



Clinical trial results: Evaluation of Safety and Immunogenicity of GARDASIL™ in Healthy Females Between 9 and 26 Years of Age in Sub-Saharan Africa Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000110-35 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 15 April 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2017 |
| First version publication date | 24 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | V501-046 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01245764 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 April 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 April 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 April 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The study was designed to determine the safety, tolerability and immunogenicity of a 3-dose regimen of GARDASIL™ administered to healthy females between 9 and 26 years of age in Sub-Saharan Africa. Data from the current study are needed in order to complement existing extensive safety data from the GARDASIL™ clinical trials program, and confirm that GARDASIL™ may be administered safely and will induce immune responses in populations from and living in Sub-Saharan Africa, as GARDASIL™ has not previously been studied in this region of the world. In Phase A of the study, healthy females between 9 and 12 years of age were randomized (4:1) to receive the 3-dose regimen of GARDASIL™ or placebo, and those between 13 and 26 years old received GARDASIL™. In Phase B of the study, participants who received placebo in Phase A had the option to receive the 3-dose regimen of GARDASIL™.

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 | 21 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Ghana: 30 |
| Country: Number of subjects enrolled | Kenya: 90 |
| Country: Number of subjects enrolled | Senegal: 130 |
| Worldwide total number of subjects | 250 |
| EEA total number of subjects | 0 |

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) | 75 |
| Adolescents (12-17 years) | 70 |
| Adults (18-64 years) | 105 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Healthy female participants between 9 and 26 years of age in sub-Saharan Africa were enrolled into the study.

Pre-assignment

Screening details:

A total of 257 participants were screened and 250 were randomized.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Study Phase A |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Arms

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

| | |
|------------------|----------------------------|
| Arm title | Gardasil 9 to 12 Years Old |
|------------------|----------------------------|

Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | GARDASIL™ |
| Investigational medicinal product code | |
| Other name | Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501 |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A

| | |
|------------------|-----------------------------|
| Arm title | Gardasil 13 to 15 Years Old |
|------------------|-----------------------------|

Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | GARDASIL™ |
| Investigational medicinal product code | |
| Other name | Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501 |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A

| | |
|------------------|-----------------------------|
| Arm title | Gardasil 16 to 26 Years Old |
|------------------|-----------------------------|

Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

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

| | |
|---|--|
| Investigational medicinal product name | GARDASIL™ |
| Investigational medicinal product code | |
| Other name | Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501 |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A | |
| Arm title | Placebo 9 to 12 Years Old |

Arm description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months)

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

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A

| Number of subjects in period 1 | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Gardasil 16 to 26 Years Old |
|---|-------------------------------|--------------------------------|--------------------------------|
| Started | 80 | 30 | 120 |
| Completed Vaccinations in Study Phase A | 77 | 28 | 117 |
| Completed | 71 | 25 | 110 |
| Not completed | 9 | 5 | 10 |
| Unknown | 3 | 2 | 3 |
| Lost to follow-up | - | - | 5 |
| Protocol deviation | 6 | 3 | 2 |

| Number of subjects in period 1 | Placebo 9 to 12 Years Old |
|---|------------------------------|
| Started | 20 |
| Completed Vaccinations in Study Phase A | 19 |
| Completed | 17 |
| Not completed | 3 |
| Unknown | 1 |
| Lost to follow-up | - |
| Protocol deviation | 2 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Study Phase B |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---|
| Arm title | Placebo 9 to 12 Years Old (Gardasil in Phase B) |
|------------------|---|

Arm description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. After database lock and unblinding for study Phase A, participants accepted the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B.

| | |
|--|---|
| Arm type | Catch-up vaccination |
| Investigational medicinal product name | GARDASIL™ |
| Investigational medicinal product code | |
| Other name | Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501 |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B

| | |
|---|---|
| Number of subjects in period 2^[1] | Placebo 9 to 12 Years Old (Gardasil in Phase B) |
| Started | 17 |
| Completed | 17 |

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: Phase B was voluntary.

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Gardasil 9 to 12 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Gardasil 13 to 15 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Gardasil 16 to 26 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Placebo 9 to 12 Years Old |
| Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months) | |

| Reporting group values | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Gardasil 16 to 26 Years Old |
|---|----------------------------|-----------------------------|-----------------------------|
| Number of subjects | 80 | 30 | 120 |
| Age Categorical Units: Subjects | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 10.7 | 13.8 | 21.3 |
| standard deviation | ± 1 | ± 0.8 | ± 2.9 |
| Gender Categorical Units: Subjects | | | |
| Female | 80 | 30 | 120 |
| Male | 0 | 0 | 0 |
| Age Units: Subjects | | | |
| <9 years | 0 | 0 | 0 |
| 9 to 12 years | 80 | 0 | 0 |
| 13 to 15 years | 0 | 30 | 0 |
| 16 to 26 years | 0 | 0 | 120 |
| >26 years | 0 | 0 | 0 |
| Race/Ethnicity Units: Subjects | | | |
| Black | 80 | 30 | 119 |
| Native Hawaiian or Other Pacific Island | 0 | 0 | 1 |

| Reporting group values | Placebo 9 to 12 Years Old | Total | |
|---|------------------------------|-------|--|
| Number of subjects | 20 | 250 | |
| Age Categorical Units: Subjects | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 10.5 ± 1.1 | - | |
| Gender Categorical Units: Subjects | | | |
| Female | 20 | 250 | |
| Male | 0 | 0 | |
| Age Units: Subjects | | | |
| <9 years | 0 | 0 | |
| 9 to 12 years | 20 | 100 | |
| 13 to 15 years | 0 | 30 | |
| 16 to 26 years | 0 | 120 | |
| >26 years | 0 | 0 | |
| Race/Ethnicity Units: Subjects | | | |
| Black | 20 | 249 | |
| Native Hawaiian or Other Pacific Island | 0 | 1 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Gardasil 9 to 12 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Gardasil 13 to 15 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Gardasil 16 to 26 Years Old |
| Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B. | |
| Reporting group title | Placebo 9 to 12 Years Old |
| Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months) | |
| Reporting group title | Placebo 9 to 12 Years Old (Gardasil in Phase B) |
| Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. After database lock and unblinding for study Phase A, participants accepted the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. | |
| Subject analysis set title | Gardasil 9 to 26 Years Old |
| Subject analysis set type | Per protocol |
| Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). This subject analysis set includes randomized participants who received at least one vaccination in Study Phase A. | |
| Subject analysis set title | Placebo 9 to 12 Years Old |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. This subject analysis set includes randomized participants who received at least one vaccination in Study Phase A. | |
| Subject analysis set title | Gardasil 9 to 12 Years Old |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A. | |
| Subject analysis set title | Gardasil 13 to 15 Years Old |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A. | |
| Subject analysis set title | Gardasil 16 to 26 Years Old |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Placebo 9 to 12 Years Old |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Placebo 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.

Primary: Number of Participants Who Seroconvert to Human Papillomavirus (HPV) Type 6

| | |
|-----------------|--|
| End point title | Number of Participants Who Seroconvert to Human Papillomavirus (HPV) Type 6 ^[1] |
|-----------------|--|

End point description:

Seroconversion was defined as achieving an anti-HPV Type 6 competitive Luminex Immunoassay (cLIA) level of ≥ 20 milli Merck U/mL. The dilution-corrected limit of detection for the Type 6 cLIA was 4.2 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

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

End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

Notes:

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

Justification: No between-group statistical analyses were conducted for this endpoint.

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|-----------------------------|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 147 | 13 | | |
| Units: Participants | 147 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 11

| | |
|-----------------|--|
| End point title | Number of Participants Who Seroconvert to HPV Type 11 ^[2] |
|-----------------|--|

End point description:

Seroconversion was defined as achieving an anti-HPV Type 11 cLIA level of ≥ 16 milli Merck U/mL. The dilution-corrected limit of detection for the Type 11 cLIA was 3.9 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

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

End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

Notes:

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

Justification: No between-group statistical analyses were conducted for this endpoint

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|-----------------------------|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 147 | 13 | | |
| Units: Participants | 147 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 16

| | |
|-----------------|--|
| End point title | Number of Participants Who Seroconvert to HPV Type 16 ^[3] |
|-----------------|--|

End point description:

Seroconversion was defined as achieving an anti-HPV Type 16 cLIA level of ≥ 20 milli Merck U/mL. The dilution-corrected limit of detection for the Type 16 cLIA was 9.7 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

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

End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

Notes:

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

Justification: No between-group statistical analyses were conducted for this endpoint

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|-----------------------------|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 160 | 14 | | |
| Units: Participants | 160 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 18

| | |
|-----------------|--|
| End point title | Number of Participants Who Seroconvert to HPV Type 18 ^[4] |
|-----------------|--|

End point description:

Seroconversion was defined as achieving an anti-HPV Type 18 cLIA level of ≥ 24 milli Merck U/mL. The dilution-corrected limit of detection for the Type 18 cLIA was 5.8 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

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

End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

Notes:

[4] - 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 between-group statistical analyses were conducted for this endpoint

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|-----------------------------|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 156 | 14 | | |
| Units: Participants | 156 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Injection-site Adverse Experiences

| | |
|-----------------|--|
| End point title | Number of Participants With Injection-site Adverse |
|-----------------|--|

End point description:

Participants were prompted to report injection-site experiences of pain, erythema, or swelling and were also asked to report any other injection-site adverse experiences. The analysis included all participants receiving at least 1 vaccination in study Phase A and who had postvaccination follow-up.

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

End point timeframe:

Up to Day 5 after any vaccination in Study Phase A

Notes:

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

Justification: No statistical analysis was conducted for this endpoint.

| End point values | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Gardasil 16 to 26 Years Old | Placebo 9 to 12 Years Old |
|-----------------------------|----------------------------|-----------------------------|-----------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79 | 29 | 119 | 19 |
| Units: Participants | 54 | 21 | 88 | 9 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Elevated Temperature (Oral Temperature $\geq 100^{\circ}\text{F}$)

| | |
|-----------------|---|
| End point title | Number of Participants With Elevated Temperature (Oral Temperature $\geq 100^{\circ}\text{F}$) |
|-----------------|---|

End point description:

The analysis included all participants receiving at least 1 vaccination in study Phase A and who had temperature data

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

End point timeframe:

Up to Day 5 after any vaccination in Study Phase A

| End point values | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Gardasil 16 to 26 Years Old | Placebo 9 to 12 Years Old |
|-----------------------------|----------------------------|-----------------------------|-----------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79 | 29 | 119 | 19 |
| Units: Participants | 9 | 6 | 7 | 5 |

Statistical analyses

| Statistical analysis title | Analysis of Maximum Temperatures |
|--|--|
| Statistical analysis description: | |
| Analysis compared the difference in percentage of participants with elevated temperature | |
| Comparison groups | Gardasil 9 to 12 Years Old v Placebo 9 to 12 Years Old |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.097 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -14.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.4 |
| upper limit | 2.2 |

Primary: Number of Participants With Serious Adverse Experiences

| End point title | Number of Participants With Serious Adverse Experiences ^[6] |
|---|--|
| End point description: | |
| A serious adverse experience is any adverse experience that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is an overdose, or is another important medical event that may jeopardize the participant and may require medical or surgical intervention. The analysis included all participants receiving at least 1 vaccination in study Phase A or B and who had postvaccination follow-up. | |
| End point type | Primary |
| End point timeframe: | |
| From the time informed consent is signed through the last study visit (up to 19 months) | |

Notes:

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

Justification: No statistical analysis was conducted for this endpoint.

| End point values | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Gardasil 16 to 26 Years Old | Placebo 9 to 12 Years Old |
|-----------------------------|----------------------------|-----------------------------|-----------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79 | 29 | 119 | 19 |
| Units: Participants | 0 | 0 | 1 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer (GMT) of Anti-HPV Type 6 Antibody

| | |
|--|--|
| End point title | Geometric Mean Titer (GMT) of Anti-HPV Type 6 Antibody |
| End point description: Anti-HPV Type 6 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <10 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo. | |
| End point type | Secondary |
| End point timeframe: Month 7 (1 month postdose 3 in Study Phase A) | |

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|--|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 147 | 13 | | |
| Units: Milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | 602 (526 to 689) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 11 Antibody

| | |
|--|----------------------------------|
| End point title | GMT of Anti-HPV Type 11 Antibody |
| End point description: Anti-HPV Type 11 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 16 milli Merck U/mL. A value of 9999 indicates that the GMT was <7 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo. | |
| End point type | Secondary |
| End point timeframe: Month 7 (1 month postdose 3 in Study Phase A) | |

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|--|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 147 | 13 | | |
| Units: Milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | 626 (545 to 718) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 16 Antibody

| | |
|--|----------------------------------|
| End point title | GMT of Anti-HPV Type 16 Antibody |
| End point description: Anti-HPV Type 16 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <9 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo. | |
| End point type | Secondary |
| End point timeframe: Month 7 (1 month postdose 3 in Study Phase A) | |

| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
|--|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 160 | 14 | | |
| Units: Milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | 3786 (3360 to 4265) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 18 Antibody

| | |
|---|----------------------------------|
| End point title | GMT of Anti-HPV Type 18 Antibody |
| End point description: Anti-HPV Type 18 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 24 milli Merck U/mL. A value of 9999 indicates that the GMT was <15 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL | |

and compared these with results for participants receiving placebo.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 7 (1 month postdose 3 in Study Phase A) | |

| | | | | |
|--|----------------------------|---------------------------|--|--|
| End point values | Gardasil 9 to 26 Years Old | Placebo 9 to 12 Years Old | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 156 | 14 | | |
| Units: Milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | 811 (708 to 928) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events were assessed up to 19 months from study start. Other adverse events were assessed up to 15 days after each vaccination in study Phase A.

Adverse event reporting additional description:

The analysis included all participants receiving at least one vaccination and had at least one postvaccination follow-up visit.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Gardasil 9 to 12 Years Old |
|-----------------------|----------------------------|

Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A.

Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Gardasil 13 to 15 Years Old |
|-----------------------|-----------------------------|

Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A.

Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo 9 to 12 Years Old |
|-----------------------|---------------------------|

Reporting group description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A.

Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months).

| | |
|-----------------------|-----------------------------|
| Reporting group title | Gardasil 16 to 26 Years Old |
|-----------------------|-----------------------------|

Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A.

Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

| Serious adverse events | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Placebo 9 to 12 Years Old |
|---|----------------------------|-----------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 29 (0.00%) | 0 / 19 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 29 (0.00%) | 0 / 19 (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 | Gardasil 16 to 26 Years Old | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|-------------------------------|--------------------------------|------------------------------|
| Non-serious adverse events | Gardasil 9 to 12 Years Old | Gardasil 13 to 15 Years Old | Placebo 9 to 12 Years Old |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 79 (77.22%) | 22 / 29 (75.86%) | 15 / 19 (78.95%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 29 (3.45%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 1 |
| Headache | | | |
| subjects affected / exposed | 27 / 79 (34.18%) | 12 / 29 (41.38%) | 5 / 19 (26.32%) |
| occurrences (all) | 37 | 16 | 7 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 29 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 3 / 29 (10.34%) | 1 / 19 (5.26%) |
| occurrences (all) | 12 | 4 | 1 |
| Injection site pain | | | |
| subjects affected / exposed | 53 / 79 (67.09%) | 20 / 29 (68.97%) | 9 / 19 (47.37%) |
| occurrences (all) | 113 | 46 | 21 |
| Injection site swelling | | | |

| | | | |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 23 / 79 (29.11%) 37 | 8 / 29 (27.59%) 9 | 4 / 19 (21.05%) 7 |
| Pyrexia subjects affected / exposed occurrences (all) | 9 / 79 (11.39%) 12 | 6 / 29 (20.69%) 7 | 5 / 19 (26.32%) 8 |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Myopia subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 7 / 79 (8.86%) 8 | 2 / 29 (6.90%) 3 | 1 / 19 (5.26%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 29 (3.45%) 1 | 1 / 19 (5.26%) 1 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 1 / 29 (3.45%) 1 | 0 / 19 (0.00%) 0 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Malaria subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 3 | 2 / 29 (6.90%) 2 | 1 / 19 (5.26%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 29 (3.45%) 2 | 0 / 19 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 19 (5.26%) 1 |

| Non-serious adverse events | Gardasil 16 to 26 Years Old | | |
|---|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 103 / 119 (86.55%) | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | | |
| occurrences (all) | 3 | | |
| Headache | | | |
| subjects affected / exposed | 41 / 119 (34.45%) | | |
| occurrences (all) | 58 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 15 / 119 (12.61%) | | |
| occurrences (all) | 21 | | |
| Injection site pain | | | |
| subjects affected / exposed | 88 / 119 (73.95%) | | |
| occurrences (all) | 188 | | |
| Injection site swelling | | | |
| subjects affected / exposed | 31 / 119 (26.05%) | | |
| occurrences (all) | 48 | | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 119 (7.56%) | | |
| occurrences (all) | 10 | | |
| Eye disorders | | | |
| Eye pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myopia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) | 8 / 119 (6.72%) 8 2 / 119 (1.68%) 4 | | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 11 / 119 (9.24%) 16 | | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Malaria subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 2 / 119 (1.68%) 2 13 / 119 (10.92%) 14 3 / 119 (2.52%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported