# EU Clinical Trials Register

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## Clinical trial results:
## An Open-Label Phase III Clinical Trial to Study the Immunogenicity and Tolerability of GARDASIL®9 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Adult Women (27 to 45 Year-Olds) compared to Young Adult Women (16 to 26 Year-Olds)

### Summary

| | |
|---|---|
| EudraCT number | 2015-005093-38 |
| Trial protocol | DE FI AT ES IT BE |
| Global end of trial date | 19 November 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 03 August 2019 |
| First version publication date | 03 August 2019 |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | V503-004 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03158220 |
| WHO universal trial number (UTN) | - |

Notes:


### Sponsors

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, 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 | 19 November 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of study is to demonstrate that the administration of the 9-valent human papillomavirus (9vHPV) vaccine in 27- to 45-year-old women induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 16, 18, 31, 33, 45, 52, and 58 compared with 16 to 26 year-old women. The primary hypothesis of the study states that anti-HPV 16, 18, 31, 33, 45, 52, and 58 titers at 4 weeks postdose 3 are non-inferior in adult women as compared with titers in young adult women.

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 | 14 September 2017 |
| 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 | Austria: 162 |
| Country: Number of subjects enrolled | Belgium: 192 |
| Country: Number of subjects enrolled | Finland: 263 |
| Country: Number of subjects enrolled | Germany: 165 |
| Country: Number of subjects enrolled | Italy: 154 |
| Country: Number of subjects enrolled | Spain: 276 |
| Worldwide total number of subjects | 1212 |
| EEA total number of subjects | 1212 |

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) | 42 |
| Adults (18-64 years) | 1170 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Healthy women aged 16-45 years of age were enrolled in the study. Other inclusion/exclusion criteria applied.

### Period 1

| | |
|---|---|
| Period 1 title | Overall (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Women 16-26 years of age |

Arm description:

Adult women 16 to 26-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gardasil ®9 |
| Investigational medicinal product code | |
| Other name | V503 |
| Pharmaceutical forms | Solution for injection, Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6

| | |
|---|---|
| **Arm title** | Women 27-45 years of age |

Arm description:

Young adult women 27 to 45-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gardasil ®9 |
| Investigational medicinal product code | |
| Other name | V503 |
| Pharmaceutical forms | Solution for injection, Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6

| Number of subjects in period 1 | Women 16-26 years of age | Women 27-45 years of age |
|---|---|---|
| Started | 570 | 642 |
| Vaccination 1 | 570 | 640 |
| Vaccination 2 | 563 | 635 |
| Vaccination 3 | 556 | 629 |

| | | |
|---|---|---|
| Completed | 553 | 626 |
| Not completed | 17 | 16 |
|     Consent withdrawn by subject | 8 | 9 |
|     Physician decision | 1 | - |
|     Screen Failure | - | 1 |
|     Status unknown | - | 1 |
|     Lost to follow-up | 8 | 5 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Women 16-26 years of age |
|---|---|
| Reporting group description: | |
| Adult women 16 to 26-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6. | |
| Reporting group title | Women 27-45 years of age |
| Reporting group description: | |
| Young adult women 27 to 45-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6. | |

| Reporting group values | Women 16-26 years of age | Women 27-45 years of age | Total |
|---|---|---|---|
| Number of subjects | 570 | 642 | 1212 |
| Age Categorical | | | |
| Units: Subjects | | | |
| Age Continuous | | | |
| Units: years | | | |
|    arithmetic mean | 21.6 | 35.8 | |
|    standard deviation | ± 2.8 | ± 5.5 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
|    Female | 570 | 642 | 1212 |
|    Male | 0 | 0 | 0 |
| Race | | | |
| Units: Subjects | | | |
|    American Indian or Alaska Native | 2 | 1 | 3 |
|    Asian | 17 | 10 | 27 |
|    Black or African American | 5 | 3 | 8 |
|    American Indian or Alaska Native, White | 1 | 1 | 2 |
|    Black or African American, White | 5 | 0 | 5 |
|    White, Asian | 1 | 0 | 1 |
|    White | 539 | 627 | 1166 |
| Ethnicity | | | |
| Units: Subjects | | | |
|    Hispanic or Latino | 21 | 7 | 28 |
|    Not Hispanic or Latino | 548 | 634 | 1182 |
|    Unknown | 1 | 1 | 2 |

## End points

### End points reporting groups

| Reporting group title | Women 16-26 years of age |
|---|---|
| Reporting group description: | |
| Adult women 16 to 26-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6. | |
| Reporting group title | Women 27-45 years of age |
| Reporting group description: | |
| Young adult women 27 to 45-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6. | |
| Subject analysis set title | Women 16-26 years of age - Immunogenicity |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Each HPV type had its own immunogenicity analysis population. Criteria for inclusion were: received all 3 vaccinations of the correct dose of the 9vHPV vaccine within acceptable day ranges as specified in the protocol, had evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges as specified in the protocol, must have been seronegative to the appropriate HPV type at Day 1 and had no protocol deviations that could interfere with the evaluation of participant's immune response to the 9vHPV vaccine. | |
| Subject analysis set title | Women 27-45 years of age - Immunogenicity |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Each HPV type had its own immunogenicity analysis population. Criteria for inclusion were: received all 3 vaccinations of the correct dose of the 9vHPV vaccine within acceptable day ranges as specified in the protocol, had evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges as specified in the protocol, must have been seronegative to the appropriate HPV type at Day 1 and had no protocol deviations that could interfere with the evaluation of participant's immune response to the 9vHPV vaccine. | |
| Subject analysis set title | Women 16-26 years of age - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All participants that received at least 1 vaccination and had available data for endpoint. | |
| Subject analysis set title | Women 27-45 years of age- Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All participants that received at least 1 vaccination and had available data for endpoint. | |

### Primary: Anti-HPV Geometric Mean Titers for Each Anti-HPV Type

| End point title | Anti-HPV Geometric Mean Titers for Each Anti-HPV Type |
|---|---|
| End point description: | |
| Antibodies to the HPV types contained in V503 were measured using a competitive luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). Statistical comparisons between arms was performed for the HPV types considered oncogenic (HPV Types 16/18/31/33/45/52/58). | |
| End point type | Primary |
| End point timeframe: | |
| 4 weeks post vaccination 3 (Month 7) | |

| End point values | Women 16-26 years of age - Immunogenicity | Women 27-45 years of age - Immunogenicity | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 485 | 533 | | |
| Units: mMU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV 6 (n=421; 448) | 787.8 (732.5 to 847.2) | 638.4 (594.9 to 685.0) | | |
| Anti-HPV 11 (n-421; 448) | 598.7 (558.7 to 641.6) | 453.5 (424.1 to 485.0) | | |
| Anti-HPV 16 (n=436; 448) | 3075.8 (2863.4 to 3303.9) | 2147.5 (2001.1 to 2304.5) | | |
| Anti-HPV 18 (n=421; 471) | 744.5 (685.0 to 809.1) | 532.1 (491.8 to 575.7) | | |
| Anti-HPV 31 (n=447; 488) | 596.1 (551.1 to 644.9) | 395.7 (367.0 to 426.6) | | |
| Anti-HPV 33 (n=457; 493) | 354.5 (331.7 to 378.9) | 259.0 (242.9 to 276.1) | | |
| Anti-HPV 45 (n=470; 515) | 214.9 (197.7 to 233.7) | 145.6 (134.4 to 157.7) | | |
| Anti-HPV 52 (n=456; 496) | 346.5 (324.0 to 370.5) | 244.7 (229.4 to 261.0) | | |
| Anti-HPV 58 (n=451; 478) | 428.0 (399.4 to 458.6) | 296.4 (277.1 to 317.0) | | |

**Statistical analyses**

| Statistical analysis title | Fold Difference Anti-HPV 16 |
|---|---|
| Statistical analysis description: | |
| Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds | |
| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.77 |

Notes:

[1] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.

| Statistical analysis title | Fold Difference Anti-HPV 18 |
|---|---|

Statistical analysis description:

Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds

| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
|---|---|
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| P-value | < 0.001 [3] |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.8 |

Notes:

[2] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.
[3] - Analysis of variance (ANOVA) model with response of log individual titers and a fixed effect for age groups.

| **Statistical analysis title** | Anti-HPV Type 31 |
|---|---|

Statistical analysis description:

Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds

| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
|---|---|
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[4] |
| P-value | < 0.001 [5] |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 0.74 |

Notes:

[4] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.
[5] - ANOVA model with response of log individual titers and a fixed effect for age groups.

| **Statistical analysis title** | Anti-HPV 33 |
|---|---|

Statistical analysis description:

Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds

| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[6] |
| P-value | < 0.001 [7] |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.73 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 0.67 |
|     upper limit | 0.8 |

Notes:

[6] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.

[7] - ANOVA model with response of log individual titers and a fixed effect for age groups.

| Statistical analysis title | Anti-HPV 45 |
|---|---|
| Statistical analysis description: | |
| Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds | |
| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[8] |
| P-value | < 0.001 [9] |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.68 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 0.6 |
|     upper limit | 0.76 |

Notes:

[8] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.

[9] - ANOVA model with response of log individual titers and a fixed effect for age groups.

| Statistical analysis title | Anti-HPV 52 |
|---|---|
| Statistical analysis description: | |
| Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds | |
| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[10] |
| P-value | < 0.001 [11] |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.71 |

| Confidence interval | |
| --- | --- |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.78 |

Notes:

[10] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.

[11] - ANOVA model with response of log individual titers and a fixed effect for age groups.

| **Statistical analysis title** | Fold Difference Anti-HPV 58 |
| --- | --- |

Statistical analysis description:

Fold difference calculated as GMT 16-26 year-olds/GMT 27-45 year-olds

| Comparison groups | Women 16-26 years of age - Immunogenicity v Women 27-45 years of age - Immunogenicity |
| --- | --- |
| Number of subjects included in analysis | 1018 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[12] |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | Fold Difference |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.76 |

Notes:

[12] - Non-inferiority of GMT in 16-26 year-olds relative to 16-26 year-olds was demonstrated if the lower limit of the 95% confidence interval (CI) for the fold difference was greater than 0.5.

## Secondary: Percentage of Participants That Experience at Least 1 Adverse Event (AE)

| End point title | Percentage of Participants That Experience at Least 1 Adverse Event (AE) |
| --- | --- |

End point description:

An AE is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The percentage of participants with 1 or more AEs was assessed.

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

End point timeframe:

Up to 1 month post vaccination 3 (up to 7 months)

| End point values | Women 16-26 years of age - Safety | Women 27-45 years of age- Safety | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 570 | 640 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 92.8 | 92.5 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Had Study Vaccine Discontinued Due to Adverse Event.

| End point title | Percentage of Participants Who Had Study Vaccine Discontinued Due to Adverse Event. |
|---|---|

End point description:

An adverse event is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. The percentage of participants who discontinued the study vaccine due to an adverse event regardless of study completion status was assessed.

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

End point timeframe:

Up to 1 month post vaccination 3 (up to 7 months)

| End point values | Women 16-26 years of age - Safety | Women 27-45 years of age- Safety | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 570 | 640 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0.0 | 0.2 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With at Least 1 Solicited Injection-site Adverse Event

| End point title | Percentage of Participants With at Least 1 Solicited Injection-site Adverse Event |
|---|---|

End point description:

Participants were asked to record any injection-site reactions prompted in the Vaccination Report Card, i.e., injection-site tenderness, swelling, or redness, occurring after each study vaccination (solicited injection-site reactions). The percentage of participants with 1 or more solicited injection-site AE was

assessed.

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

End point timeframe:

Up to 5 days post any vaccination

| **End point values** | Women 16-26 years of age - Safety | Women 27-45 years of age- Safety | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 570 | 640 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 87.2 | 84.7 | | |

### Statistical analyses

| **Statistical analysis title** | Difference in Percentages |
|---|---|

Statistical analysis description:

Difference in percentages calculated as % Women 27-45 Years of Age minus % Women 16-26 Years of Age.

| Comparison groups | Women 16-26 years of age - Safety v Women 27-45 years of age- Safety |
|---|---|
| Number of subjects included in analysis | 1210 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.212 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Difference in Percentages |
| Point estimate | -2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.4 |
| upper limit | 1.4 |

### Secondary: Percentage of Participants That Report at Least 1 Systemic Adverse Event

| End point title | Percentage of Participants That Report at Least 1 Systemic Adverse Event |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study vaccine. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study vaccine or a protocol-specified procedure, whether or not considered related to the study vaccine or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study vaccine or protocol-specified procedure is also an AE. Systemic AEs are those not categorized as injection-site AEs. The percentage of participants that reported at least 1 systemic AE was assessed

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

End point timeframe:

Up to 15 days post any vaccination

| End point values | Women 16-26 years of age - Safety | Women 27-45 years of age- Safety | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 570 | 640 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 66.3 | 64.4 | | |

## Statistical analyses

| Statistical analysis title | Difference in Percentages |
|---|---|
| Statistical analysis description: | |
| Difference in percentages calculated as % Women 27-45 Years of Age minus % Women 16-26 Years of Age. | |
| Comparison groups | Women 16-26 years of age - Safety v Women 27-45 years of age- Safety |
| Number of subjects included in analysis | 1210 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentages |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 3.4 |

## Secondary: Percentage of Participants With Elevated Temperature (Fever)

| End point title | Percentage of Participants With Elevated Temperature (Fever) |
|---|---|
| End point description: | |
| Participants were asked to record oral body temperature in the Vaccination Report Card. The percentage of participants with elevated temperature (≥37.8°C or 100.0°F) was assessed. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 days post any vaccination | |

| End point values | Women 16-26 years of age - Safety | Women 27-45 years of age- Safety | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 569 | 640 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 3.5 | 2.5 | | |

## Statistical analyses

| Statistical analysis title | Difference in Percentages |
|---|---|
| Statistical analysis description: | |
| Difference in percentages calculated as % Women 27-45 Years of Age minus % Women 16-26 Years of Age. | |
| Comparison groups | Women 16-26 years of age - Safety v Women 27-45 years of age- Safety |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Difference in Percentages |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.1 |
| upper limit | 0.9 |

## Secondary: Percentage of Participants Who Seroconvert to Each of the Anti-HPV Types

| End point title | Percentage of Participants Who Seroconvert to Each of the Anti-HPV Types |
|---|---|
| End point description: | |
| Antibodies to the HPV types contained in V503 were measured using a competitive luminex immunoassay. The percentage of participants who were seronegative on Day 1 and have anti-HPV titer greater or equal to the type-specific serostatus cutoff at 4 weeks postdose 3 was assessed. | |
| End point type | Secondary |
| End point timeframe: | |
| 4 weeks post vaccination 3 (Month 7) | |

| End point values | Women 16-26 years of age - Immunogenicity | Women 27-45 years of age - Immunogenicity | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 485 | 533 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Anti HPV 6 (n=421; 448) | 99.8 (98.7 to 100.0) | 100.0 (99.2 to 100.0) | | |
| Anti HPV 11 (n=421; 448) | 100.0 (99.1 to 100.0) | 99.8 (98.8 to 100.0) | | |
| Anti HPV 16 (n=436; 448) | 100.0 (99.2 to 100.0) | 100.0 (99.2 to 100.0) | | |
| Anti HPV 18 (n=421; 471) | 100.0 (99.1 to 100.0) | 99.6 (98.5 to 99.9) | | |
| Anti HPV 31 (n=447; 488) | 100.0 (99.2 to 100.0) | 99.8 (98.9 to 100.0) | | |
| Anti HPV 33 (n=457; 493) | 100.0 (99.2 to 100.0) | 99.8 (98.9 to 100.0) | | |
| Anti HPV 45 (n=470; 515) | 99.6 (98.5 to 99.9) | 99.2 (98.0 to 99.8) | | |
| Anti HPV 52 (n=456; 496) | 100.0 (99.2 to 100.0) | 100.0 (99.3 to 100.0) | | |
| Anti HPV 58 (n=451; 478) | 100.0 (99.2 to 100.0) | 99.8 (98.8 to 100.0) | | |

## Statistical analyses

No statistical analyses for this end point

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

Up to 1 month post vaccination 3 (up to 7 months)

Adverse event reporting additional description:

Population included all participants that received at least 1 vaccination.

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

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 21.1 |

## Reporting groups

| Reporting group title | Women 16-26 years of age |
|---|---|

Reporting group description:

Adult women 16 to 26-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6.

| Reporting group title | Women 27-45 years of age |
|---|---|

Reporting group description:

Adult women 27 to 45-years old received V503 vaccination, 0.5 mL in a 3-dose regimen administered on Day 1, Month 2, and Month 6.

| Serious adverse events | Women 16-26 years of age | Women 27-45 years of age | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 570 (1.05%) | 8 / 640 (1.25%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 570 (0.18%) | 0 / 640 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament injury | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Surgical and medical procedures** | | | |
| Abortion induced | | | |
| subjects affected / exposed | 2 / 570 (0.35%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nervous system disorders** | | | |
| Basilar migraine | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| Foetal death | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Gastrointestinal disorders** | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 570 (0.18%) | 0 / 640 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Infections and infestations** | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 570 (0.00%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 570 (0.18%) | 0 / 640 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 570 (0.18%) | 1 / 640 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Women 16-26 years of age | Women 27-45 years of age | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 518 / 570 (90.88%) | 574 / 640 (89.69%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 185 / 570 (32.46%) | 200 / 640 (31.25%) | |
| occurrences (all) | 297 | 320 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 28 / 570 (4.91%) | 33 / 640 (5.16%) | |
| occurrences (all) | 36 | 42 | |
| Injection site erythema | | | |
| subjects affected / exposed | 112 / 570 (19.65%) | 111 / 640 (17.34%) | |
| occurrences (all) | 166 | 163 | |
| Injection site pain | | | |
| subjects affected / exposed | 492 / 570 (86.32%) | 532 / 640 (83.13%) | |
| occurrences (all) | 1246 | 1244 | |
| Injection site swelling | | | |
| subjects affected / exposed | 137 / 570 (24.04%) | 152 / 640 (23.75%) | |
| occurrences (all) | 206 | 224 | |
| Pyrexia | | | |
| subjects affected / exposed | 36 / 570 (6.32%) | 28 / 640 (4.38%) | |
| occurrences (all) | 40 | 31 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 31 / 570 (5.44%) | 27 / 640 (4.22%) | |
| occurrences (all) | 35 | 32 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 51 / 570 (8.95%) | 22 / 640 (3.44%) | |
| occurrences (all) | 65 | 27 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 40 / 570 (7.02%) | 46 / 640 (7.19%) | |
| occurrences (all) | 44 | 53 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 53 / 570 (9.30%) | 56 / 640 (8.75%) | |
| occurrences (all) | 57 | 69 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 31 March 2017 | Amendement 2: The primary reason for the amendment was change in sponsor of the study from MSD Vaccins, a French société par actions simplifiée to Merck Sharp & Dohme Corp. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

None reported