Clinical trial results:
A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)

Summary

EudraCT number	2009-011617-25
Trial protocol	FI BE AT SE ES PL Outside EU/EEA
Global end of trial date	22 April 2021

Results information

Result version number	v1
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	V503-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00943722
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000654-PIP01-09
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 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to demonstrate that the 9-valent HPV L1 VLP vaccine induces noninferior 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 preadolescent and adolescent boys and girls 9 to 15 years of age compared to young women 16 to 26 years of age. A protocol-specified lot consistency (Lots 1, 2, 3 separate) outcome analysis in 9 to 15 year-old girls was done in the base study only.

Extension studies (EXT 1 and 2) were conducted up to Month 36 and ~11 years respectively. No study vaccine was given and 16-26 year olds were excluded from extensions; per protocol, extensions provided data for 9- to15-year-old girls (Lots 1, 2, 3 pooled) and 9- to 15-year-old boys.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 200
Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Peru: 160
Country: Number of subjects enrolled	United States: 649
Country: Number of subjects enrolled	South Africa: 165
Country: Number of subjects enrolled	Belgium: 122
Country: Number of subjects enrolled	Costa Rica: 75
Country: Number of subjects enrolled	Colombia: 303
Country: Number of subjects enrolled	Austria: 46
Country: Number of subjects enrolled	Spain: 209
Country: Number of subjects enrolled	Taiwan: 159
Country: Number of subjects enrolled	Poland: 120
Country: Number of subjects enrolled	Chile: 40
Country: Number of subjects enrolled	Korea, Republic of: 149

Country: Number of subjects enrolled	Finland: 284
Country: Number of subjects enrolled	Sweden: 118
Country: Number of subjects enrolled	India: 225
Worldwide total number of subjects	3074
EEA total number of subjects	899

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)	1283
Adolescents (12-17 years)	1360
Adults (18-64 years)	431
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The base study V503-002 was a 12-month study that is collecting safety and immunogenicity information for six months following the participants' third dose of study vaccine.

Pre-assignment

Screening details:

Extension study 1 (EXT1) collected data to Month 36. Extension study 2 (EXT2) collected long-term data through ~11 years. No study vaccine was administered.

Period 1

Period 1 title	Base Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Base Study: 9- to 15-Year-Old Females (Lot 1)

Arm description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Arm type	Experimental
Investigational medicinal product name	V503
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Multivalent human papillomavirus [HPV] L1 virus-like particle [VLP] vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Arm title	Base Study: 9- to 15-Year-Old Females (Lot 2)

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.

Arm type	Experimental
Investigational medicinal product name	V503
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Arm title	Base Study: 9- to 15-Year-Old Females (Lot 3)

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.

Arm type	Experimental

Investigational medicinal product name	V503
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Arm title	Base Study: 9- to 15-Year-Old Males (Lot 1)

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Arm type	Experimental
Investigational medicinal product name	V503
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Arm title	Base Study: 16- to 26-Year-Old Females (Lot 1)

Arm description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Arm type	Experimental
Investigational medicinal product name	V503
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Number of subjects in period 1	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lot 2)	Base Study: 9- to 15-Year-Old Females (Lot 3)
Started	648	643	644
Vaccination 1	646	642	644
Vaccination 2	637	633	638
Vaccination 3	635	627	637
Completed	623	621	631
Not completed	25	22	13
Physician decision	1	-	-
Consent withdrawn by subject	12	13	2
Adverse event, non-fatal	-	-	-
Pregnancy	-	-	1

Lost to follow-up	12	8	10
unknown status	-	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)
Started	669	470
Vaccination 1	666	468
Vaccination 2	658	462
Vaccination 3	653	455
Completed	647	444
Not completed	22	26
Physician decision	-	1
Consent withdrawn by subject	13	8
Adverse event, non-fatal	1	-
Pregnancy	-	-
Lost to follow-up	8	11
unknown status	-	4
Protocol deviation	-	2

Period 2

Period 2 title	Extension Study 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension Study: 9- to 15-Year-Old Females

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Extension Study: 9- to 15-Year-Old Males

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Extension Study: 9- to 15-Year-Old Females	Extension Study: 9- to 15-Year-Old Males
Started	1604	568
Completed	1489	527
Not completed	115	41
Consent withdrawn by subject	32	10
Adverse event, non-fatal	1	-
Unknown	44	21
Lost to follow-up	38	10

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Per protocol, the subject disposition for this extension study included 2 treatment arms: 9 to15 year-old males and 9 to 15 year-old females.

Period 3

Period 3 title	Extension Study 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension Study: 9- to 15-Year-Old Females

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Extension Study: 9- to 15-Year-Old Males

Arm description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3[2]	Extension Study: 9- to 15-Year-Old Females	Extension Study: 9- to 15-Year-Old Males
Started	971	301
Completed	720	202
Not completed	251	99
Physician decision	1	3
Consent withdrawn by subject	137	50
Adverse event, non-fatal	1	-
Pregnancy	1	-
Lost to follow-up	111	46

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Per protocol, the subject disposition for this extension study included 2 treatment arms: 9 to15 year-old males and 9 to 15 year-old females.

Baseline characteristics

Reporting groups	
Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 1)
Reporting group description:	
Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.	
Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 2)
Reporting group description:	
Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.	
Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 3)
Reporting group description:	
Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.	
Reporting group title	Base Study: 9- to 15-Year-Old Males (Lot 1)
Reporting group description:	
Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.	
Reporting group title	Base Study: 16- to 26-Year-Old Females (Lot 1)
Reporting group description:	
Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.	

Reporting group values	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lot 2)	Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects	648	643	644
Age Categorical			
Base Study			
Units: Years			
9 to 12 years	440	432	432
13 to 15 years	208	211	212
16 to 26 years	0	0	0
Sex: Female, Male Units:			
Female	648	643	644
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	150	141	139
Black or African American	50	59	52
Multi-Racial	81	91	86
Native Hawaiian or Other Pacific Islander	0	0	0
White	366	351	367
Ethnicity Units: Subjects			
Hispanic or Latino	176	191	193
Not Hispanic or Latino	472	452	451

Reporting group values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)	Total
Number of subjects	669	470	3074
Age Categorical			
Base Study			
Units: Years			
9 to 12 years	450	0	1754
13 to 15 years	219	0	850
16 to 26 years	0	470	470
Sex: Female, Male Units:			
Female	0	470	2405
Male	669	0	669
Race Units: Subjects			
American Indian or Alaska Native	2	0	4
Asian	186	128	744
Black or African American	37	48	246
Multi-Racial	149	53	460
Native Hawaiian or Other Pacific Islander	3	1	4
White	292	240	1616
Ethnicity Units: Subjects			
Hispanic or Latino	195	128	883
Not Hispanic or Latino	474	342	2191

End points reporting groups

Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 1)

Reporting group description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 2)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.

Reporting group title	Base Study: 9- to 15-Year-Old Females (Lot 3)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.

Reporting group title	Base Study: 9- to 15-Year-Old Males (Lot 1)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Base Study: 16- to 26-Year-Old Females (Lot 1)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Extension Study: 9- to 15-Year-Old Females

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Reporting group title	Extension Study: 9- to 15-Year-Old Males

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Reporting group title	Extension Study: 9- to 15-Year-Old Females

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Reporting group title	Extension Study: 9- to 15-Year-Old Males

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Subject analysis set title	Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing

Lots 1, 2, or 3

Subject analysis set title	Base Study: 9- to 15-Year-Old Females (Lots 1, 2, or 3)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received the multivalent HPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lots 1, 2, or 3.

Primary: Base Study: Geometric Mean Titers (GMTs) for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])

End point title	Base Study: Geometric Mean Titers (GMTs) for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])[1]

End point description:

Serum antibody titers for HPV virus-like particles (VLPs), Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using a competitive luminex immunoassay (cLIA). Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old females and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Primary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the seroconversion of females 9 to 15 years of age (Lot 1) compared to females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	378		
Units: milli Merck Units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 (n=517; 328)	1715.4 (1595.1 to 1844.7)	900.8 (822.3 to 986.9)		
Anti-HPV 11 (n=517; 332)	1295.1 (1204.1 to 1393.0)	706.6 (645.2 to 773.8)		
Anti-HPV 16 (n=529; 329)	6979.8 (6508.1 to 7485.8)	3522.6 (3223.5 to 3849.5)		
Anti-HPV 18 (n=531; 345)	2153.7 (1980.4 to 2342.1)	882.7 (795.4 to 979.5)		
Anti-HPV 31 (n=522; 340)	1891.6 (1745.7 to 2049.7)	753.9 (682.5 to 832.7)		
Anti-HPV 33 (n=534; 354)	980.4 (911.7 to 1054.3)	466.8 (426.9 to 510.3)		
Anti-HPV 45 (n=534; 368)	714.4 (651.9 to 782.8)	272.2 (243.8 to 303.9)		
Anti-HPV 52 (n=533; 337)	932.9 (864.8 to 1006.4)	419.6 (381.4 to 461.5)		

Anti-HPV 58 (n=531; 332)	1286.7 (1195.7 to 1384.6)	590.5 (538.2 to 647.9)		

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Females
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001 [3]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	2.14

Notes:

[2] - non-inferiority requires that the lower bound of two-sided 95% confidence interval (CI) of GMT ratio be greater than 0.67.

[3] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	< 0.001 [5]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.63
upper limit	2.06

Notes:

[4] - Non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[5] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	< 0.001 [7]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.77
upper limit	2.22

Notes:

[6] - Non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[7] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	< 0.001 [9]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.13
upper limit	2.8

Notes:

[8] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[9] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)

Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	< 0.001 [11]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.21
upper limit	2.85

Notes:

[10] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[11] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	< 0.001 [13]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	2.36

Notes:

[12] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[13] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females

Statistical analysis description:

Anti-HPV 45

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	< 0.001 [15]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.27
upper limit	3.03

Notes:

[14] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[15] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females

Statistical analysis description:

Anti-HPV 52

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	< 0.001 [17]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.97
upper limit	2.51

Notes:

[16] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[17] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Females

Statistical analysis description:

Anti-HPV 58

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	< 0.001 [19]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.93
upper limit	2.45

Notes:

[18] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[19] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Primary: Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])

End point title	Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])[20]

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using a cLIA. Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old males and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Primary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the GMTs of males 9 to 15 years of age (Lot 1) compared to females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	570	378		
Units: milli Merck Units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 (n=559; 328)	2084.7 (1944.0 to 2235.7)	900.8 (822.3 to 986.9)		
Anti-HPV 11 (n=559; 332)	1487.1 (1386.5 to 1595.0)	706.6 (645.2 to 773.8)		
Anti-HPV 16 (n=569; 329)	8628.9 (8065.9 to 9231.3)	3522.6 (3223.5 to 3849.5)		
Anti-HPV 18 (n=567; 345)	2822.8 (2602.8 to 3061.5)	882.7 (795.4 to 979.5)		
Anti-HPV 31 (n=564; 340)	2221.2 (2056.1 to 2399.5)	753.9 (682.5 to 832.7)		
Anti-HPV 33 (n=567; 354)	1198.7 (1117.1 to 1286.2)	466.8 (426.9 to 510.3)		
Anti-HPV 45 (n=570; 368)	907.0 (830.2 to 991.0)	272.2 (243.8 to 303.9)		
Anti-HPV 52 (n=568; 337)	1037.8 (964.4 to 1116.9)	419.6 (381.4 to 461.5)		
Anti-HPV 58 (n=566; 332)	1567.7 (1460.2 to 1683.1)	590.5 (538.2 to 647.9)		

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Males
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	< 0.001 [22]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.07
upper limit	2.59

Notes:

[21] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[22] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	< 0.001 [24]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.88
upper limit	2.36

Notes:

[23] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[24] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
P-value	< 0.001 [26]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.19
upper limit	2.74

Notes:

[25] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[26] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
P-value	< 0.001 [28]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	3.65

Notes:

[27] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[28] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)

Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
P-value	< 0.001 [30]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	3.34

Notes:

[29] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[30] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[31]
P-value	< 0.001 [32]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.29
upper limit	2.88

Notes:

[31] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[32] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males

Statistical analysis description:

Anti-HPV 45

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
P-value	< 0.001 [34]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	3.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	3.84

Notes:

[33] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[34] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males

Statistical analysis description:

Anti-HPV 52

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[35]
P-value	< 0.001 [36]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.19
upper limit	2.79

Notes:

[35] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67
[36] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Statistical analysis title	GMTs for HPV VLPs-Males

Statistical analysis description:

Anti-HPV 58

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[37]
P-value	< 0.001 [38]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.37
upper limit	2.98

Notes:

[37] - non-inferiority requires that the lower bound of two-sided 95% CI of GMT ratio be greater than 0.67

[38] - one-sided tests of non-inferiority conducted at the alpha=0.025 level; model with a response of log individual titers and a fixed effect for comparison group

Primary: Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)

End point title	Base Study: GMTs for Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)[39]

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. Titers are reported in milli Merck Units/mL. The analysis population included 9-15-year-old females who received 3 vaccinations from Lots 1, 2, or 3 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Primary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the GMTs of females 9 to 15 years of age in Lots 1, 2 or 3.

End point values	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lot 2)	Base Study: 9- to 15-Year-Old Females (Lot 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	549	565	
Units: milli Merck Units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 (n=517; 536; 544)	1715.4 (1588.7 to 1852.2)	1763.3 (1635.4 to 1901.3)	1659.9 (1540.3 to 1788.7)	
Anti-HPV 11 (n=517; 536; 544)	1295.1 (1197.8 to 1400.3)	1311.7 (1214.9 to 1416.3)	1232.0 (1141.7 to 1329.5)	
Anti-HPV 16 (n=529; 542; 556)	6979.8 (6476.1 to 7522.8)	7292.9 (6772.7 to 7853.1)	6948.2 (6458.7 to 7474.9)	
Anti-HPV 18 (n=531; 547; 563)	2153.7 (1970.9 to 2353.5)	2134.1 (1955.6 to 2329.0)	1966.6 (1804.3 to 2143.5)	
Anti-HPV 31 (n=522; 542; 553)	1891.6 (1738.5 to 2058.2)	1867.8 (1719.3 to 2029.1)	1879.0 (1731.0 to 2039.6)	
Anti-HPV 33 (n=534; 543; 560)	980.4 (909.2 to 1057.2)	922.7 (856.2 to 994.4)	931.1 (865.0 to 1002.3)	
Anti-HPV 45 (n=534; 548; 565)	714.4 (650.1 to 785.0)	827.7 (754.1 to 908.5)	678.4 (619.0 to 743.6)	
Anti-HPV 52 (n=533; 547; 562)	932.9 (860.8 to 1011.0)	1007.9 (931.0 to 1091.2)	971.2 (898.1 to 1050.3)	
Anti-HPV 58 (n=531; 539; 560)	1286.7 (1190.0 to 1391.3)	1344.9 (1244.6 to 1453.3)	1208.1 (1119.6 to 1303.6)	

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 6

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[40]
Parameter estimate	GMT ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.08

Notes:

[40] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 6

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[41]
Parameter estimate	GMT ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.16

Notes:

[41] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 6

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[42]
Parameter estimate	GMT ratio
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.19

Notes:

[42] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 11

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[43]
Parameter estimate	GMT ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.11

Notes:

[43] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 11

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[44]
Parameter estimate	GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.2

Notes:

[44] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 11

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)

Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[45]
Parameter estimate	GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.2

Notes:

[45] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 16

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[46]
Parameter estimate	GMT ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.06

Notes:

[46] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0).

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 16

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[47]
Parameter estimate	GMT ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.12

Notes:

[47] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[48]
Parameter estimate	GMT ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.17

Notes:

[48] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[49]
Parameter estimate	GMT ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.14

Notes:

[49] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[50]
Parameter estimate	GMT ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.26

Notes:

[50] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[51]
Parameter estimate	GMT ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.26

Notes:

[51] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[52]
Parameter estimate	GMT ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.13

Notes:

[52] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[53]
Parameter estimate	GMT ratio
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.16

Notes:

[53] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 31

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[54]
Parameter estimate	GMT ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.15

Notes:

[54] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[55]
Parameter estimate	GMT ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.16

Notes:

[55] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)

Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[56]
Parameter estimate	GMT ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.17

Notes:

[56] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[57]
Parameter estimate	GMT ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.12

Notes:

[57] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 45

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[58]
Parameter estimate	GMT ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.95

Notes:

[58] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[59]
Parameter estimate	GMT ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.18

Notes:

[59] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[60]
Parameter estimate	GMT ratio
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.42

Notes:

[60] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[61]
Parameter estimate	GMT ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.03

Notes:

[61] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[62]
Parameter estimate	GMT ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.07

Notes:

[62] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[63]
Parameter estimate	GMT ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.16

Notes:

[63] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency
Statistical analysis description:	
Anti-HPV 58	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[64]
Parameter estimate	GMT ratio
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.06

Notes:

[64] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 58

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[65]
Parameter estimate	GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.2

Notes:

[65] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Statistical analysis title	GMTs for HPV VLPs-Lot Consistency

Statistical analysis description:

Anti-HPV 58

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[66]
Parameter estimate	GMT ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.26

Notes:

[66] - equivalence requires that the two-sided 95% CI for the ratio of the GMTs be entirely contained within the interval (0.5, 2.0)

Primary: Base Study: Percentage of Participants with Injection Site Adverse Experiences (AEs)

End point title	Base Study: Percentage of Participants with Injection Site Adverse Experiences (AEs)[67][68]

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 vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. AEs such as redness, swelling, and pain/tenderness/soreness at the injection site were recorded. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data for body temperature. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

End point type	Primary

End point timeframe:

up to 5 days after any vaccination

Notes:

[67] - 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 analyses were planned or conducted for this endpoint.

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the injection site AEs of males 9 to 15 years of age (Lot 1), females 9 to 15 years of age (Lots 1, 2 or 3), and females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	662	466	1923	
Units: Percentage of Participants				
number (not applicable)	72.8	85.4	81.9	

Statistical analyses

No statistical analyses for this end point

Primary: Base Study: Percentage of Participants with Systemic AEs

End point title	Base Study: Percentage of Participants with Systemic AEs[69][70]

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 vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. Systemic AEs were those not categorized as injection-site AEs. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

End point type	Primary

End point timeframe:

up to 15 days after any vaccination

Notes:

[69] - 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 analyses were planned or conducted for this endpoint.

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the systemic AEs of males 9 to 15 years of age (Lot 1), females 9 to 15 years of age (Lots 1, 2 or 3), and females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lots 1, 2 or 3)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	662	466	1923	
Units: Percentage of Participants				
number (not applicable)	41.8	57.1	45.0	

Statistical analyses

No statistical analyses for this end point

Primary: Base Study: Percentage of Participants with Body Temperature ≥100.0°F (≥37.8ºC)

End point title	Base Study: Percentage of Participants with Body Temperature ≥100.0°F (≥37.8ºC)[71][72]

End point description:

Participants collected their oral body temperature in the evening of their vaccination day and at the same time each day thereafter for 4 days. The maximum body temperature obtained within 5 days of any of the 3 vaccinations was recorded. The percentage of participants who had at least 1 oral body temperature reading that was ≥100.0°F (≥37.8ºC) was summarized. The analysis population included all participants who received at least one dose of 9vHPV vaccine and had available follow-up data for body temperature. Per protocol, data from 9- to 15-year-old females were pooled regardless of lot administered.

End point type	Primary

End point timeframe:

up to 5 days after any vaccination

Notes:

[71] - 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 analyses were planned or conducted for this endpoint.

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the body temperature of males 9 to 15 years of age (Lot 1), females 9 to 15 years of age (Lots 1, 2 or 3), and females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lots 1, 2, or 3)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	660	463	1908	
Units: Percentage of Participants				
number (not applicable)	10.0	8.4	8.4	

Statistical analyses

No statistical analyses for this end point

Primary: Extension Study: GMTs For Each of the HPV Types Contained in the Vaccine

End point title	Extension Study: GMTs For Each of the HPV Types Contained in the Vaccine[73]

End point description:

Serum antibody titers (milli Merck Units/mL) measured by cLIA to each of the 9vHPV types were assessed. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. To be included in the analysis population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the analysis population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type being analyzed.

End point type	Primary

End point timeframe:

126 months after post-vaccination 3 (Up to ~11 years)

Notes:

[73] - 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 analyses were planned or conducted for this endpoint.

End point values	Extension Study: 9- to 15-Year-Old Females	Extension Study: 9- to 15-Year-Old Males		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	971	301		
Units: milli Merck Units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 (n=341,176)	122.3 (111.1 to 134.7)	129.5 (112.5 to 149.1)		
Anti-HPV 11 (n=332,169)	80.2 (72.5 to 88.8)	91.0 (78.4 to 105.6)		
Anti-HPV 16 (n=338,173)	403.0 (357.3 to 454.5)	414.3 (353.8 to 485.3)		
Anti-HPV 18 (n=347,178)	128.1 (116.7 to 140.7)	148.4 (130.2 to 169.2)		
Anti-HPV 31 (n=343,177)	108.9 (97.6 to 121.6)	128.6 (111.2 to 148.8)		
Anti-HPV 33 (n=344,178)	59.2 (53.7 to 65.2)	69.6 (60.7 to 79.7)		
Anti-HPV 45 (n=325,169)	42.1 (37.7 to 47.1)	49.8 (43.0 to 57.8)		
Anti-HPV 52 (n=348,176)	55.3 (50.5 to 60.6)	59.6 (52.0 to 68.4)		
Anti-HPV 58 (n=342,175)	76.5 (69.2 to 84.6)	90.5 (78.4 to 104.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Extension Study: Percentage of Participants who are Seropositive to Each of the HPV Types Contained in the Vaccine

End point title	Extension Study: Percentage of Participants who are Seropositive to Each of the HPV Types Contained in the Vaccine

	[74]

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined and reported in milli Merck Units/mL. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. To be included in the analysis population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the analysis population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type being analyzed.

End point type	Primary

End point timeframe:

126 months after post-vaccination 3 (Up to ~11 years)

Notes:

[74] - 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 analyses were planned or conducted for this endpoint.

End point values	Extension Study: 9- to 15-Year-Old Females	Extension Study: 9- to 15-Year-Old Males		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	971	301		
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV 6 (n=341,176)	82.7 (78.3 to 86.6)	84.1 (77.8 to 89.2)		
Anti-HPV 11 (n=332,169)	85.2 (81.0 to 88.9)	87.0 (81.0 to 91.7)		
Anti-HPV 16 (n=338,173)	97.3 (95.0 to 98.8)	98.3 (95.0 to 99.6)		
Anti-HPV 18 (n=347,178)	80.1 (75.5 to 84.2)	83.7 (77.4 to 88.8)		
Anti-HPV 31 (n=343,177)	90.1 (86.4 to 93.0)	92.7 (87.8 to 96.0)		
Anti-HPV 33 (n=344,178)	85.2 (81.0 to 88.8)	89.3 (83.8 to 93.4)		
Anti-HPV 45 (n=325,169)	81.8 (77.2 to 85.9)	92.3 (87.2 to 95.8)		
Anti-HPV 52 (n=348,176)	88.2 (84.4 to 91.4)	89.2 (83.7 to 93.4)		
Anti-HPV 58 (n=342,175)	96.5 (94.0 to 98.2)	97.1 (93.5 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])

End point title	Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Females [Lot 1] versus 16- to 26-Year-Old Females [Lot

	1])[75]

End point description:

Serum antibody titers for HPV virus-like particles (VLPs), Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. 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 Type 33: ≥8, HPV Type 45: ≥8, HPV Type 52: ≥8, and HPV Type 58: ≥8. The analysis population included 9-15-year-old females and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Secondary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the seroconversion of females 9 to 15 years of age (Lot 1) compared to females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	378		
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV 6 cLIA ≥30 mMU/mL (n=517; 328)	99.8 (98.9 to 100)	99.7 (98.3 to 100)		
Anti-HPV 11 cLIA ≥16 mMU/mL (n=517; 332)	100 (99.3 to 100.0)	100 (98.9 to 100.0)		
Anti-HPV 16 cLIA ≥20 mMU/mL (n=529; 329)	100 (99.3 to 100.0)	100 (98.9 to 100.0)		
Anti-HPV 18 cLIA ≥24 mMU/mL (n=531; 345)	99.8 (99.0 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 31 cLIA ≥10 mMU/mL (n=522; 340)	100.0 (99.3 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 33 cLIA ≥8 mMU/mL (n=534; 354)	100.0 (99.3 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 45 cLIA ≥8 mMU/mL (n=534; 368)	99.8 (99.0 to 100.0)	99.5 (98.1 to 99.9)		
Anti-HPV 52 cLIA ≥8 mMU/mL (n=533; 337)	100.0 (99.3 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 58 cLIA ≥8 mMU/mL (n=531; 332)	100.0 (99.3 to 100.0)	100.0 (98.9 to 100.0)		

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion

Statistical analysis description:

Anti-HPV 6

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)

Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[76]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.5

Notes:

[76] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[77]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[77] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[78]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[78] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion

Statistical analysis description:

Anti-HPV 18

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[79]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.5

Notes:

[79] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion

Statistical analysis description:

Anti-HPV 31

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[80]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[80] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion

Statistical analysis description:	
Anti-HPV 33	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[81]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.6

Notes:

[81] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion
Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[82]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.8

Notes:

[82] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5.Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[83]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[83] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Female Seroconversion

Statistical analysis description:

Anti-HPV 58

Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	non-inferiority[84]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[84] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])

End point title	Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (9- to 15-Year-Old Males [Lot 1] versus 16- to 26-Year-Old Females [Lot 1])[85]

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post-vaccination 3 using cLIA. 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 Type 33: ≥8, HPV Type 45: ≥8, HPV Type 52: ≥8, and HPV Type 58: ≥8. The analysis population included 9-15-year-old males and 16-26-year-old females who received 3 vaccinations from Lot 1 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Secondary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint included the seroconversion of males 9 to 15 years of age (Lot 1) compared to females 16 to 26 years of age (Lot 1).

End point values	Base Study: 9- to 15-Year-Old Males (Lot 1)	Base Study: 16- to 26-Year-Old Females (Lot 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	570	378		
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV 6 cLIA ≥30 mMU/mL (n=559; 328)	99.8 (99.0 to 100.0)	99.7 (98.3 to 100.0)		
Anti-HPV 11 cLIA ≥16 mMU/mL (n=559; 332)	100.0 (99.3 to 100.0)	100.0 (98.9 to 100.0)		
Anti-HPV 16 cLIA ≥20 mMU/mL (n=569; 329)	100.0 (99.4 to 100.0)	100.0 (98.9 to 100.0)		
Anti-HPV 18 cLIA ≥24 mMU/mL (n=567; 345)	100.0 (99.4 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 31 cLIA ≥10 mMU/mL (n=564; 340)	100.0 (99.3 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 33 cLIA ≥8 mMU/mL (n=567; 354)	100.0 (99.4 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 45 cLIA ≥8 mMU/mL (n=570; 368)	100.0 (99.4 to 100.0)	99.5 (98.1 to 99.9)		
Anti-HPV 52 cLIA ≥8 mMU/mL (n=568; 337)	100.0 (99.4 to 100.0)	99.7 (98.4 to 100.0)		
Anti-HPV 58 cLIA ≥8 mMU/mL (n=566; 332)	100.0 (99.4 to 100.0)	100.0 (98.9 to 100.0)		

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[86]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.5

Notes:

[86] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16-

	to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[87]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[87] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[88]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[88] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[89]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.6

Notes:

[89] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion

Statistical analysis description:

Anti-HPV 31

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[90]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[90] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion

Statistical analysis description:

Anti-HPV 33

Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[91]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.6

Notes:

[91] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion

Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[92]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	2

Notes:

[92] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[93]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[93] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Male Seroconversion
Statistical analysis description:	
Anti-HPV 58	
Comparison groups	Base Study: 9- to 15-Year-Old Males (Lot 1) v Base Study: 16- to 26-Year-Old Females (Lot 1)
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority[94]
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2

Notes:

[94] - Noninferiority is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5. Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)

End point title	Base Study: Percentage of Participants who Seroconvert to Each of the HPV Types Contained in the Vaccine (Lot Consistency Study)[95]

End point description:

Serum antibody titers for HPV VLPs, Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 were determined 4 weeks post- vaccination 3 using cLIA. 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 Type 33: ≥8, HPV Type 45: ≥8, HPV Type 52: ≥8, and HPV Type 58: ≥8. The analysis population included 9-15-year-old females who received 3 vaccinations from Lot 1, 2 or 3 and met following criteria for at least 1 of the 9 HPV types: no general protocol violations, received all 3 vaccinations within acceptable day ranges, seronegative at Day 1 for HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

End point type	Secondary

End point timeframe:

4 weeks post-vaccination 3 (Month 7)

Notes:

[95] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint included the seroconversion of females 9 to 15 years of age in Lots 1, 2 or 3.

End point values	Base Study: 9- to 15-Year-Old Females (Lot 1)	Base Study: 9- to 15-Year-Old Females (Lot 2)	Base Study: 9- to 15-Year-Old Females (Lot 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	549	565	
Units: Percentage of Participants				
number (confidence interval 95%)				
HPV 6 cLIA ≥30 mMU/mL(n=517; 536; 544)	99.8 (98.9 to 100.0)	99.8 (99.0 to 100.0)	99.3 (98.1 to 99.8)	
HPV 11 cLIA ≥16 mMU/mL (n=517; 536; 544)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 16 cLIA ≥20 mMU/mL (n= 529; 542; 556)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 18 cLIA ≥24 mMU/mL (n= 531; 547; 563)	99.8 (99.0 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 31 cLIA ≥10 mMU/mL (n=522; 542; 553)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.8 (99.0 to 100.0)	
HPV 33 cLIA ≥8 mMU/mL (534; 543; 560)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 45 cLIA ≥8 mMU/mL (n= 534; 548; 565)	99.8 (99.0 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 52 cLIA ≥8 mMU/mL (n=533; 547; 562)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	
HPV 58 cLIA ≥8 mMU/mL (n=531; 539; 560)	100.0 (99.3 to 100.0)	100.0 (99.3 to 100.0)	99.6 (98.7 to 100.0)	

Statistical analyses

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[96]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.9

Notes:

[96] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[97]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[97] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 6	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study:

	9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[98]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7

Notes:

[98] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[99]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[99] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[100]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[100] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 11	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[101]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[101] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[102]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[102] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)

Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[103]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[103] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 16	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[104]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[104] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[105]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.5

Notes:

[105] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[106]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.1

Notes:

[106] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 18	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[107]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[107] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)

Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[108]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[108] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[109]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1

Notes:

[109] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 31	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[110]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1

Notes:

[110] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 33	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[111]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[111] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 33	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[112]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[112] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 33	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)

Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[113]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[113] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[114]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.5

Notes:

[114] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[115]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.1

Notes:

[115] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 45	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[116]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[116] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[117]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[117] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)

Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[118]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[118] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 52	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[119]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[119] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 58	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 2)
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	equivalence[120]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

Notes:

[120] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 58	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 1) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1100
Analysis specification	Pre-specified
Analysis type	equivalence[121]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[121] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Statistical analysis title	GMTs for HPV VLPs-Lot Seroconversion
Statistical analysis description:	
Anti-HPV 58	
Comparison groups	Base Study: 9- to 15-Year-Old Females (Lot 2) v Base Study: 9- to 15-Year-Old Females (Lot 3)
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	equivalence[122]
Method	Miettinen and Nurminen
Parameter estimate	Percentage Point Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.3

Notes:

[122] - equivalence requires that the two-sided 95% CI for the difference in percentages between lots be entirely contained within the interval (-5, 5). Percentage point difference was based on the Miettinen & Nurminen method.

Secondary: Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Females

End point title	Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Females

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥2 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at

≥2 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Per protocol, the extension study included 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Females			
Subject group type	Reporting group			
Number of subjects analysed	872			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	52.4 (33.6 to 78.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Males

End point title	Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 6 Months in Males

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥2 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at ≥2 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Males			
Subject group type	Reporting group			
Number of subjects analysed	261			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	54.6 (21.9 to 112.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 12 Months in Females

End point title	Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 12 Months in Females

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥3 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at ≥3 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Females			
Subject group type	Reporting group			
Number of subjects analysed	872			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	19.5 (8.9 to 37.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of HPV

6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 12 Months in Males

End point title	Extension Study: Combined Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection for a Duration of 12 Months in Males

End point description:

Persistent infection is when a participant is positive to at least 1 common gene for the same HPV type in the HPV PCR assay in ≥3 cervicovaginal/external genital swab, biopsy, or definitive therapy samples at ≥3 visits, 6 months apart. Person-years follow-up was from beginning of long-term follow-up or when study participant reached 16 years of age, whichever came later. Incidence was estimated as cases per 10,000 person-years. The analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Males			
Subject group type	Reporting group			
Number of subjects analysed	261			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	15.5 (1.9 to 55.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of Cervical Intraepithelial Neoplasia, Adenocarcinoma In Situ, Vulvar Intraepithelial Neoplasia, Vaginal Intraepithelial Neoplasia, and Cervical/Vulvar/Vaginal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Females

End point title	Extension Study: Combined Incidence of Cervical Intraepithelial Neoplasia, Adenocarcinoma In Situ, Vulvar Intraepithelial Neoplasia, Vaginal Intraepithelial Neoplasia, and Cervical/Vulvar/Vaginal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Females

End point description:

The combined incidence of all cervical/vulvar/vaginal cancers was assessed. Person-years follow-up was calculated starting from the beginning of the long-term follow-up study or the date when the study participant reached 16 years of age, whichever came later. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The primary effectiveness analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Females			
Subject group type	Reporting group			
Number of subjects analysed	866			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	2.2 (0.1 to 12.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Percentage of Participants with Vaccine-Related or Procedure-Related Serious Adverse Event who Received 9vHPV Vaccine at 9 to 15 Years of Age

End point title	Extension Study: Percentage of Participants with Vaccine-Related or Procedure-Related Serious Adverse Event who Received 9vHPV Vaccine at 9 to 15 Years of Age

End point description:

A serious adverse event (SAE) included a death which resulted in the participant discontinuing the study, a serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related or study procedure related. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. The analysis population included all participants who received at least 1 study vaccination in the base study and had follow-up data.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Females	Extension Study: 9- to 15-Year-Old Males		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	971	301		
Units: Percentage of Participants				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Combined Incidence of Condyloma, Penile Intraepithelial Neoplasia, and Penile/Perineal/Perianal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Males

End point title	Extension Study: Combined Incidence of Condyloma, Penile Intraepithelial Neoplasia, and Penile/Perineal/Perianal Cancer Related to HPV 6/11/16/18/31/33/45/52/58 in Males

End point description:

The combined incidence of penile/perineal/perianal cancer related to HPV in males was assessed. For each study participant, person-years follow-up was calculated starting from the beginning of the long-term follow-up study (i.e., Month 42 visit) or the date when the study participant reached 16 years of age, whichever came later. Per protocol, the extension study included data from 9- to 15-year-old females regardless of lot administered. Incidence was estimated as cases per 10,000 person-years. The primary effectiveness analysis population was the per-protocol effectiveness population, which included participants who were seronegative (by cLIA) to the relevant HPV type(s) at Day 1 (seronegative to both HPV 6 and 11 for analysis of HPV 6 and 11 HPV11-related endpoints), received all 3 doses of 9vHPV vaccine with the correct dose of the clinical material within 1 year, and had no other protocol violation that could interfere with evaluation of vaccine effectiveness.

End point type	Secondary

End point timeframe:

Up to ~11 years

End point values	Extension Study: 9- to 15-Year-Old Males			
Subject group type	Reporting group			
Number of subjects analysed	261			
Units: Cases per 10,000 person-years				
number (confidence interval 95%)	0.0 (0.0 to 28.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Base Study: Up to 5 days after any vaccination for nonserious injection site AEs, Up to 15 days after any vaccination for nonserious systemic AEs, and up to 7 months for SAEs. Extension Study, and all cause mortality: Up to ~11 years post vaccination 3.

Adverse event reporting additional description:

Base Study and Extension Study: All participants who received at least one dose of 9vHPV and had available follow-up data. All randomized participants were included in the all cause mortality.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Base Study: 9-to 15- Year Old Females (Lot 1)

Reporting group description:

Participants received the 9-valent human papillomavirus (9vHPV) L1 virus-like particle (VLP) vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Base Study: 9-to 15- Year Old Females (Lot 2)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 2.

Reporting group title	Base Study: 9-to 15- Year Old Females (Lot 3)

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 3.

Reporting group title	Base Study: 9-to 15- Year Old Males

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Base Study: 16-to 26- Year- Old Females Base

Reporting group description:

Participants received the 9vHPV L1 VLP vaccine, 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Vaccine dose administered is obtained from manufacturing Lot 1.

Reporting group title	Extension Study: Females

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Reporting group title	Extension Study: Males

Reporting group description:

In the base study, participants received the 9vHPV L1 VLP vaccine (0.5 mL intramuscular injection) at Day 1, Month 2, and Month 6 and were evaluated at Month 7 and followed up to Month 12. In the extension studies after Month 12, the participants were followed up for safety and immunogenicity up to Month 36 (EXT1) and for immunogenicity, effectiveness, and safety up to Month 126 (~11 years postdose 3 [EXT2]).

Serious adverse events	Base Study: 9-to 15- Year Old Females (Lot 1)	Base Study: 9-to 15- Year Old Females (Lot 2)	Base Study: 9-to 15- Year Old Females (Lot 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 643 (0.93%)	2 / 639 (0.31%)	8 / 641 (1.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue injury			

subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 643 (0.00%)	1 / 639 (0.16%)	0 / 641 (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 disorders			
Brain injury			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion threatened			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical incompetence			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Foetal distress syndrome			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature baby			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	1 / 643 (0.16%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 643 (0.16%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthmatic crisis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	1 / 643 (0.16%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 643 (0.16%)	1 / 639 (0.16%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 643 (0.16%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	1 / 641 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 643 (0.16%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 643 (0.00%)	0 / 639 (0.00%)	0 / 641 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Base Study: 9-to 15- Year Old Males	Base Study: 16-to 26- Year- Old Females Base	Extension Study: Females
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 662 (1.66%)	15 / 466 (3.22%)	5 / 1664 (0.30%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Foot fracture			

subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Gun shot wound			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Limb injury			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue injury			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 662 (0.00%)	5 / 466 (1.07%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal			

conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Abortion threatened			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	1 / 1664 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical incompetence			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Ectopic pregnancy			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Foetal distress syndrome			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Premature baby			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	2 / 1664 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthmatic crisis			

subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 662 (0.45%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	1 / 1664 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastroenteritis			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			

subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	1 / 662 (0.15%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	1 / 1664 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tonsillitis			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 662 (0.00%)	0 / 466 (0.00%)	0 / 1664 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 662 (0.00%)	1 / 466 (0.21%)	0 / 1664 (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

Serious adverse events	Extension Study: Males		

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 580 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gun shot wound			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue injury			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

Abortion induced				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain injury				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abortion threatened				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical incompetence				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ectopic pregnancy				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foetal distress syndrome				
subjects affected / exposed	0 / 580 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Premature baby			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary colic			

subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthmatic crisis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disseminated tuberculosis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious mononucleosis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngotonsillitis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			

subjects affected / exposed	0 / 580 (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 / 580 (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	Base Study: 9-to 15- Year Old Females (Lot 1)	Base Study: 9-to 15- Year Old Females (Lot 2)	Base Study: 9-to 15- Year Old Females (Lot 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	538 / 643 (83.67%)	537 / 639 (84.04%)	554 / 641 (86.43%)
Nervous system disorders			
Headache			
subjects affected / exposed	122 / 643 (18.97%)	123 / 639 (19.25%)	113 / 641 (17.63%)
occurrences (all)	184	171	156
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	184 / 643 (28.62%)	194 / 639 (30.36%)	195 / 641 (30.42%)
occurrences (all)	265	291	282
Injection site pain			
subjects affected / exposed	508 / 643 (79.00%)	513 / 639 (80.28%)	530 / 641 (82.68%)
occurrences (all)	1177	1192	1224
Injection site swelling			
subjects affected / exposed	208 / 643 (32.35%)	240 / 639 (37.56%)	227 / 641 (35.41%)
occurrences (all)	320	376	384
Pyrexia			
subjects affected / exposed	76 / 643 (11.82%)	58 / 639 (9.08%)	65 / 641 (10.14%)
occurrences (all)	91	68	75

Non-serious adverse events	Base Study: 9-to 15- Year Old Males	Base Study: 16-to 26- Year- Old Females Base	Extension Study: Females
Total subjects affected by non-serious adverse events			
subjects affected / exposed	505 / 662 (76.28%)	404 / 466 (86.70%)	0 / 1664 (0.00%)

Nervous system disorders			
Headache			
subjects affected / exposed	99 / 662 (14.95%)	106 / 466 (22.75%)	0 / 1664 (0.00%)
occurrences (all)	144	166	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	159 / 662 (24.02%)	132 / 466 (28.33%)	0 / 1664 (0.00%)
occurrences (all)	220	223	0
Injection site pain			
subjects affected / exposed	465 / 662 (70.24%)	393 / 466 (84.33%)	0 / 1664 (0.00%)
occurrences (all)	929	984	0
Injection site swelling			
subjects affected / exposed	175 / 662 (26.44%)	154 / 466 (33.05%)	0 / 1664 (0.00%)
occurrences (all)	252	273	0
Pyrexia			
subjects affected / exposed	84 / 662 (12.69%)	43 / 466 (9.23%)	0 / 1664 (0.00%)
occurrences (all)	94	53	0

Non-serious adverse events	Extension Study: Males		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 580 (0.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences (all)	0		
Injection site swelling			
subjects affected / exposed	0 / 580 (0.00%)		
occurrences (all)	0		
Pyrexia			

subjects affected / exposed occurrences (all)	0 / 580 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2010	V503-002-10-This amendment extended the duration of the immunogenicity follow-up from 7 months to 3 years duration for the 9-15 year old pre-adolescent and adolescent boys and girls.
08 November 2012	V503-002-20- This amendment increased the long-term immunogenicity, safety, and effectiveness follow-up of 9-15 year old girls and boys administered 9vHPV vaccine to 10 years post-dose three.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported