EU Clinical Trials Register

Clinical trial results:

A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™, Dose-Ranging Study of Octavalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18, 31, 45, 52, and 58) L1 Virus-Like Particle (VLP) Vaccine Administered to 16-23-Year-Old Women

Summary

EudraCT number	2017-000109-19
Trial protocol	Outside EU/EEA
Global end of trial date	22 August 2007

Results information

Result version number	v1 (current)
This version publication date	10 March 2017
First version publication date	10 March 2017

Trial information

Trial identification

Sponsor protocol code	V502-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00260039
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 August 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2007
Global end of trial reached?	Yes
Global end of trial date	22 August 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This dose-ranging study evaluated an investigational vaccine with the following objectives: (1) To demonstrate that the vaccine is well-tolerated in women (2) To evaluate immune responses in women who are between 16 and 23 years of age at enrollment. The primary hypothesis for the study are as follows: 1) the geometric mean titers (GMTs) at 4 weeks Postdose 3 for each of the Human Papillomavirus (HPV) Types 6, 11, 16, 18 for participants receiving V502 vaccination are non-inferior to those induced by qHPV vaccine (Gardasil), and 2) V502 administered to 16 to 23-year old women is generally well-tolerated.

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	06 December 2005
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	United States: 225
Country: Number of subjects enrolled	Peru: 150
Country: Number of subjects enrolled	Colombia: 305
Worldwide total number of subjects	680
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	16
Adults (18-64 years)	664
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy female participants between 16 and 23 years of age were enrolled into the study.

Pre-assignment

Screening details:

A total of 738 participants were screened and 680 were randomized into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	qHPV Vaccine

Arm description:

Participants received qHPV vaccine (Gardasil) 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.

Arm type	Active comparator
Investigational medicinal product name	qHPV Vaccine
Investigational medicinal product code	
Other name	Gardasil™ quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-like Particle (VLP) vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Arm title	Low-dose Octavalent HPV Vaccine

Arm description:

Participants received Low-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.

Arm type	Experimental
Investigational medicinal product name	Low-dose Octavalent HPV Vaccine
Investigational medicinal product code	
Other name	Low-dose Octavalent HPV (Types 6, 11, 16, 18, 31, 45, 52, 58) L1 Virus-like Particle (VLP) vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Arm title	Mid-dose Octavalent HPV Vaccine

Arm description:

Participants received Mid-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.

Arm type	Experimental

Investigational medicinal product name	Mid-dose Octavalent HPV Vaccine
Investigational medicinal product code	
Other name	Mid-dose Octavalent HPV (Types 6, 11, 16, 18, 31, 45, 52, 58) L1 Virus-like Particle (VLP) vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Arm title	High-dose Octavalent HPV Vaccine

Arm description:

Participants received High-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.

Arm type	Experimental
Investigational medicinal product name	High-dose Octavalent HPV Vaccine
Investigational medicinal product code	
Other name	High-dose Octavalent HPV (Types 6, 11, 16, 18, 31, 45, 52, 58) L1 Virus-like Particle (VLP) vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Number of subjects in period 1	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine
Started	168	172	168
Completed	157	162	162
Not completed	11	10	6
Consent withdrawn by subject	4	2	1
Adverse event, non-fatal	-	1	-
Other reasons	-	-	1
Lost to follow-up	5	6	3
Moved	2	1	1

Number of subjects in period 1	High-dose Octavalent HPV Vaccine
Started	172
Completed	165
Not completed	7
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Other reasons	-
Lost to follow-up	6
Moved	1

Baseline characteristics

Reporting groups

Reporting group title	qHPV Vaccine
Reporting group description:	
Participants received qHPV vaccine (Gardasil) 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Low-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Low-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Mid-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Mid-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	High-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received High-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	

Reporting group values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine
Number of subjects	168	172	168
Age Categorical			
Units: Subjects			
Adolescents (12-17 years)	5	2	3
Adults (18-64 years)	163	170	165
Age Continuous			
Units: years			
arithmetic mean	20.4	20.7	20.3
standard deviation	± 1.6	± 1.7	± 1.6
Gender Categorical			
Units: Subjects			
Female	168	172	168
Male	0	0	0

Reporting group values	High-dose Octavalent HPV Vaccine	Total	
Number of subjects	172	680	
Age Categorical			
Units: Subjects			
Adolescents (12-17 years)	6	16	
Adults (18-64 years)	166	664	
Age Continuous			
Units: years			
arithmetic mean	20.4		
standard deviation	± 1.7	-	
Gender Categorical			
Units: Subjects			
Female	172	680	
Male	0	0	

End points

End points reporting groups

Reporting group title	qHPV Vaccine
Reporting group description:	
Participants received qHPV vaccine (Gardasil) 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Low-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Low-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Mid-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Mid-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	High-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received High-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	

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

End point title	Geometric Mean Titer (GMT) of Anti-HPV 6 Antibody
End point description:	
Anti-HPV Type 6 antibodies were measured by a Competitive Luminex Immunoassay (cLIA). The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and polymerase chain reaction (PCR) negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 6 antibody.	
End point type	Primary
End point timeframe:	
Month 7 (1 month postdose 3)	

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	104	107	106
Units: mMU/mL				
geometric mean (confidence interval 95%)	1612.5 (1400 to 1857.3)	1349.4 (1139.9 to 1597.5)	1464.3 (1247.9 to 1718.3)	1472.8 (1239.9 to 1749.5)

Statistical analyses

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [1]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1

Notes:

[1] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [2]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.12

Notes:

[2] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [3]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.15

Notes:

[3] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Primary: GMT of Anti-HPV 11 Antibody

End point title	GMT of Anti-HPV 11 Antibody

End point description:

Anti-HPV Type 11 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <10 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 11 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	104	107	106
Units: mMU/mL				
geometric mean (confidence interval 95%)	2354.6 (2074.1 to 2673.1)	2085 (1808.1 to 2404.2)	2242.6 (1956.8 to 2570.2)	2078.8 (1759.9 to 2455.6)

Statistical analyses

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [4]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.05

Notes:

[4] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [5]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.18

Notes:

[5] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [6]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.08

Notes:

[6] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Primary: GMT of Anti-HPV 16 Antibody

End point title	GMT of Anti-HPV 16 Antibody

End point description:

Anti-HPV Type 16 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 16 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	104	111	104
Units: mMU/mL				
geometric mean (confidence interval 95%)	3310.3 (2905.8 to 3771.2)	2700.5 (2328.1 to 3132.5)	3057.9 (2624.3 to 3563)	2987.9 (2544.2 to 3509.1)

Statistical analyses

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [7]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.99

Notes:

[7] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [8]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.12

Notes:

[8] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [9]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.09

Notes:

[9] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Primary: GMT of Anti-HPV 18 Antibody

End point title	GMT of Anti-HPV 18 Antibody

End point description:

Anti-HPV Type 18 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 18 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	120	118	126	122
Units: mMU/mL				
geometric mean (confidence interval 95%)	846.8 (708.9 to 1011.4)	704.4 (584.6 to 848.6)	709.9 (596.1 to 845.4)	795.4 (654.3 to 967)

Statistical analyses

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [10]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.05

Notes:

[10] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [11]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.08

Notes:

[11] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Statistical analysis title	Non-inferiority Analysis

Statistical analysis description:

The criterion for non-inferiority is that the lower bound of the 95% confidence interval for the fold-difference in
GMT (experimental / control) is >0.5.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [12]
Method	ANOVA
Parameter estimate	Fold difference in GMT
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.16

Notes:

[12] - The estimated GMT, fold difference, confidence intervals, and p-value is based on a statistical analysis model adjusting for country.

Primary: GMT of Anti-HPV 31 Antibody

End point title	GMT of Anti-HPV 31 Antibody[13]

End point description:

Anti-HPV Type 31 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 31 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

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: There was no protocol pre-planned statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	120	119	116
Units: mMU/mL				
geometric mean (confidence interval 95%)	28.4 (22.1 to 36.4)	829.5 (700 to 982.9)	1429.9 (1189.8 to 1718.4)	2318.7 (1972.1 to 2726.3)

Statistical analyses

No statistical analyses for this end point

Primary: GMT of Anti-HPV 45 Antibody

End point title	GMT of Anti-HPV 45 Antibody[14]

End point description:

Anti-HPV Type 45 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 16 milli Merck U/mL. A value of 9999 indicates that the GMT was <16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 45 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[14] - 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: There was no protocol pre-planned statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	128	128	118
Units: mMU/mL				
geometric mean (confidence interval 95%)	9999 (9999 to 9999)	321.1 (262.3 to 393)	618.1 (487.8 to 783.2)	1030.5 (837.6 to 1267.9)

Statistical analyses

No statistical analyses for this end point

Primary: GMT of Anti-HPV 52 Antibody

End point title	GMT of Anti-HPV 52 Antibody[15]

End point description:

Anti-HPV Type 52 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and

tested for anti-HPV 52 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[15] - 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: There was no protocol pre-planned statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	115	119	112	113
Units: mMU/mL				
geometric mean (confidence interval 95%)	9999 (9999 to 9999)	776.9 (654.6 to 922)	1622.1 (1348.8 to 1950.7)	2801.1 (2289.1 to 3427.5)

Statistical analyses

No statistical analyses for this end point

Primary: GMT of Anti-HPV 58 Antibody

End point title	GMT of Anti-HPV 58 Antibody[16]

End point description:

Anti-HPV Type 58 antibodies were measured by a cLIA. The unit of measure was milli Merck Units/mL (mMU/mL). The seropositive cut-off threshold for this assay is defined as 16 milli Merck U/mL. A value of 9999 indicates that the GMT was <16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 58 antibody .

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[16] - 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: There was no protocol pre-planned statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	117	123	115
Units: mMU/mL				
geometric mean (confidence interval 95%)	9999 (9999 to 9999)	354.8 (301.3 to 417.8)	640.8 (533 to 770.3)	957.8 (817.8 to 1121.8)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 6

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 6 cLIA level of >=20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 6 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[17] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	104	107	106
Units: Percentage of participants				
number (confidence interval 95%)	100 (96.7 to 100)	100 (96.5 to 100)	100 (96.6 to 100)	100 (96.6 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 11

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 11 cLIA level of >=20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 11 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[18] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	104	107	106
Units: Percentage of participants				
number (confidence interval 95%)	100 (96.7 to 100)	100 (96.5 to 100)	100 (96.6 to 100)	100 (96.6 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 16

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 16 cLIA level of >=20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 16 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[19] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	104	111	104
Units: Percentage of participants				
number (confidence interval 95%)	100 (96.6 to 100)	100 (96.5 to 100)	100 (96.7 to 100)	100 (96.5 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 18

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 18 cLIA level of >=20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 18 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[20] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	120	118	126	122
Units: Percentage of participants				
number (confidence interval 95%)	100 (97 to 100)	100 (96.9 to 100)	100 (97.1 to 100)	100 (97 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 31

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 31 cLIA level of >=16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 31 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[21] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	120	119	116
Units: Percentage of participants				
number (confidence interval 95%)	64.7 (55.2 to 73.3)	100 (97 to 100)	99.2 (95.4 to 100)	100 (96.9 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 45

End point title	Percentage of Participants Who Seroconverted to HPV Type 45

[22]

End point description:

Seroconversion was defined as achieving an anti-HPV Type 45 cLIA level of >=16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 45 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[22] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	128	128	118
Units: Percentage of participants				
number (confidence interval 95%)	17.9 (11.6 to 25.8)	99.2 (95.7 to 100)	97.7 (93.3 to 99.5)	100 (96.9 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 52

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 52 cLIA level of >=20 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 52 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[23] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	115	119	112	113
Units: Percentage of participants				
number (confidence interval 95%)	6.1 (2.5 to 12.1)	100 (96.9 to 100)	99.1 (95.1 to 100)	99.1 (95.2 to 100)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Seroconverted to HPV Type 58

End point title	Percentage of Participants Who Seroconverted to HPV Type

End point description:

Seroconversion was defined as achieving an anti-HPV Type 58 cLIA level of >=16 milli Merck U/mL. Participants analyzed included those who were not protocol violators, received all 3 vaccinations, were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the relevant HPV Type, and had a Month 7 serum sample collected and tested for anti-HPV 58 antibody.

End point type	Primary

End point timeframe:

Month 7 (1 month postdose 3)

Notes:

[24] - 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: There was no protocol pre-planned between-group statistical analysis for this endpoint.

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	117	123	115
Units: Percentage of participants				
number (confidence interval 95%)	22 (14.9 to 30.6)	100 (96.9 to 100)	99.2 (95.6 to 100)	100 (96.8 to 100)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Participants used the Vaccination Report Card to record oral temperature. The participants analyzed included those who received at least one vaccination and had follow-up.

End point type	Primary

End point timeframe:

Up to Day 5 after any vaccination

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	169	167	172
Units: Percentage of participants				
number (not applicable)	8.9	11.8	7.8	9.3

Statistical analyses

Statistical analysis title	Risk Difference Analysis

Statistical analysis description:

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal approximation for p-values.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.383
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	3.7

Statistical analysis title	Risk Difference Analysis

Statistical analysis description:

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal
approximation for p-values.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.706
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	7.4

Statistical analysis title	Risk Difference Analysis

Statistical analysis description:

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal
approximation for p-values.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.905
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	6

Primary: Percentage of Participants with One or More Injection-site Adverse Experiences

End point title	Percentage of Participants with One or More Injection-site Adverse Experiences

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 sponsor's product, 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 sponsor's product is also an AE. Participants used the Vaccination Report Card to record injection-site AEs. The participants analyzed included those who received at least one vaccination and had follow-up.

End point type	Primary

End point timeframe:

Up to Day 5 after any vaccination

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	169	167	172
Units: Percentage of participants				
number (not applicable)	84.5	89.3	87.4	86

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal
approximation for p-values.

Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.189
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	2.4

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal
approximation for p-values.

Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.445
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	4.7

Statistical analysis title	Risk Difference Analysis

Statistical analysis description:

The analysis used the Miettinen and Nurminen method for 95% confidence intervals and a test-based normal
approximation for p-values.

Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.692
Method	Test-based normal approximation
Parameter estimate	Risk difference (RD)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	6.1

Primary: Percentage of Participants with One or More Systemic Adverse Experiences

End point title	Percentage of Participants with One or More Systemic Adverse Experiences

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 sponsor's product, 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 sponsor's product is also an AE. Percentage of participants with a systemic AE was recorded. The participants analyzed included those who received at least one vaccination and had follow-up.

End point type	Primary

End point timeframe:

Up to Day 15 after any vaccination

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	169	167	172
Units: Percentage of participants				
number (not applicable)	67.3	76.3	70.1	72.1

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method.	
Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.6
upper limit	0.6

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method	
Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	7.2

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method	
Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.6
upper limit	5

Primary: Percentage of Participants with One or More Serious Vaccine-related Adverse Experiences

End point title	Percentage of Participants with One or More Serious Vaccine-related Adverse Experiences

End point description:

A serious AE is an AE that results in death, is life threatening, results in persistent or significant disability or incapacity, results in or prolongs a hospitalization, is a congenital anomaly or birth defect, is a cancer, or is an overdose. A vaccine-related AE was deemed by the investigator to be possibly, probably, or definitely related to a study procedure. The participants analyzed included those who received at least one vaccination and had follow-up.

End point type	Primary

End point timeframe:

Up to Month 7

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	169	167	172
Units: Percentage of participants				
number (not applicable)	0	0	0	0

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	2.2

Statistical analysis title	Risk Difference Analysis
Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	2.2

Statistical analysis title	Risk Difference Analysis
Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	2.2

Primary: Percentage of Participants with One or More Severe Injection-site Adverse Experiences

End point title	Percentage of Participants with One or More Severe Injection-site Adverse Experiences

End point description:

A severe AE is an AE that is deemed by the investigator to be incapacitating with inability to work or do usual activity. For injection-site erythema and injection-site swelling, severe is defined as a maximum size of >2 inches, or 5 centimeters. The participants analyzed included those who received at least one vaccination and had follow-up.

End point type	Primary

End point timeframe:

Up to Day 5 after any vaccination

End point values	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine	High-dose Octavalent HPV Vaccine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	169	167	172
Units: Percentage of participants				
number (not applicable)	6	5.3	4.8	4.7

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method	
Comparison groups	qHPV Vaccine v Low-dose Octavalent HPV Vaccine
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	6

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method	
Comparison groups	qHPV Vaccine v Mid-dose Octavalent HPV Vaccine
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	6.4

Statistical analysis title	Risk Difference Analysis
Statistical analysis description:	
The analysis used the Miettinen and Nurminen method	
Comparison groups	qHPV Vaccine v High-dose Octavalent HPV Vaccine

Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	6.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Up to Month 7	
Adverse event reporting additional description:	
Adverse events are reported for all participants who received at least one vaccination.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	qHPV Vaccine
Reporting group description:	
Participants received qHPV vaccine (Gardasil) 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Low-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Low-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	Mid-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received Mid-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	
Reporting group title	High-dose Octavalent HPV Vaccine
Reporting group description:	
Participants received High-dose Octavalent HPV Vaccine 0.5 mL intramuscular injection at the Day 1, Month 2, and Month 6 visits.	

Serious adverse events	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 168 (0.60%)	3 / 169 (1.78%)	1 / 167 (0.60%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 169 (0.59%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 168 (0.00%)	1 / 169 (0.59%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Influenza			
subjects affected / exposed	0 / 168 (0.00%)	1 / 169 (0.59%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 168 (0.00%)	1 / 169 (0.59%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 169 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	High-dose Octavalent HPV Vaccine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 172 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	0 / 172 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 172 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic inflammatory disease			

subjects affected / exposed	0 / 172 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 172 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	qHPV Vaccine	Low-dose Octavalent HPV Vaccine	Mid-dose Octavalent HPV Vaccine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 168 (88.10%)	165 / 169 (97.63%)	159 / 167 (95.21%)
Investigations			
Body temperature decreased			
subjects affected / exposed	9 / 168 (5.36%)	14 / 169 (8.28%)	10 / 167 (5.99%)
occurrences (all)	10	19	10
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 168 (8.93%)	11 / 169 (6.51%)	10 / 167 (5.99%)
occurrences (all)	20	14	13
Headache			
subjects affected / exposed	61 / 168 (36.31%)	63 / 169 (37.28%)	55 / 167 (32.93%)
occurrences (all)	117	113	103
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	26 / 168 (15.48%)	33 / 169 (19.53%)	35 / 167 (20.96%)
occurrences (all)	37	48	50
Injection site pain			
subjects affected / exposed	137 / 168 (81.55%)	151 / 169 (89.35%)	147 / 167 (88.02%)
occurrences (all)	319	336	354
Injection site swelling			
subjects affected / exposed	32 / 168 (19.05%)	35 / 169 (20.71%)	44 / 167 (26.35%)
occurrences (all)	42	54	73
Pyrexia			

subjects affected / exposed	18 / 168 (10.71%)	22 / 169 (13.02%)	16 / 167 (9.58%)
occurrences (all)	25	29	17
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 168 (3.57%)	10 / 169 (5.92%)	9 / 167 (5.39%)
occurrences (all)	6	16	10
Nausea			
subjects affected / exposed	17 / 168 (10.12%)	9 / 169 (5.33%)	17 / 167 (10.18%)
occurrences (all)	18	10	18
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 168 (1.19%)	7 / 169 (4.14%)	1 / 167 (0.60%)
occurrences (all)	2	10	1
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	8 / 168 (4.76%)	12 / 169 (7.10%)	6 / 167 (3.59%)
occurrences (all)	9	12	6
Infections and infestations			
Influenza			
subjects affected / exposed	12 / 168 (7.14%)	24 / 169 (14.20%)	17 / 167 (10.18%)
occurrences (all)	16	26	19
Nasopharyngitis			
subjects affected / exposed	9 / 168 (5.36%)	6 / 169 (3.55%)	8 / 167 (4.79%)
occurrences (all)	9	6	9

Non-serious adverse events	High-dose Octavalent HPV Vaccine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	161 / 172 (93.60%)		
Investigations			
Body temperature decreased			
subjects affected / exposed	2 / 172 (1.16%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 172 (7.56%)		
occurrences (all)	17		

Headache			
subjects affected / exposed	64 / 172 (37.21%)		
occurrences (all)	101		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	37 / 172 (21.51%)		
occurrences (all)	54		
Injection site pain			
subjects affected / exposed	148 / 172 (86.05%)		
occurrences (all)	375		
Injection site swelling			
subjects affected / exposed	45 / 172 (26.16%)		
occurrences (all)	72		
Pyrexia			
subjects affected / exposed	19 / 172 (11.05%)		
occurrences (all)	20		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 172 (3.49%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	4 / 172 (2.33%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	11 / 172 (6.40%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	5 / 172 (2.91%)		
occurrences (all)	5		
Infections and infestations			
Influenza			
subjects affected / exposed	19 / 172 (11.05%)		
occurrences (all)	21		
Nasopharyngitis			

| subjects affected / exposed | 10 / 172 (5.81%) | | |
| occurrences (all) | 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2006	Protocol Amendment 1 changes included the following: added the U.S. IND number, revised language regarding participants who become pregnant after Day 1, clarified the definition of out-of-context study visits, clarified triage for abnormal Pap and biopsy tests obtained at Month 7, corrected the seropositivity cutoffs for HPV types, and replaced with the most recent version of the Subject Pregnancy Reporting and Follow-up Standard Operating Procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported