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