Clinical trial results:
A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, in 16- to 26-Year-Old Men and 16- to 26-Year-Old Women

Summary

EudraCT number	2012-002758-22
Trial protocol	DE ES FI SE DK
Global end of trial date	04 August 2014

Results information

Result version number	v2 (current)
This version publication date	31 March 2016
First version publication date	24 January 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V503-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, New Jersey, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2014
Global end of trial reached?	Yes
Global end of trial date	04 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

(1) To evaluate the tolerability of the 9vHPV (9-valent HPV L1 VLP, V503) vaccine in young men and women 16 to 26 years of age. (2) To demonstrate that administration of the 9vHPV vaccine induces non-inferior Geometric Mean Titers (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in young heterosexual men 16 to 26 years of age compared to young women 16 to 26 years of age.

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	29 October 2012
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	Thailand: 90
Country: Number of subjects enrolled	Turkey: 50
Country: Number of subjects enrolled	United States: 627
Country: Number of subjects enrolled	Norway: 83
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Spain: 255
Country: Number of subjects enrolled	Sweden: 75
Country: Number of subjects enrolled	Denmark: 250
Country: Number of subjects enrolled	Germany: 155
Country: Number of subjects enrolled	South Africa: 50
Country: Number of subjects enrolled	Canada: 110
Country: Number of subjects enrolled	Colombia: 281
Country: Number of subjects enrolled	Israel: 50
Country: Number of subjects enrolled	Malaysia: 51
Country: Number of subjects enrolled	Mexico: 93
Country: Number of subjects enrolled	Peru: 170
Country: Number of subjects enrolled	Philippines: 60

Worldwide total number of subjects	2520
EEA total number of subjects	888

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)	309
Adults (18-64 years)	2211
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study enrolled healthy males and females 16 to 26 years of age who have never had Papanicolaou (Pap; cervical or anal) testing or have had only normal Pap testing results. Other inclusion and exclusion criteria applied.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Heterosexual Males

Arm description:

Healthy heterosexual males 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Arm type	Experimental
Investigational medicinal product name	9vHPV Vaccine
Investigational medicinal product code	
Other name	V503, Multivalent Human Papillomavirus (HPV)L1 Virus-like Particle (VLP) Vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Arm title	Females

Arm description:

Healthy females 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Arm type	Experimental
Investigational medicinal product name	9vHPV Vaccine
Investigational medicinal product code	
Other name	V503, Multivalent Human Papillomavirus (HPV)L1 Virus-like Particle (VLP) Vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Arm title	Men Who Have Sex With Men (MSM)

Arm description:

Healthy MSM 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Arm type	Experimental

Investigational medicinal product name	9vHPV Vaccine
Investigational medicinal product code	
Other name	V503, Multivalent Human Papillomavirus (HPV)L1 Virus-like Particle (VLP) Vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6

Number of subjects in period 1	Heterosexual Males	Females	Men Who Have Sex With Men (MSM)
Started	1106	1101	313
Vaccination 1	1103	1099	313
Vaccination 2	1089	1069	298
Vaccination 3	1067	1037	291
Completed	1053	1015	282
Not completed	53	86	31
Consent withdrawn by subject	17	18	9
Physician decision	-	2	-
Adverse event, non-fatal	-	2	1
Screen failure	2	2	-
Unknown status	4	4	-
Lost to follow-up	30	56	20
Protocol deviation	-	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Heterosexual Males
Reporting group description:	
Healthy heterosexual males 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	
Reporting group title	Females
Reporting group description:	
Healthy females 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	
Reporting group title	Men Who Have Sex With Men (MSM)
Reporting group description:	
Healthy MSM 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	

Reporting group values	Heterosexual Males	Females	Men Who Have Sex With Men (MSM)
Number of subjects	1106	1101	313
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	20.8	21.3	22.2
standard deviation	± 3	± 2.9	± 2.4
Gender categorical Units: Subjects			
Female	0	1101	0
Male	1106	0	313

Reporting group values	Total		
Number of subjects	2520		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1101		
Male	1419		

End points

End points reporting groups

Reporting group title	Heterosexual Males
Reporting group description:	
Healthy heterosexual males 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	
Reporting group title	Females
Reporting group description:	
Healthy females 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	
Reporting group title	Men Who Have Sex With Men (MSM)
Reporting group description:	
Healthy MSM 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6	
Subject analysis set title	Heterosexual and MSM Males - Safety Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Healthy heterosexual males and MSMs 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received >=1 vaccination and had safety follow-up.	
Subject analysis set title	Females - Safety Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Healthy females 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received >=1 vaccination and had safety follow-up.	
Subject analysis set title	Heterosexual Males - Immunogenicity Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Healthy heterosexual males 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received the 3 vaccinations, were seronegative to the appropriate HPV type at baseline, and had Month 7 immunogenicity results for the appropriate HPV type.	
Subject analysis set title	Females - Immunogenicity Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Healthy females 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received the 3 vaccinations, were seronegative to the appropriate HPV type at baseline, and had Month 7 immunogenicity results for the appropriate HPV type.	
Subject analysis set title	Men Who Have Sex With Men - Immunogenicity Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Healthy MSM 16 to 26 years of age received 9vHPV vaccine 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received the 3 vaccinations, were seronegative to the appropriate HPV type at baseline, and had Month 7 immunogenicity results for the appropriate HPV type.	

Primary: Geometric Mean Titers (GMTs) to the HPV Types Contained in the 9vHPV Vaccine

End point title	Geometric Mean Titers (GMTs) to the HPV Types Contained in the 9vHPV Vaccine
End point description:	
Serum antibodies to HPV types 6/11/16/18/31/33/45/52/58 were measured with a Competitive Luminex Immunoassay. Titers are reported in milli Merck Units/mL. Statistical analysis compared GMT values	

between heterosexual males and females.

End point type	Primary

End point timeframe:

Four weeks post vaccination 3 (Month 7)

End point values	Heterosexual Males - Immunogenicity Population	Females - Immunogenicity Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	914	884		
Units: milli Merck Units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV Type 6 (n=847, 708)	782 (738 to 828.7)	703.9 (660.6 to 749.9)		
Anti-HPV Type 11 (n=851, 712)	616.7 (582.4 to 653)	564.9 (530.6 to 601.3)		
Anti-HPV Type 16 (n=899, 781)	3346 (3158.9 to 3544.1)	2788.3 (2621.4 to 2965.8)		
Anti-HPV Type 18 (n=906, 831)	808.2 (754.9 to 865.4)	679.8 (633.1 to 730.1)		
Anti-HPV Type 31 (n=908, 826)	708.5 (662.7 to 757.6)	570.1 (531.5 to 611.5)		
Anti-HPV Type 33 (n=901, 853)	384.8 (362.5 to 408.4)	322 (302.9 to 342.3)		
Anti-HPV Type 45 (n=909, 871)	235.6 (219 to 253.6)	185.7 (172.3 to 200.2)		
Anti-HPV Type 52 (n=907, 849)	386.8 (363.4 to 411.6)	335.2 (314.3 to 357.6)		
Anti-HPV Type 58 (n=897, 839)	509.8 (479.9 to 541.6)	409.3 (384.5 to 435.7)		

Statistical analyses

Statistical analysis title	Non-inferiority Anti-HPV Type 6

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 6 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.21

Notes:

[1] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-Inferiority Anti-HPV Type 11

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 11 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.19

Notes:

[2] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 16

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 16 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Notes:

[3] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 18

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 18 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.31

Notes:

[4] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 31

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 31 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	1.37

Notes:

[5] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 33

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 33 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Notes:

[6] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 45

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 45 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.41

Notes:

[7] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 52

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 52 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population

Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.26

Notes:

[8] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Statistical analysis title	Non-inferiority Anti-HPV Type 58

Statistical analysis description:

Primary analysis evaluated non-inferiority of the GMT for anti-HPV Type 58 for heterosexual males compared with females.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT Ratio
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.36

Notes:

[9] - Criterion for non-inferiority with respect to GMT ratio (heterosexual males / females) required that the lower bound of the 95% confidence interval was >0.67, to exclude a decrease of 1.5-fold or more. An analysis of variance model with a response of log individual titers and fixed effect for group was used.

Primary: Percentage of Participants with one or more Injection-site Adverse Experiences Prompted on the Vaccine Report Card

End point title	Percentage of Participants with one or more Injection-site Adverse Experiences Prompted on the Vaccine Report Card

End point description:

An adverse experience (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. Injection-site AEs prompted on the Vaccine Report Card were erythema, pain, and swelling. Participants were instructed to use the Vaccine Report Card to record adverse events daily after each study vaccination.

End point type	Primary

End point timeframe:

Up to 5 days after any vaccination

End point values	Heterosexual and MSM Males - Safety Analysis	Females - Safety Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1394	1075		
Units: Percentage of participants				
number (not applicable)				
Overall VRC-prompted Injection-site AEs	66.7	84		
Injection-site Erythema	20.7	32.2		
Injection-site Pain	63.4	82.5		
Injection-site Swelling	20.2	37.5		

Statistical analyses

Statistical analysis title	Injection-site Erythema
Statistical analysis description:	
The incidence of AEs of injection-site erythema reported on the Vaccine Report Card was compared between heterosexual / MSM male participants and female participants.	
Comparison groups	Heterosexual and MSM Males - Safety Analysis v Females - Safety Analysis
Number of subjects included in analysis	2469
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	-8

Statistical analysis title	Injection-site Pain
Statistical analysis description:	
The incidence of AEs of injection-site pain reported on the Vaccine Report Card was compared between heterosexual / MSM male participants and female participants.	
Comparison groups	Heterosexual and MSM Males - Safety Analysis v Females - Safety Analysis

Number of subjects included in analysis	2469
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	-15.7

Statistical analysis title	Injection-site Swelling

Statistical analysis description:

The incidence of AEs of injection-site swelling reported on the Vaccine Report Card was compared between heterosexual / MSM male participants and female participants.

Comparison groups	Heterosexual and MSM Males - Safety Analysis v Females - Safety Analysis
Number of subjects included in analysis	2469
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	-13.7

Primary: Percentage of Participants with Elevated Oral Body Temperature (>=37.8° C, >=100° F)

End point title	Percentage of Participants with Elevated Oral Body Temperature (>=37.8° C, >=100° F)

End point description:

Participants were instructed by the investigator to use the Vaccination Report Card to document evening oral temperature daily after each study vaccination

End point type	Primary

End point timeframe:

Up to 5 days after any vaccination

End point values	Heterosexual and MSM Males - Safety Analysis	Females - Safety Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1386[10]	1066[11]		
Units: Percentage of participants				
number (not applicable)	4.4	5.9		

Notes:

[10] - Participants who received >=1 vaccination and had oral or oral equivalent temperature results

[11] - Participants who received >=1 vaccination and had oral or oral equivalent temperature results

Statistical analyses

Statistical analysis title	Elevated Body Temperature

Statistical analysis description:

The incidence of maximum body temperature >37.8° C reported on the Vaccine Report Card was compared between heterosexual / MSM male participants and female participants.

Comparison groups	Heterosexual and MSM Males - Safety Analysis v Females - Safety Analysis
Number of subjects included in analysis	2452
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.091
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.2

Primary: Percentage of Participants with an Adverse Event

End point title	Percentage of Participants with an Adverse Event[12]

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. Injection-site AEs include both those prompted on the Vaccine Report Card and those not prompted. Systemic AEs include all that are not classified as injection-site AEs.

End point type	Primary

End point timeframe:

Up to Day 15 after any vaccination

Notes:

[12] - 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 Percentage of Participants with an Adverse Event

End point values	Heterosexual and MSM Males - Safety Analysis	Females - Safety Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1394	1075		
Units: Percentage of participants				
number (not applicable)	75.4	88.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants who had Study Vaccine Discontinued Due to an Adverse Event

End point title	Percentage of Participants who had Study Vaccine Discontinued Due to an Adverse Event[13]

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE.

End point type	Primary

End point timeframe:

Up to Month 6

Notes:

[13] - 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 Percentage of Participants who had Study Vaccine Discontinued Due to an Adverse Event

End point values	Heterosexual and MSM Males - Safety Analysis	Females - Safety Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1394	1075		
Units: Percentage of participants				
number (not applicable)	0.1	0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Seroconversion to the HPV Types Contained in the 9vHPV Vaccine

End point title	Percentage of Participants with Seroconversion to the HPV Types Contained in the 9vHPV Vaccine

End point description:

Serum antibodies to HPV types were measured with a Competitive Luminex Immunoassay. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: ≥30; HPV Type 11: ≥16; HPV Type 16: ≥20; HPV Type 18: ≥24; HPV Type 31: ≥10; HPV Types 33, 45, 52, and 58: ≥8.

Statistical analysis compared seroconversion rates between heterosexual males and females.

End point type	Secondary

End point timeframe:

Four weeks post vaccination 3 (Month 7)

End point values	Heterosexual Males - Immunogenicity Population	Females - Immunogenicity Population	Men Who Have Sex With Men - Immunogenicity Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	914	884	239	
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV Type 6 (n=847, 708, 164)	99.6 (99 to 99.9)	99.6 (98.8 to 99.9)	99.4 (96.6 to 100)	
Anti-HPV Type 11 (n=851, 712, 165)	100 (99.6 to 100)	99.9 (99.2 to 100)	100 (97.8 to 100)	
Anti-HPV Type 16 (n=899, 781, 212)	100 (99.6 to 100)	99.9 (99.3 to 100)	100 (98.3 to 100)	
Anti-HPV Type 18 (n=906, 831, 220)	99.9 (99.4 to 100)	99.8 (99.1 to 100)	99.5 (97.5 to 100)	
Anti-HPV Type 31 (n=908, 826, 227)	100 (99.6 to 100)	100 (99.6 to 100)	100 (98.4 to 100)	
Anti-HPV Type 33 (n=901, 853, 230)	100 (99.6 to 100)	99.9 (99.3 to 100)	100 (98.4 to 100)	
Anti-HPV Type 45 (n=909, 871, 232)	99.8 (99.2 to 100)	99.5 (98.8 to 99.9)	100 (98.4 to 100)	
Anti-HPV Type 52 (n=907, 849, 232)	100 (99.6 to 100)	99.8 (99.2 to 100)	100 (98.4 to 100)	
Anti-HPV Type 58 (n=897, 839, 223)	100 (99.6 to 100)	99.8 (99.1 to 100)	100 (98.4 to 100)	

Statistical analyses

Statistical analysis title	Non-inferiority Anti-HPV Type 6

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 6 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.9

Notes:

[14] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 11

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 11 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.8

Notes:

[15] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 16

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 16 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.7

Notes:

[16] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 18

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 18 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.8

Notes:

[17] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 31

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 31 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.5

Notes:

[18] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 33

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 33 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population

Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.7

Notes:

[19] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 45

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 45 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1

Notes:

[20] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 52

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 52 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9

Notes:

[21] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Statistical analysis title	Non-inferiority Anti-HPV Type 58

Statistical analysis description:

Analysis evaluated non-inferiority of the difference in percentage of participants who seroconverted for Anti-HPV Type 58 for heterosexual males compared with females. Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Comparison groups	Heterosexual Males - Immunogenicity Population v Females - Immunogenicity Population
Number of subjects included in analysis	1798
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9

Notes:

[22] - Criterion for non-inferiority with respect to seroconversion percentage (heterosexual males minus females) required that the lower bound of the 95% confidence interval was greater than -5.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Females - Safety Analysis

Reporting group description:

Healthy females 16 to 26 years of age received V503 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received >-1 vaccination and had safety follow-up.

Reporting group title	Heterosexual and MSM Males - Safety Analysis

Reporting group description:

Healthy heterosexual males and MSMs 16 to 26 years of age received V503 0.5 mL intramuscular injection on Day 1, Month 1, and Month 6. The analysis set includes participants who received >=1 vaccination and had safety follow-up.

Serious adverse events	Females - Safety Analysis	Heterosexual and MSM Males - Safety Analysis	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 1075 (2.42%)	23 / 1394 (1.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
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	4 / 1075 (0.37%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			

subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	4 / 1075 (0.37%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	2 / 1075 (0.19%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal malpresentation			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cyst rupture			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophreniform disorder			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 1075 (0.00%)	2 / 1394 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to communicable disease			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Familial periodic paralysis			

subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 1075 (0.09%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 1075 (0.19%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ligament disorder			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 1075 (0.09%)	2 / 1394 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			

subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 1075 (0.09%)	0 / 1394 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 1075 (0.00%)	1 / 1394 (0.07%)	
occurrences causally related to treatment / all	0 / 0	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	Females - Safety Analysis	Heterosexual and MSM Males - Safety Analysis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	924 / 1075 (85.95%)	976 / 1394 (70.01%)	
Nervous system disorders			
Headache			
subjects affected / exposed	246 / 1075 (22.88%)	200 / 1394 (14.35%)	
occurrences (all)	378	271	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	348 / 1075 (32.37%)	291 / 1394 (20.88%)	
occurrences (all)	539	422	
Injection site pain			
subjects affected / exposed	893 / 1075 (83.07%)	886 / 1394 (63.56%)	
occurrences (all)	2101	1877	
Injection site swelling			
subjects affected / exposed	408 / 1075 (37.95%)	285 / 1394 (20.44%)	
occurrences (all)	661	431	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2013	The primary purpose of the Protocol V503-003-03 amendment was to revise the inclusion criterion regarding the definition of sexual partners to make it consistent with that used in prior HPV vaccine studies, and to revise the maximum number of lifetime male or female sexual partners allowable for MSM subjects in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported