



Clinical trial results:

A Phase III Placebo-controlled Clinical Trial to Study the Tolerability, Immunogenicity and Efficacy of V501 in 16- to 26-year-old Japanese men

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002931-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 30 August 2017 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 15 August 2018 |
| First version publication date | 15 August 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | V501-122 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01862874 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | JAPIC-CTI: 132237 |

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 | 30 August 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and tolerability of V501 (quadrivalent Human Papilloma Virus [HPV] [Type 6, 11, 16 and 18] L1 Virus-Like Particle vaccine, GARDASIL™) in healthy, 16- to 26-year old Japanese males. The hypotheses tested are: 1) V501 reduces the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection compared with placebo, and 2) V501 reduces the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia, or penile, perianal, or perineal cancer compared with placebo.

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 June 2013 |
| 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 | Japan: 1124 |
| Worldwide total number of subjects | 1124 |
| 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) | 0 |
| Adolescents (12-17 years) | 3 |
| Adults (18-64 years) | 1121 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 1129 participants were screened and 1124 were randomized.

Pre-assignment

Screening details:

Healthy Japanese males age 16 to 26 years were enrolled in the study.

Period 1

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

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | Yes |
| Arm title | V501 |

Arm description:

Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Quadrivalent human papillomavirus vaccine |
| Investigational medicinal product code | |
| Other name | (Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine. Formulated with aluminum hydroxyphosphate sulfate (AAHS) adjuvant. |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL intramuscular injection at Day 1, Month 2, and Month 6

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

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

Dosage and administration details:

0.5 mL intramuscular injection at Day 1, Month 2, and Month 6

| Number of subjects in period 1 | V501 | Placebo |
|---------------------------------------|------|---------|
| Started | 562 | 562 |
| Vaccination 1 | 561 | 562 |
| Vaccination 2 | 539 | 542 |
| Vaccination 3 | 530 | 532 |
| Completed | 483 | 485 |
| Not completed | 79 | 77 |
| Withdrawn by parent/guardian | 1 | 1 |
| Adverse event, serious fatal | - | 1 |
| Physician decision | 5 | 3 |
| Consent withdrawn by subject | 46 | 40 |
| Randomized not treated | 1 | - |
| Adverse event, non-fatal | - | 3 |
| Lost to follow-up | 26 | 29 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | V501 |
|-----------------------|------|

Reporting group description:

Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

| Reporting group values | V501 | Placebo | Total |
|---|-------|---------|-------|
| Number of subjects | 562 | 562 | 1124 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 0 | 3 | 3 |
| Adults (18-64 years) | 562 | 559 | 1121 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 22.6 | 22.6 | |
| standard deviation | ± 2.1 | ± 2.0 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 562 | 562 | 1124 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 562 | 562 | 1124 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 0 | 0 | 0 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | V501 |
| Reporting group description: Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36. | |

Primary: Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection

| | |
|---|--|
| End point title | Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection |
| End point description: Persistent infection was defined as 1) polymerase chain reaction (PCR) positive to HPV Type 6, 11, 16, or 18 in 2 consecutive anogenital or biopsy samples collected ≥ 4 months apart, or 2) Pathology Panel consensus diagnosis of condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal, or perineal cancer and PCR detection of HPV Type 6, 11, 16, or 18 in an adjacent section and PCR positive for the same HPV type at a separate adjacent visit. The combined incidence of HPV Type 6, 11, 16, or 18 persistent infection detected in samples from ≥ 2 consecutive visits ≥ 6 months apart was assessed. The population was participants who were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, received all 3 vaccinations, did not deviate from the study protocol in ways that might interfere with vaccine efficacy, and had ≥ 1 follow-up visit after Month 7. | |
| End point type | Primary |
| End point timeframe: Up to Month 36 | |

| End point values | V501 | Placebo | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 497 ^[1] | 498 ^[2] | | |
| Units: Cases per 100 person-years of follow-up | | | | |
| number (not applicable) | 0.3 | 1.9 | | |

Notes:

[1] - 1137 person-years follow-up

[2] - 1123 person-years follow-up

Statistical analyses

| | |
|--|------------------|
| Statistical analysis title | Vaccine Efficacy |
| Statistical analysis description: Vaccine efficacy is defined as the percentage reduction in relative risk for the V501 group versus the placebo group. | |
| Comparison groups | V501 v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 995 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.001 |
| Method | One-sided exact test |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 85.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 52.7 |
| upper limit | 97.3 |

Notes:

[3] - If the lower bound of the 95% confidence interval for vaccine efficacy excludes 0%, then superiority of the V501 group is demonstrated.

Primary: Percentage of Participants with Maximum Temperature $\geq 37.5^{\circ}\text{C}$ Reported on the Vaccination Report Card

| | |
|-----------------|---|
| End point title | Percentage of Participants with Maximum Temperature $\geq 37.5^{\circ}\text{C}$ Reported on the Vaccination Report Card |
|-----------------|---|

End point description:

Body temperature (oral or oral equivalent) was recorded on the Vaccination Report Card (VRC). The percentage of participants with a maximum temperature $\geq 37.5^{\circ}\text{C}$ was summarized. The population was participants who received ≥ 1 study vaccination and had follow-up data available.

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

End point timeframe:

Up to 5 days after any vaccination

| End point values | V501 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 551 | 557 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 2.7 | 3.9 | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Incidence of elevated temperature |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1108 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.256 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 0.9 |

Notes:

[4] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with an Injection-site Adverse Event Prompted on the Vaccination Report Card

| | |
|-----------------|---|
| End point title | Percentage of Participants with an Injection-site Adverse Event Prompted on the Vaccination Report Card |
|-----------------|---|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. The percentage of participants with an injection-site AE prompted on the VRC (erythema, pain, and swelling) was summarized. The population was participants who received ≥ 1 study vaccination and had follow-up data available.

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

End point timeframe:

Up to 5 days after any vaccination

| End point values | V501 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 559 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Injection-site erythema | 24.5 | 21.6 | | |
| Injection-site pain | 54.9 | 48.5 | | |
| Injection-site swelling | 21.3 | 14.5 | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Incidence of injection-site erythema |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1113 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.251 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 7.9 |

Notes:

[5] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

| | |
|---|----------------------------------|
| Statistical analysis title | Incidence of injection-site pain |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1113 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.033 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 6.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 12.2 |

Notes:

[6] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

| | |
|---|--------------------------------------|
| Statistical analysis title | Incidence of injection-site swelling |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1113 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.003 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 6.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.3 |
| upper limit | 11.3 |

Notes:

[7] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with a Systemic Adverse Event

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Systemic Adverse Event |
|-----------------|--|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. The percentage of participants with a systemic AE was

summarized. The population was participants who received ≥ 1 study vaccination and had follow-up data available.

| | |
|-------------------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to 15 days after any vaccination | |

| End point values | V501 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 559 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 14.4 | 15.4 | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Incidence of systemic AEs |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1113 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.2 |
| upper limit | 3.3 |

Notes:

[8] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with a Vaccine-related Systemic Adverse Event

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Vaccine-related Systemic Adverse Event |
|-----------------|--|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. Vaccine-related AEs are those that were deemed possibly, probably, or definitely related to vaccine administration by the investigator. The percentage of participants with a vaccine-related systemic AE was summarized. The population was participants who received ≥ 1 study vaccination and had follow-up data available

| | |
|-------------------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to 15 days after any vaccination | |

| End point values | V501 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 559 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 3.4 | 5.0 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Incidence of vaccine-related systemic AEs |
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 1113 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | 0.8 |

Notes:

[9] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Secondary: Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection or Disease

| | |
|-----------------|---|
| End point title | Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection or Disease |
|-----------------|---|

End point description:

Persistent infection was defined as in the first primary endpoint above. Disease was defined as HPV Type 6, 11, 16, or 18-related condyloma acuminata, PIN, penile, perianal, or perineal cancer. The combined incidence of HPV Type 6, 11, 16, or 18 persistent infection or disease was assessed. The population was participants who were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, received all 3 vaccinations, did not deviate from the study protocol in ways that might interfere with vaccine efficacy, and had ≥ 1 follow-up visit after Month 7.

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

End point timeframe:

Up to Month 36

| End point values | V501 | Placebo | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 498 ^[10] | 498 ^[11] | | |
| Units: Cases per 100 person-years at risk | | | | |
| number (not applicable) | 0.3 | 1.9 | | |

Notes:

[10] - 1148 person-years follow-up

[11] - 1132 person-years follow-up

Statistical analyses

| Statistical analysis title | Vaccine Efficacy |
|-----------------------------------|------------------|
|-----------------------------------|------------------|

Statistical analysis description:

Vaccine efficacy is defined as the percentage reduction in relative risk for the V501 versus the placebo group.

| | |
|---|-----------------------------|
| Comparison groups | V501 v Placebo |
| Number of subjects included in analysis | 996 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | < 0.001 |
| Method | One-sided exact test |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 86.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 55.2 |
| upper limit | 97.4 |

Notes:

[12] - If the lower bound of the 95% confidence interval for vaccine efficacy excludes 0%, superiority of the V501 group is demonstrated.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 36 months

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

| | |
|-----------------------|------|
| Reporting group title | V501 |
|-----------------------|------|

Reporting group description:

Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

| Serious adverse events | Placebo | V501 | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 559 (0.18%) | 0 / 554 (0.00%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 559 (0.18%) | 0 / 554 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | V501 | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 303 / 559 (54.20%) | 329 / 554 (59.39%) | |
| General disorders and administration site conditions | | | |
| Injection-site erythema | | | |
| subjects affected / exposed | 122 / 559 (21.82%) | 137 / 554 (24.73%) | |
| occurrences (all) | 179 | 217 | |
| Injection-site swelling | | | |

| | | | |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 82 / 559 (14.67%) | 118 / 554 (21.30%) | |
| occurrences (all) | 121 | 181 | |
| Injection-site pain | | | |
| subjects affected / exposed | 271 / 559 (48.48%) | 304 / 554 (54.87%) | |
| occurrences (all) | 480 | 563 | |

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