |
| Units: milli Merck Units/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=517; 536; 544) | 1715.4 (1588.7 to 1852.2) | 1763.3 (1635.4 to 1901.3) | 1659.9 (1540.3 to 1788.7) | |
| Anti-HPV 11 (n=517; 536; 544) | 1295.1 (1197.8 to 1400.3) | 1311.7 (1214.9 to 1416.3) | 1232.0 (1141.7 to 1329.5) | |
| Anti-HPV 16 (n=529; 542; 556) | 6979.8 (6476.1 to 7522.8) | 7292.9 (6772.7 to 7853.1) | 6948.2 (6458.7 to 7474.9) | |
| Anti-HPV 18 (n=531; 547; 563) | 2153.7 (1970.9 to 2353.5) | 2134.1 (1955.6 to 2329.0) | 1966.6 (1804.3 to 2143.5) | |
| Anti-HPV 31 (n=522; 542; 553) | 1891.6 (1738.5 to 2058.2) | 1867.8 (1719.3 to 2029.1) | 1879.0 (1731.0 to 2039.6) | |
| Anti-HPV 33 (n=534; 543; 560) | 980.4 (909.2 to 1057.2) | 922.7 (856.2 to 994.4) | 931.1 (865.0 to 1002.3) | |
| Anti-HPV 45 (n=534; 548; 565) | 714.4 (650.1 to 785.0) | 827.7 (754.1 to 908.5) | 678.4 (619.0 to 743.6) | |
| Anti-HPV 52 (n=533; 547; 562) | 932.9 (860.8 to 1011.0) | 1007.9 (931.0 to 1091.2) | 971.2 (898.1 to 1050.3) | |
| Anti-HPV 58 (n=531; 539; 560) | 1286.7 (1190.0 to 1391.3) | 1344.9 (1244.6 to 1453.3) | 1208.1 (1119.6 to 1303.6) | |

Statistical analyses

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|---|---|
| Statistical analysis description: Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[40] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.08 |

Notes:

[40] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[41] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.2 |

Notes:

[41] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[42] |
| Parameter estimate | GMT ratio |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.11 |

Notes:

[42] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[43] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.19 |

Notes:

[43] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[44] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.16 |

Notes:

[44] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[45] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.26 |

Notes:

[45] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[46] |
| Parameter estimate | GMT ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.14 |

Notes:

[46] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[47] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.17 |

Notes:

[47] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 16

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[48] |
| Parameter estimate | GMT ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.12 |

Notes:

[48] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 16

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[49] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.06 |

Notes:

[49] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 18

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[50] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.26 |

Notes:

[50] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[51] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.2 |

Notes:

[51] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[52] |
| Parameter estimate | GMT ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.13 |

Notes:

[52] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[53] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.02 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.16 |

Notes:

[53] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[54] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.18 |

Notes:

[54] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[55] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 0.95 |

Notes:

[55] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[56] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.12 |

Notes:

[56] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[57] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.17 |

Notes:

[57] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
| Statistical analysis description: | |
| Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[58] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.16 |

Notes:

[58] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 31

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[59] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.15 |

Notes:

[59] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 58

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[60] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.2 |

Notes:

[60] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 58

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[61] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.06 |

Notes:

[61] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[62] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.16 |

Notes:

[62] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[63] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.07 |

Notes:

[63] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|--|---|
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[64] |
| Parameter estimate | GMT ratio |
| Point estimate | 0.92 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.03 |

Notes:

[64] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 45

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[65] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.24 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 1.42 |

Notes:

[65] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Lot Consistency |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Anti-HPV 58

| | |
|---|---|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[66] |
| Parameter estimate | GMT ratio |
| Point estimate | 1.12 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.26 |

Notes:

[66] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Primary: Base Study: Percentage of Participants with Injection Site Adverse Experiences (AEs)

| | |
|-----------------|--|
| End point title | Base Study: Percentage of Participants with Injection Site Adverse Experiences (AEs) ^{[67][68]} |
|-----------------|--|

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to

the use of the vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine was also an AE. AEs such as redness, swelling, and pain/tenderness/soreness at the injection site were recorded. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

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

End point timeframe:

up to 5 days after any vaccination

Notes:

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

Justification: No statistical analyses were planned or conducted for this endpoint.

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

Justification: This endpoint included only girls 9 to 15 years of age, women 16 to 26 years of age, and males 9 to 15 years of age.

| End point values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3) | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 662 | 466 | 1923 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 72.8 | 85.4 | 81.9 | |

Statistical analyses

No statistical analyses for this end point

Primary: Base Study: Percentage of Participants with Systemic AEs

| | |
|-----------------|---|
| End point title | Base Study: Percentage of Participants with Systemic AEs ^[69] [70] |
|-----------------|---|

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine was also an AE. Systemic AEs were those not categorized as injection-site AEs. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

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

End point timeframe:

up to 15 days after any vaccination

Notes:

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

Justification: No statistical analyses were planned or conducted for this endpoint.

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

Justification: This endpoint included only girls 9 to 15 years of age, women 16 to 26 years of age, and males 9 to 15 years of age.

| End point values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3) | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 662 | 466 | 1923 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 41.8 | 57.1 | 45.0 | |

Statistical analyses

No statistical analyses for this end point

Primary: Base Study: Percentage of Participants with Body Temperature $\geq 100.0^{\circ}\text{F}$ ($\geq 37.8^{\circ}\text{C}$)

| | |
|-----------------|---|
| End point title | Base Study: Percentage of Participants with Body Temperature $\geq 100.0^{\circ}\text{F}$ ($\geq 37.8^{\circ}\text{C}$) ^{[71][72]} |
|-----------------|---|

End point description:

Participants collected their oral body temperature in the evening of their vaccination day and at the same time each day thereafter for 4 days. The maximum body temperature obtained within 5 days of any of the 3 vaccinations was recorded. The percentage of participants who had at least 1 oral body temperature reading that was $\geq 100.0^{\circ}\text{F}$ ($\geq 37.8^{\circ}\text{C}$) was summarized. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

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

End point timeframe:

up to 5 days after any vaccination

Notes:

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

Justification: No statistical analyses were planned or conducted for this endpoint.

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

Justification: This endpoint included only girls 9 to 15 years of age, women 16 to 26 years of age, and males 9 to 15 years of age.

| End point values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lots 1, 2, or 3) | |
|-----------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 660 | 463 | 1908 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 10.0 | 8.4 | 8.4 | |

Statistical analyses

No statistical analyses for this end point

Primary: Extension Study: GMTs For Each of the HPV Types Contained in the Vaccine

| | |
|-----------------|--|
| End point title | Extension Study: GMTs For Each of the HPV Types Contained in |
|-----------------|--|

End point description:

Serum antibody titers (milli Merck Units/mL) measured by cLIA to each of the 9vHPV types were assessed. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. To be included in the analysis population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the analysis population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type being analyzed.

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

End point timeframe:

126 months after post-vaccination 3 (Up to ~11 years)

Notes:

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

Justification: No statistical analyses were planned or conducted for this endpoint.

| End point values | Extension Study: 9- to 15-Year-Old Females | Extension Study: 9- to 15-Year-Old Males | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 971 | 301 | | |
| Units: milli Merck Units/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=341,176) | 122.3 (111.1 to 134.7) | 129.5 (112.5 to 149.1) | | |
| Anti-HPV 11 (n=332,169) | 80.2 (72.5 to 88.8) | 91.0 (78.4 to 105.6) | | |
| Anti-HPV 16 (n=338,173) | 403.0 (357.3 to 454.5) | 414.3 (353.8 to 485.3) | | |
| Anti-HPV 18 (n=347,178) | 128.1 (116.7 to 140.7) | 148.4 (130.2 to 169.2) | | |
| Anti-HPV 31 (n=343,177) | 108.9 (97.6 to 121.6) | 128.6 (111.2 to 148.8) | | |
| Anti-HPV 33 (n=344,178) | 59.2 (53.7 to 65.2) | 69.6 (60.7 to 79.7) | | |
| Anti-HPV 45 (n=325,169) | 42.1 (37.7 to 47.1) | 49.8 (43.0 to 57.8) | | |
| Anti-HPV 52 (n=348,176) | 55.3 (50.5 to 60.6) | 59.6 (52.0 to 68.4) | | |
| Anti-HPV 58 (n=342,175) | 76.5 (69.2 to 84.6) | 90.5 (78.4 to 104.6) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Extension Study: Percentage of Participants who are Seropositive to Each of the HPV Types Contained in the Vaccine

| | |
|-----------------|--|
| End point title | Extension Study: Percentage of Participants who are Seropositive to Each of the HPV Types Contained in the Vaccine ^[74] |
|-----------------|--|

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined and reported in milli Merck Units/mL. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. To be included in the analysis population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the analysis population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type being analyzed.

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

End point timeframe:

126 months after post-vaccination 3 (Up to ~11 years)

Notes:

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

Justification: No statistical analyses were planned or conducted for this endpoint.

| End point values | Extension Study: 9- to 15-Year-Old Females | Extension Study: 9- to 15-Year-Old Males | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 971 | 301 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=341,176) | 82.7 (78.3 to 86.6) | 84.1 (77.8 to 89.2) | | |
| Anti-HPV 11 (n=332,169) | 85.2 (81.0 to 88.9) | 87.0 (81.0 to 91.7) | | |
| Anti-HPV 16 (n=338,173) | 97.3 (95.0 to 98.8) | 98.3 (95.0 to 99.6) | | |
| Anti-HPV 18 (n=347,178) | 80.1 (75.5 to 84.2) | 83.7 (77.4 to 88.8) | | |
| Anti-HPV 31 (n=343,177) | 90.1 (86.4 to 93.0) | 92.7 (87.8 to 96.0) | | |
| Anti-HPV 33 (n=344,178) | 85.2 (81.0 to 88.8) | 89.3 (83.8 to 93.4) | | |
| Anti-HPV 45 (n=325,169) | 81.8 (77.2 to 85.9) | 92.3 (87.2 to 95.8) | | |
| Anti-HPV 52 (n=348,176) | 88.2 (84.4 to 91.4) | 89.2 (83.7 to 93.4) | | |
| Anti-HPV 58 (n=342,175) | 96.5 (94.0 to 98.2) | 97.1 (93.5 to 99.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] and 16- to 26-Year-Old Females [Lot 1])

| | |
|-----------------|---|
| End point title | Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] and 16- to 26-Year-Old Females [Lot 1]) ^[75] |
|-----------------|---|

End point description:

Serum antibody titers for HPV virus-like particles (VLPs), Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: ≥ 30 , HPV Type 11: ≥ 16 ; HPV Type 16: ≥ 20 , HPV Type 18: ≥ 24 , HPV Type 31: ≥ 10 , HPV Type 33: ≥ 8 , HPV Type 45: ≥ 8 , HPV Type 52: ≥ 8 , and HPV Type 58: ≥ 8 . The analysis population included 9-15-year-old females and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

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

Justification: This endpoint included only girls 9 to 15 years of age compared to women 16 to 26 years of age.

| End point values | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 535 | 378 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Anti-HPV 6 cLIA ≥ 30 mMU/mL (n=517; 328) | 99.8 (98.9 to 100) | 99.7 (98.3 to 100) | | |
| Anti-HPV 11 cLIA ≥ 16 mMU/mL (n=517; 332) | 100 (99.3 to 100.0) | 100 (98.9 to 100.0) | | |
| Anti-HPV 16 cLIA ≥ 20 mMU/mL (n=529; 329) | 100 (99.3 to 100.0) | 100 (98.9 to 100.0) | | |
| Anti-HPV 18 cLIA ≥ 24 mMU/mL (n=531; 345) | 99.8 (99.0 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 31 cLIA ≥ 10 mMU/mL (n=522; 340) | 100.0 (99.3 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 33 cLIA ≥ 8 mMU/mL (n=534; 354) | 100.0 (99.3 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 45 cLIA ≥ 8 mMU/mL (n=534; 368) | 99.8 (99.0 to 100.0) | 99.5 (98.1 to 99.9) | | |
| Anti-HPV 52 cLIA ≥ 8 mMU/mL (n=533; 337) | 100.0 (99.3 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 58 cLIA ≥ 8 mMU/mL (n=531; 332) | 100.0 (99.3 to 100.0) | 100.0 (98.9 to 100.0) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|----------------------------|---|

Statistical analysis description:

Anti-HPV 6

| | |
|-------------------|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
|-------------------|--|

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[76] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 1.5 |

Notes:

[76] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[77] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 1.8 |

Notes:

[77] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[78] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[78] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 31

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[79] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[79] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 33

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[80] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.6 |

Notes:

[80] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 16

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[81] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[81] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 18

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[82] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 1.5 |

Notes:

[82] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 52

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[83] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[83] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Female Seroconversion |
|-----------------------------------|---|

Statistical analysis description:

Anti-HPV 58

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 913 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[84] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[84] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])

| | |
|-----------------|--|
| End point title | Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1]) ^[85] |
|-----------------|--|

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: ≥ 30 , HPV Type 11: ≥ 16 ; HPV Type 16: ≥ 20 , HPV Type 18: ≥ 24 , HPV Type 31: ≥ 10 , HPV Type 33: ≥ 8 , HPV Type 45: ≥ 8 , HPV Type 52: ≥ 8 , and HPV Type 58: ≥ 8 . The analysis population included 9-15-year-old males and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

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

Justification: This endpoint included only males 9 to 15 years of age compared to females 16 to 26 years of age.

| End point values | Base Study: 9- to 15-Year-Old Males (Lot 1) | Base Study: 16- to 26-Year-Old Females (Lot 1) | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 570 | 378 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Anti-HPV 6 cLIA ≥ 30 mMU/mL (n=559; 328) | 99.8 (99.0 to 100.0) | 99.7 (98.3 to 100.0) | | |
| Anti-HPV 11 cLIA ≥ 16 mMU/mL (n=559; 332) | 100.0 (99.3 to 100.0) | 100.0 (98.9 to 100.0) | | |
| Anti-HPV 16 cLIA ≥ 20 mMU/mL (n=569; 329) | 100.0 (99.4 to 100.0) | 100.0 (98.9 to 100.0) | | |
| Anti-HPV 18 cLIA ≥ 24 mMU/mL (n=567; 345) | 100.0 (99.4 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 31 cLIA ≥ 10 mMU/mL (n=564; 340) | 100.0 (99.3 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 33 cLIA ≥ 8 mMU/mL (n=567; 354) | 100.0 (99.4 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 45 cLIA ≥ 8 mMU/mL (n=570; 368) | 100.0 (99.4 to 100.0) | 99.5 (98.1 to 99.9) | | |
| Anti-HPV 52 cLIA ≥ 8 mMU/mL (n=568; 337) | 100.0 (99.4 to 100.0) | 99.7 (98.4 to 100.0) | | |
| Anti-HPV 58 cLIA ≥ 8 mMU/mL (n=566; 332) | 100.0 (99.4 to 100.0) | 100.0 (98.9 to 100.0) | | |

Statistical analyses

| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
|---|--|
| Statistical analysis description: Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[86] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.5 |

Notes:

[86] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- |

| | |
|---|---------------------------------|
| | to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[87] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[87] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[88] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[88] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[89] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.6 |

Notes:

[89] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Anti-HPV 31

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[90] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[90] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Anti-HPV 33

| | |
|---|--|
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[91] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.6 |

Notes:

[91] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
|-----------------------------------|---------------------------------------|

| | |
|---|--|
| Statistical analysis description: | |
| Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[92] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 2 |

Notes:

[92] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[93] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[93] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|--|
| Statistical analysis title | GMTs for HPV VLPs-Male Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 58 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1) |
| Number of subjects included in analysis | 948 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[94] |
| P-value | < 0.001 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.2 |

Notes:

[94] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)

| | |
|-----------------|--|
| End point title | Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (Lot Consistency Study) ^[95] |
|-----------------|--|

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post- vaccination 3 using cLIA. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: ≥ 30 , HPV Type 11: ≥ 16 ; HPV Type 16: ≥ 20 , HPV Type 18: ≥ 24 , HPV Type 31: ≥ 10 , HPV Type 33: ≥ 8 , HPV Type 45: ≥ 8 , HPV Type 52: ≥ 8 , and HPV Type 58: ≥ 8 . The analysis population included 9-15-year-old females who received 3 vaccinations from Lot 1, 2 or 3 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

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

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

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

Justification: This endpoint included only females across 3 lots.

| End point values | Base Study: 9- to 15-Year-Old Females (Lot 1) | Base Study: 9- to 15-Year-Old Females (Lot 2) | Base Study: 9- to 15-Year-Old Females (Lot 3) | |
|---|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 535 | 549 | 565 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| HPV 6 cLIA ≥ 30 mMU/mL (n=517; 536; 544) | 99.8 (98.9 to 100.0) | 99.8 (99.0 to 100.0) | 99.3 (98.1 to 99.8) | |
| HPV 11 cLIA ≥ 16 mMU/mL (n=517; 536; 544) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 16 cLIA ≥ 20 mMU/mL (n= 529; 542; 556) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 18 cLIA ≥ 24 mMU/mL (n= 531; 547; 563) | 99.8 (99.0 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 31 cLIA ≥ 10 mMU/mL (n=522; 542; 553) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.8 (99.0 to 100.0) | |
| HPV 33 cLIA ≥ 8 mMU/mL (534; 543; 560) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 45 cLIA ≥ 8 mMU/mL (n= 534; 548; 565) | 99.8 (99.0 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 52 cLIA ≥ 8 mMU/mL (n=533; 547; 562) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |
| HPV 58 cLIA ≥ 8 mMU/mL (n=531; 539; 560) | 100.0 (99.3 to 100.0) | 100.0 (99.3 to 100.0) | 99.6 (98.7 to 100.0) | |

Statistical analyses

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[96] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[96] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[97] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[97] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 11 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[98] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[98] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[99] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[99] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[100] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.7 |

Notes:

[100] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|---|---|
| Statistical analysis description: Anti-HPV 6 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[101] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.9 |

Notes:

[101] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[102] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[102] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
|--|---|
| Statistical analysis description: Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[103] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.1 |

Notes:

[103] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 18 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[104] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.5 |

Notes:

[104] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[105] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[105] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[106] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[106] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[107] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[107] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|-----------------------------------|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 16 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[108] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[108] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5).

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[109] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 1 |

Notes:

[109] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[110] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.5 |

Notes:

[110] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[111] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[111] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[112] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[112] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 33 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[113] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[113] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 31 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[114] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 1 |

Notes:

[114] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|---|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: | |
| Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[115] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.1 |

Notes:

[115] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 45 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[116] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[116] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 58 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[117] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[117] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 58 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[118] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[118] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[119] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[119] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[120] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[120] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 52 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2) |
| Number of subjects included in analysis | 1084 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[121] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.7 |

Notes:

[121] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

| | |
|--|---|
| Statistical analysis title | GMTs for HPV VLPs-Lot Seroconversion |
| Statistical analysis description: Anti-HPV 58 | |
| Comparison groups | Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3) |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[122] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Percentage Point Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 1.3 |

Notes:

[122] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Extension Study: Combined Incidence of Condyloma, Penile Intraepithelial Neoplasia, and Penile/Perineal/Perianal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Males

| | |
|-----------------|---|
| End point title | Extension Study: Combined Incidence of Condyloma, Penile Intraepithelial Neoplasia, and Penile/Perineal/Perianal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Males |
|-----------------|---|

End point description:

The combined incidence of penile/perineal/perianal cancer related to HPV in males was assessed. For each study participant, person-years follow-up was calculated starting from the beginning of the long-

term follow-up study (i.e., Month 42 visit) or the date when the study participant reached 16 years of age, whichever came later. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The primary effectiveness analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to ~11 years | |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Extension Study: 9- to 15-Year-Old Males | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 261 | | | |
| Units: Cases per 10,000 person-years | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 28.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Females

| | |
|-----------------|---|
| End point title | Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Females |
|-----------------|---|

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥ 2 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at ≥ 2 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Per protocol, the extension study included 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to ~11 years | |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Extension Study: 9- to 15-Year-Old Females | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 872 | | | |
| Units: Cases per 10,000 person-years | | | | |
| number (confidence interval 95%) | 52.4 (33.6 to 78.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of Cervical Intraepithelial Neoplasia, Adenocarcinoma In Situ, Vulvar Intraepithelial Neoplasia, Vaginal Intraepithelial Neoplasia, and Cervical/Vulvar/Vaginal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Females

| | |
|-----------------|--|
| End point title | Extension Study: Combined Incidence of Cervical Intraepithelial Neoplasia, Adenocarcinoma In Situ, Vulvar Intraepithelial Neoplasia, Vaginal Intraepithelial Neoplasia, and Cervical/Vulvar/Vaginal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Females |
|-----------------|--|

End point description:

The combined incidence of all cervical/vulvar/vaginal cancers was assessed. Person-years follow-up was calculated starting from the beginning of the long-term follow-up study or the date when the study participant reached 16 years of age, whichever came later. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The primary effectiveness analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

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

End point timeframe:

Up to ~11 years

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Extension Study: 9- to 15-Year-Old Females | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 866 | | | |
| Units: Cases per 10,000 person-years | | | | |
| number (confidence interval 95%) | 2.2 (0.1 to 12.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Percentage of Participants with Vaccine-Related or Procedure-Related Serious Adverse Event who Received 9vHPV Vaccine at 9 to 15 Years of Age

| | |
|-----------------|--|
| End point title | Extension Study: Percentage of Participants with Vaccine-Related or Procedure-Related Serious Adverse Event who Received 9vHPV Vaccine at 9 to 15 Years of Age |
|-----------------|--|

End point description:

A serious adverse event (SAE) included a death which resulted in the participant discontinuing the study, a serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related or study procedure related. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who received at least 1 study vaccination in the base study and had follow-up data.

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

End point timeframe:

Up to ~11 years

| End point values | Extension Study: 9- to 15-Year-Old Females | Extension Study: 9- to 15-Year-Old Males | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 971 | 301 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0.0 | 0.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Males

| | |
|-----------------|---|
| End point title | Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Males |
|-----------------|---|

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥ 2 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at ≥ 2 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

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

End point timeframe:

Up to ~11 years

| | | | | |
|--------------------------------------|---|--|--|--|
| End point values | Extension Study: 9- to 15-Year-Old Males | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 265 | | | |
| Units: Cases per 10,000 person-years | | | | |
| number (confidence interval 95%) | 54.6 (21.9 to 112.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Base Study: Up to 5 days after any vaccination for nonserious injection site AEs, Up to 15 days after any vaccination for nonserious systemic AEs, and up to 7 months for SAEs. Extension Study, and all cause mortality: Up to ~11 years post vaccination 3.

Adverse event reporting additional description:

Base Study and Extension Study: All participants who received at least one dose of 9vHPV and had available follow-up data. All randomized participants were included in the all cause mortality.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Base Study: 9-to 15- Year Old Females (Lot 2) |
|-----------------------|---|

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.

| | |
|-----------------------|---|
| Reporting group title | Base Study: 9-to 15- Year Old Females (Lot 1) |
|-----------------------|---|

Reporting group description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| | |
|-----------------------|--|
| Reporting group title | Base Study: 16-to 26- Year- Old Females Base |
|-----------------------|--|

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| | |
|-----------------------|--------------------------|
| Reporting group title | Extension Study: Females |
|-----------------------|--------------------------|

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|-----------------------|------------------------|
| Reporting group title | Extension Study: Males |
|-----------------------|------------------------|

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

| | |
|-----------------------|---|
| Reporting group title | Base Study: 9-to 15- Year Old Females (Lot 3) |
|-----------------------|---|

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Base Study: 9-to 15- Year Old Males |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

| Serious adverse events | Base Study: 9-to 15- Year Old Females (Lot 2) | Base Study: 9-to 15- Year Old Females (Lot 1) | Base Study: 16-to 26- Year- Old Females Base |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 639 (0.31%) | 6 / 643 (0.93%) | 15 / 466 (3.22%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tongue injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 639 (0.16%) | 0 / 643 (0.00%) | 5 / 466 (1.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical incompetence | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion threatened | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Foetal distress syndrome | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature baby | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 639 (0.16%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Tonsillitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 0 / 466 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 1 / 643 (0.16%) | 0 / 466 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 639 (0.00%) | 0 / 643 (0.00%) | 1 / 466 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Extension Study: Females | Extension Study: Males | Base Study: 9-to 15- Year Old Females (Lot 3) |
|---|-----------------------------|---------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 1664 (0.30%) | 0 / 580 (0.00%) | 8 / 641 (1.25%) |
| number of deaths (all causes) | 2 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tongue injury | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal | | | |

| | | | |
|--|------------------|-----------------|-----------------|
| conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical incompetence | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion threatened | | | |
| subjects affected / exposed | 1 / 1664 (0.06%) | 0 / 580 (0.00%) | 0 / 641 (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 |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature baby | | | |
| subjects affected / exposed | 2 / 1664 (0.12%) | 0 / 580 (0.00%) | 0 / 641 (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 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| 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 | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 1 / 1664 (0.06%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 1 / 641 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 1664 (0.06%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 0 / 641 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------|-------------------------------------|--|--|
| Serious adverse events | Base Study: 9-to 15- Year Old Males | | |
|-------------------------------|-------------------------------------|--|--|

| | | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 662 (1.66%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tongue injury | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|---|-----------------|--|--|
| Abortion induced | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical incompetence | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abortion threatened | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Premature baby | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 662 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious mononucleosis | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal infection | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paronychia | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngotonsillitis | | | | |
| subjects affected / exposed | 1 / 662 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillitis | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 662 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Base Study: 9-to 15- Year Old Females (Lot 2) | Base Study: 9-to 15- Year Old Females (Lot 1) | Base Study: 16-to 26- Year- Old Females Base |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 537 / 639 (84.04%) | 538 / 643 (83.67%) | 404 / 466 (86.70%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 123 / 639 (19.25%) | 122 / 643 (18.97%) | 106 / 466 (22.75%) |
| occurrences (all) | 171 | 184 | 166 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 513 / 639 (80.28%) | 508 / 643 (79.00%) | 393 / 466 (84.33%) |
| occurrences (all) | 1192 | 1177 | 984 |
| Injection site erythema | | | |
| subjects affected / exposed | 194 / 639 (30.36%) | 184 / 643 (28.62%) | 132 / 466 (28.33%) |
| occurrences (all) | 291 | 265 | 223 |
| Pyrexia | | | |
| subjects affected / exposed | 58 / 639 (9.08%) | 76 / 643 (11.82%) | 43 / 466 (9.23%) |
| occurrences (all) | 68 | 91 | 53 |
| Injection site swelling | | | |
| subjects affected / exposed | 240 / 639 (37.56%) | 208 / 643 (32.35%) | 154 / 466 (33.05%) |
| occurrences (all) | 376 | 320 | 273 |

| Non-serious adverse events | Extension Study: Females | Extension Study: Males | Base Study: 9-to 15- Year Old Females (Lot 3) |
|---|--------------------------|------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 554 / 641 (86.43%) |

| | | | |
|--|------------------|-----------------|--------------------|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 113 / 641 (17.63%) |
| occurrences (all) | 0 | 0 | 156 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 530 / 641 (82.68%) |
| occurrences (all) | 0 | 0 | 1224 |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 195 / 641 (30.42%) |
| occurrences (all) | 0 | 0 | 282 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 65 / 641 (10.14%) |
| occurrences (all) | 0 | 0 | 75 |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 1664 (0.00%) | 0 / 580 (0.00%) | 227 / 641 (35.41%) |
| occurrences (all) | 0 | 0 | 384 |

| | | | |
|---|-------------------------------------|--|--|
| Non-serious adverse events | Base Study: 9-to 15- Year Old Males | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 505 / 662 (76.28%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 99 / 662 (14.95%) | | |
| occurrences (all) | 144 | | |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 465 / 662 (70.24%) | | |
| occurrences (all) | 929 | | |
| Injection site erythema | | | |
| subjects affected / exposed | 159 / 662 (24.02%) | | |
| occurrences (all) | 220 | | |
| Pyrexia | | | |
| subjects affected / exposed | 84 / 662 (12.69%) | | |
| occurrences (all) | 94 | | |
| Injection site swelling | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 175 / 662 (26.44%) | | |
| occurrences (all) | 252 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 January 2010 | V503-002-10-This amendment extended the duration of the immunogenicity follow-up from 7 months to 3 years duration for the 9-15 year old pre-adolescent and adolescent boys and girls. |
| 08 November 2012 | V503-002-20- This amendment increased the long-term immunogenicity, safety, and effectiveness follow-up of 9-15 year old girls and boys administered 9vHPV vaccine to 10 years post-dose three. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported