



Clinical trial results: An Investigational Vaccine in Reducing the Incidence of Anogenital Warts in Young Men

Summary

EudraCT number	2004-002945-10
Trial protocol	FI SE DE ES Outside EU/EEA
Global end of trial date	03 April 2017

Results information

Result version number	v1 (current)
This version publication date	08 April 2018
First version publication date	08 April 2018

Trial information

Trial identification

Sponsor protocol code	V501-020
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00090285
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to demonstrate that Gardasil™ (qHPV vaccine) 1) is well tolerated in young men, 2) reduces incidence of external genital lesions in young men, 3) reduces the incidence of anal intraepithelial neoplasia (AIN) or anal cancer in men having sex with men (MSM), and 4) reduces incidence of Human Papillomavirus (HPV) infection in young men.

In the 7-month Base Study participants received randomly assigned qHPV vaccine or placebo at Day 1, Month 2, and Month 6. Base Study follow-up continued through Month 36.

In Extension 1 (EXT1), participants who received placebo or an incomplete qHPV vaccine regimen in the Base Study were offered qHPV vaccine. Participants were followed in EXT1 for 7 months.

In Extension 2 [LTFU (EXT2)], long-term effectiveness, immunogenicity, and safety of qHPV vaccine were followed up to 10 years following study enrollment. Participants who received ≥1 dose of qHPV vaccine in the Base Study or EXT1 were eligible to enroll in LTFU (EXT2).

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	03 September 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 1048
Country: Number of subjects enrolled	Finland: 90
Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Portugal: 90
Country: Number of subjects enrolled	Brazil: 402
Country: Number of subjects enrolled	Peru: 450
Country: Number of subjects enrolled	Mexico: 573
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Taiwan: 221
Country: Number of subjects enrolled	Costa Rica: 150
Country: Number of subjects enrolled	Norway: 100

Country: Number of subjects enrolled	Philippines: 51
Country: Number of subjects enrolled	South Africa: 538
Country: Number of subjects enrolled	Sweden: 53
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Australia: 89
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Germany: 99
Worldwide total number of subjects	4065
EEA total number of subjects	496

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	187
Adults (18-64 years)	3878
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 4164 participants were screened and 4065 were randomized.

Pre-assignment

Screening details:

Participants were healthy males between the ages of 16 years and 26 years + 364 days.

Period 1

Period 1 title	Base Study Vaccination Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	qHPV Vaccine in Base Study

Arm description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.

Arm type	Experimental
Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Arm title	Placebo in Base Study
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Arm description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Number of subjects in period 1	qHPV Vaccine in Base Study	Placebo in Base Study
Started	2032	2033
Vaccinated	2025	2030
Completed	1818	1814
Not completed	214	219
Consent withdrawn by subject	64	69
Participant incarcerated	2	2
Randomized not treated	7	3
HIV positive	1	1
Site terminated	1	-
Adverse event	2	4
Uncooperative	2	2
Unspecified	2	2
Lost to follow-up	111	112
Moved	20	21
Protocol deviation	2	3

Period 2

Period 2 title	Base Study Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	qHPV Vaccine in Base Study

Arm description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.

Follow-up for the Base Study encompassed Month 7 through Month 36. No vaccinations were administered during the follow-up.

Arm type	Experimental
Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Arm title	Placebo in Base Study
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Arm description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.

Follow-up for the Base Study encompassed Month 7 through Month 36. No vaccinations were administered during the follow-up.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Number of subjects in period 2	qHPV Vaccine in Base Study	Placebo in Base Study
Started	1818	1814
Completed	1487	1479
Not completed	335	342
Consent withdrawn by subject	53	64
Participant incarcerated	-	2
Adverse event	3	10
Uncooperative	3	4
Unspecified	2	-
Lost to follow-up	232	226
Moved	41	36
Protocol deviation	1	-
Joined	4	7
Did not complete qHPV regimen in Base Study	4	7

Period 3

Period 3 title	Extension 1 (EXT1)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	EXT1: Placebo in Base Study
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Arm description:

Participants in the placebo arm in the Base Study were offered 3 doses of open-label qHPV vaccine at EXT1 Day 1, Month 2, and Month 6.

Participants were followed to EXT1 Month 7.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in EXT1.

Arm title	EXT1: Incomplete qHPV Regimen in Base Study
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Arm description:

Participants who received who received only 1 dose of qHPV vaccine in the Base Study were offered a complete 3-dose open-label qHPV vaccine regimen (administered at EXT1 Day 1, Month 2, and Month 6). Participants who received only 2 doses of qHPV vaccine in the Base Study were offered a single additional open-label dose of qHPV vaccine (administered at EXT1 Day 1).

Participants were followed to EXT1 Month 7.

Arm type	Experimental
Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle, a full 3-dose regimen or 2 doses at Day 1, Month 2, and Month 6 in EXT1.

Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle, 1 or 2 doses in the Base Study.

Number of subjects in period 3	EXT1: Placebo in Base Study	EXT1: Incomplete qHPV Regimen in Base Study
Started	1098	16
Completed	1041	15
Not completed	57	1
Consent withdrawn by subject	13	1
Adverse event	2	-
Unspecified	4	-
Lost to follow-up	35	-
Moved	3	-

Period 4

Period 4 title	Long-term Follow-up (EXT2)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	LTFU (EXT2): Early Vaccination Group

Arm description:

Participants received ≥ 1 dose of qHPV vaccine in Base Study and were followed up to a total of 10 years after their first dose of qHPV vaccine.

No vaccinations were administered during LTFU (EXT2).

Arm type	Experimental
Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Arm title	LTFU (EXT2): Catch-up Vaccination Group
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Arm description:

Participants received placebo in Base Study and qHPV vaccine in EXT1 and were followed up to a total of 7 years after their first dose of qHPV vaccine.

No vaccinations were administered during LTFU (EXT2).

Arm type	Experimental
Investigational medicinal product name	qHPV vaccine, quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle in EXT1.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL intramuscular injection in the deltoid muscle at Day 1, Month 2, and Month 6 in the Base Study

Number of subjects in period 4	LTFU (EXT2): Early Vaccination Group	LTFU (EXT2): Catch-up Vaccination Group
Started	936	867
Completed	709	664
Not completed	227	203
Consent withdrawn by subject	60	53
Physician decision	6	5
Adverse event	5	2
Lost to follow-up	156	143

Baseline characteristics

Reporting groups

Reporting group title	qHPV Vaccine in Base Study
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Reporting group description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.

Reporting group title	Placebo in Base Study
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Reporting group description:

The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.

Reporting group values	qHPV Vaccine in Base Study	Placebo in Base Study	Total
Number of subjects	2032	2033	4065
Age Categorical Units: Subjects			
Adolescents (12-17 years)	89	98	187
Adults (18-64 years)	1943	1935	3878
Age Continuous Units: years			
arithmetic mean	20.6	20.5	
standard deviation	± 2.0	± 2.0	-
Gender Categorical Units: Subjects			
Female	0	0	0
Male	2032	2033	4065
Race/Ethnicity Units: Subjects			
Asian	201	205	406
Black	405	400	805
Hispanic American	412	423	835
Native American	1	2	3
White	719	712	1431
Multi-racial	291	283	574
Indian (subcontinent)	1	8	9
Polynesian	2	0	2
Age Units: Years			
median	20	20	
full range (min-max)	16 to 26	15 to 27	-

End points

End points reporting groups

Reporting group title	qHPV Vaccine in Base Study
Reporting group description: The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.	
Reporting group title	Placebo in Base Study
Reporting group description: The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.	
Reporting group title	qHPV Vaccine in Base Study
Reporting group description: The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.	
Follow-up for the Base Study encompassed Month 7 through Month 36. No vaccinations were administered during the follow-up.	
Reporting group title	Placebo in Base Study
Reporting group description: The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.	
Follow-up for the Base Study encompassed Month 7 through Month 36. No vaccinations were administered during the follow-up.	
Reporting group title	EXT1: Placebo in Base Study
Reporting group description: Participants in the placebo arm in the Base Study were offered 3 doses of open-label qHPV vaccine at EXT1 Day 1, Month 2, and Month 6.	
Participants were followed to EXT1 Month 7.	
Reporting group title	EXT1: Incomplete qHPV Regimen in Base Study
Reporting group description: Participants who received only 1 dose of qHPV vaccine in the Base Study were offered a complete 3-dose open-label qHPV vaccine regimen (administered at EXT1 Day 1, Month 2, and Month 6). Participants who received only 2 doses of qHPV vaccine in the Base Study were offered a single additional open-label dose of qHPV vaccine (administered at EXT1 Day 1).	
Participants were followed to EXT1 Month 7.	
Reporting group title	LTFU (EXT2): Early Vaccination Group
Reporting group description: Participants received ≥ 1 dose of qHPV vaccine in Base Study and were followed up to a total of 10 years after their first dose of qHPV vaccine.	
No vaccinations were administered during LTFU (EXT2).	
Reporting group title	LTFU (EXT2): Catch-up Vaccination Group
Reporting group description: Participants received placebo in Base Study and qHPV vaccine in EXT1 and were followed up to a total of 7 years after their first dose of qHPV vaccine.	
No vaccinations were administered during LTFU (EXT2).	
Subject analysis set title	MSM qHPV Vaccine in Base Study
Subject analysis set type	Per protocol
Subject analysis set description: The Vaccination Period for the Base study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6. This per protocol population includes MSM participants who received ≥ 1 dose of qHPV in Base Study.	

Primary: Base Study: Incidence of Human Papillomavirus (HPV) Type 6/11/16/18-related External Genital Warts, Penile/Perianal/Perineal Intraepithelial Neoplasia (PIN), Penile, Perianal or Perineal Cancer

End point title	Base Study: Incidence of Human Papillomavirus (HPV) Type 6/11/16/18-related External Genital Warts, Penile/Perianal/Perineal Intraepithelial Neoplasia (PIN), Penile, Perianal or Perineal Cancer
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End point description:

Participants with HPV 6/11/16/18-related external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer per 100 person-years of follow-up was assessed. Per-protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by Competitive Luminex Immunoassay, cLIA) at Day 1 and polymerase chain reaction (PCR) negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7.

End point type	Primary
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End point timeframe:

Base study: through Month 36

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1394	1404		
Units: Incidence per 100 person-years				
number (not applicable)	0.1	1.0		

Statistical analyses

Statistical analysis title	Percent Relative Risk Reduction
Comparison groups	Placebo in Base Study v qHPV Vaccine in Base Study
Number of subjects included in analysis	2798
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Risk difference (RD)
Point estimate	90.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.1
upper limit	98.2

Notes:

[1] - Confidence Interval (CI) based on binomial tail probabilities and not from a dispersion parameter.

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

End point title	Base Study: Number of Participants with Severe Injection Site Adverse Experiences (AEs) ^[2]
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End point description:

An adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR'S product, whether or not

considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the SPONSOR'S product, is also an adverse experience. A severe AE is incapacitating with inability to work or do usual activities. The analysis population included all vaccinated participants excluding 6 participants who received non-compliant mixed regimens of qHPV vaccine and placebo.

End point type	Primary
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End point timeframe:

Base study: through Day 5 after any vaccination

Notes:

[2] - 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 between-group statistical analyses were planned or conducted for this endpoint.

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2020	2029		
Units: Participants	25	20		

Statistical analyses

No statistical analyses for this end point

Primary: Base Study: Number of Participants with Vaccine-Related Serious Adverse Events (SAEs)

End point title	Base Study: Number of Participants with Vaccine-Related Serious Adverse Events (SAEs) ^[3]
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End point description:

A serious adverse event is an AE that 1) results in death, 2) is life threatening, 3) results in persistent or significant disability or incapacity, 4) results in or prolongs an existing hospitalization, 5) is a congenital anomaly or birth defect, 6) is a cancer, 7) is an overdose, or 8) based on appropriate medical judgment may jeopardize the participant and may require medical or surgical intervention. A vaccine-related AE is one deemed to be possibly, probably or definitely related to study vaccine by the investigator. The analysis population included all vaccinated participants excluding 6 participants who received non-compliant mixed regimens of qHPV vaccine and placebo.

End point type	Primary
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End point timeframe:

Base study: through Month 36

Notes:

[3] - 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 between-group statistical analyses were planned or conducted for this endpoint.

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2020	2029		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Study: Incidence of HPV Type 6/11-related Genital Warts

End point title	Overall Study: Incidence of HPV Type 6/11-related Genital Warts ^{[4][5]}
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End point description:

Incidence of HPV Type 6/11-related genital warts is expressed as events per 10,000 person-years of follow-up. Per protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with the evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7. This endpoint applied only to participants in the Base Study qHPV vaccine group.

End point type	Primary
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End point timeframe:

Up to 10 years after the first dose of qHPV vaccine

Notes:

[4] - 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 between-group statistical analyses were planned or conducted for this endpoint.

[5] - 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 applied only to participants in the Base Study qHPV vaccine group.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	1243			
Units: Incidence per 10,000 person-years				
number (confidence interval 95%)	4.3 (0.9 to 12.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Study: Incidence of HPV Type 6/11/16/18-related External Genital Warts, PIN, Penile, Perianal or Perineal Cancer

End point title	Overall Study: Incidence of HPV Type 6/11/16/18-related External Genital Warts, PIN, Penile, Perianal or Perineal Cancer ^{[6][7]}
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End point description:

Incidence of HPV Type 6/11/16/18-related external genital warts, PIN, penile, perianal or perineal cancer is expressed as events per 10,000 person-years of follow-up. Per protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with the evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7. This endpoint applied only to participants in the Base Study qHPV vaccine group.

End point type	Primary
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End point timeframe:

Up to 10 years after the first dose of qHPV vaccine

Notes:

[6] - 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 between-group statistical analyses were planned or conducted for this endpoint.

[7] - 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 applied only to participants in the Base Study qHPV vaccine group.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	1395			
Units: Incidence per 10,000 person-years				
number (confidence interval 95%)	3.8 (0.8 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Study: Incidence of HPV Type 6/11/16/18-related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer

End point title	Overall Study: Incidence of HPV Type 6/11/16/18-related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer ^[8]
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End point description:

Incidence of HPV Type 6/11/16/18-related AIN and anal cancer is expressed as events per 10,000 person-years of follow-up. Per protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with the evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7. This endpoint applied only to MSM participants in the Base Study qHPV vaccine group.

End point type	Primary
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End point timeframe:

Up to 10 years after the first dose of qHPV vaccine

Notes:

[8] - 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: This endpoint applied only to MSM participants in the Base Study qHPV vaccine group.

End point values	MSM qHPV Vaccine in Base Study			
Subject group type	Subject analysis set			
Number of subjects analysed	194			
Units: Incidence per 10,000 person-years				
number (confidence interval 95%)	69.3 (25.4 to 150.8)			

Statistical analyses

No statistical analyses for this end point

Primary: LTFU (EXT2): Number of Participants with Vaccine-Related SAEs

End point title	LTFU (EXT2): Number of Participants with Vaccine-Related SAEs ^[9]
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End point description:

An SAE is an AE that 1) results in death, 2) is life threatening, 3) results in persistent or significant disability or incapacity, 4) results in or prolongs an existing hospitalization, 5) is a congenital anomaly or birth defect, 6) is a cancer, 7) is an overdose, or 8) based on appropriate medical judgment may jeopardize the participant and may require medical or surgical intervention. A vaccine-related AE is one deemed to be possibly, probably or definitely related to study vaccine by the investigator. The population analyzed was all randomized participants receiving at least 1 dose of qHPV vaccine in the Base Study or EXT1 and enrolled in LTFU (EXT2).

End point type	Primary
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End point timeframe:

qHPV Vaccine in Base Study: up to 12 years after last dose of qHPV vaccine; Placebo in Base Study: up to 7 years after last dose of qHPV vaccine

Notes:

[9] - 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: The population analyzed included only participants who enrolled in LTFU (EXT2).

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	936	867		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: LTFU (EXT2): Number of Participants who Died

End point title	LTFU (EXT2): Number of Participants who Died ^[10]
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End point description:

The number of participants who died was assessed. The population analyzed was all randomized participants receiving at least 1 dose of qHPV vaccine in the Base Study or EXT1 and enrolled in LTFU (EXT2).

End point type	Primary
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End point timeframe:

qHPV Vaccine in Base Study: up to 12 years after last dose of qHPV vaccine; Placebo in Base Study: up to 7 years after last dose of qHPV vaccine

Notes:

[10] - 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: The population analyzed included only participants who enrolled in LTFU (EXT2).

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	936	867		
Units: Participants	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Base Study: Incidence of HPV Type 6/11/16/18-related Persistent Infection

End point title	Base Study: Incidence of HPV Type 6/11/16/18-related Persistent Infection
End point description:	
Participants with HPV Type 6/11/16/18-related persistent infection per 100 person-years of follow-up was assessed. Per-protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7.	
End point type	Secondary
End point timeframe:	
Base study: through Month 36	

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1390	1402		
Units: Infection per 100 person-years				
number (not applicable)	0.7	4.8		

Statistical analyses

Statistical analysis title	Percent Relative Risk Reduction
Comparison groups	qHPV Vaccine in Base Study v Placebo in Base Study
Number of subjects included in analysis	2792
Analysis specification	Pre-specified
Analysis type	other ^[11]
Parameter estimate	Risk difference (RD)
Point estimate	85.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	77
upper limit	91.3

Notes:

[11] - Confidence interval based on binomial tail probabilities and not from a dispersion parameter. Hochberg multiplicity adjustment applied to the CI.

Secondary: Base Study: Incidence of HPV 6/11/16/18-related Deoxyribonucleic Acid (DNA) Detection

End point title	Base Study: Incidence of HPV 6/11/16/18-related Deoxyribonucleic Acid (DNA) Detection
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End point description:

Participants with HPV 6/11/16/18-related DNA detection per 100 person-years of follow-up was assessed. Per protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with the evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7.

End point type	Secondary
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End point timeframe:

Base study: through Month 36

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1390	1402		
Units: Detection per 100 person-years				
number (not applicable)	5.3	10.7		

Statistical analyses

Statistical analysis title	Percent Relative Risk Reduction
Comparison groups	qHPV Vaccine in Base Study v Placebo in Base Study
Number of subjects included in analysis	2792
Analysis specification	Pre-specified
Analysis type	other ^[12]
Parameter estimate	Risk difference (RD)
Point estimate	51
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.3
upper limit	59.9

Notes:

[12] - Confidence interval based on binomial tail probabilities and not from a dispersion parameter. Hochberg multiplicity adjustment applied to the CI.

Secondary: Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 7 Assessed by cLIA

End point title	Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 7 Assessed by cLIA ^[13]
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End point description:

Antibodies to HPV types were measured using cLIA. Antibody titers were expressed as cLIA milli Merck

units/mL (cLIA mMU/mL). The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 7

Notes:

[13] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: cLIA mMU/mL				
number (confidence interval 95%)				
HPV Type 6 (n=1090)	447.7 (415.9 to 481.9)			
HPV Type 11 (n=1090)	624.4 (588.4 to 662.6)			
HPV Type 16 (n=1133)	2406.1 (2245.0 to 2578.8)			
HPV Type 18 (n=1173)	402.8 (373.9 to 433.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 36 Assessed by cLIA

End point title	Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 36 Assessed by cLIA ^[14]
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End point description:

Antibodies to HPV types were measured using cLIA. Antibody titers were expressed as cLIA milli Merck units/mL (cLIA mMU/mL). The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 36

Notes:

[14] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: cLIA mMU/mL				
number (confidence interval 95%)				
HPV Type 6 (n=845)	71.5 (66.7 to 76.7)			
HPV Type 11 (n=845)	82.5 (77.0 to 88.5)			
HPV Type 16 (n=875)	293.6 (271.6 to 317.4)			
HPV Type 18 (n=904)	33.2 (30.2 to 36.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 72 Assessed by cLIA

End point title	Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 72 Assessed by cLIA ^[15]
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End point description:

Antibodies to HPV types were measured using cLIA. Antibody titers were expressed as cLIA milli Merck units/mL (cLIA mMU/mL). The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 72 [first sample in LTFU (EXT2) ranged from Month 48 to 84 with a median of Month 72]

Notes:

[15] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: cLIA mMU/mL				
number (confidence interval 95%)				
HPV Type 6 (n=575)	57.2 (52.3 to 62.5)			
HPV Type 11 (n=575)	62.1 (56.7 to 68.1)			
HPV Type 16 (n=609)	249.4 (225.6 to 275.8)			
HPV Type 18 (n=633)	25.9 (23.2 to 28.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 120 Assessed by cLIA

End point title	Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 120 Assessed by cLIA ^[16]
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End point description:

Antibodies to HPV types were measured using cLIA. Antibody titers were expressed as cLIA milli Merck units/mL (cLIA mMU/mL). The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 120

Notes:

[16] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: cLIA mMU/mL				
geometric mean (confidence interval 95%)				
HPV Type 6 (n=374)	49.4 (44.1 to 55.4)			
HPV Type 11 (n=374)	38.7 (34.5 to 43.5)			
HPV Type 16 (n=393)	182.9 (161.4 to 207.3)			
HPV Type 18 (n=408)	17.6 (15.5 to 19.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Seropositive for HPV Type 6, 11, 16, and 18 at Month 7 Assessed by cLIA

End point title	Percentage of Participants Seropositive for HPV Type 6, 11, 16, and 18 at Month 7 Assessed by cLIA ^[17]
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End point description:

Antibodies to HPV types were measured using cLIA. Thresholds for seropositive were ≥ 20 , 16, 20, and 24 cLIA mMU/mL for HPV Types 6, 11, 16, and 18, respectively. The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 7

Notes:

[17] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: Percentage of participants				
number (confidence interval 95%)				
HPV Type 6 (n=1090)	98.9 (98.1 to 99.4)			
HPV Type 11 (n=1090)	99.2 (98.4 to 99.6)			
HPV Type 16 (n=1133)	98.8 (97.9 to 99.3)			
HPV Type 18 (n=1173)	97.4 (96.3 to 98.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 36 Assessed by cLIA

End point title	Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 36 Assessed by cLIA ^[18]
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End point description:

Antibodies to HPV types were measured using cLIA. Thresholds for seropositive were ≥ 20 , 16, 20, and 24 cLIA mMU/mL for HPV Types 6, 11, 16, and 18, respectively. The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 36

Notes:

[18] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: Percentage of participants				
number (confidence interval 95%)				
HPV Type 6 (n=845)	88.9 (86.6 to 90.9)			
HPV Type 11 (n=845)	94.0 (92.1 to 95.5)			
HPV Type 16 (n=875)	97.9 (96.8 to 98.8)			
HPV Type 18 (n=904)	57.1 (53.8 to 60.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 72 Assessed by cLIA

End point title	Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 72 Assessed by cLIA ^[19]
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End point description:

Antibodies to HPV types were measured using cLIA. Thresholds for seropositive were ≥ 20 , 16, 20, and 24 cLIA mMU/mL for HPV Types 6, 11, 16, and 18, respectively. The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 72 [first sample in LTFU (EXT2) ranged from Month 48 to 84 with a median of Month 72]

Notes:

[19] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: Percentage of participants				
number (confidence interval 95%)				
HPV Type 6 (n=575)	84.3 (81.1 to 87.2)			

HPV Type 11 (n=575)	88.0 (85.1 to 90.5)			
HPV Type 16 (n=609)	97.0 (95.4 to 98.2)			
HPV Type 18 (n=633)	49.6 (45.6 to 53.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 120 Assessed by cLIA

End point title	Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 120 Assessed by cLIA ^[20]
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End point description:

Antibodies to HPV types were measured using cLIA. Thresholds for seropositive were ≥ 20 , 16, 20, and 24 cLIA mMU/mL for HPV Types 6, 11, 16, and 18, respectively. The per-protocol population included all participants who 1) were seronegative (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 120

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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: Percentage of participants				
number (confidence interval 95%)				
HPV Type 6 (n=374)	79.1 (74.7 to 83.2)			
HPV Type 11 (n=374)	79.9 (75.5 to 83.9)			
HPV Type 16 (n=393)	94.9 (92.2 to 96.9)			
HPV Type 18 (n=408)	40.2 (35.4 to 45.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 120 Assessed by Immunoglobulin G Luminex Immunoassay (IgG LIA)

End point title	Geometric Mean Titers to HPV Types 6, 11, 16, and 18 at Month 120 Assessed by Immunoglobulin G Luminex Immunoassay (IgG LIA) ^[21]
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End point description:

Antibodies to HPV types were measured using Luminex immunoassay (IgG-LIA). The unit of measure for this assay is IgG LIA mMU/mL; this unit cannot be directly compared with the cLIA mMU/mL unit reported for the cLIA results. The per-protocol population included all participants who 1) were seronegative at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 120

Notes:

[21] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: IgG LIA mMU/mL				
geometric mean (confidence interval 95%)				
HPV Type 6 (n=278)	38.8 (34.0 to 44.2)			
HPV Type 11 (n=274)	31.0 (27.2 to 35.3)			
HPV Type 16 (n=291)	162.0 (141.2 to 185.7)			
HPV Type 18 (n=305)	19.7 (17.0 to 22.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 120 Assessed by IgG LIA

End point title	Percentage of Participants Seropositive to HPV Type 6, 11, 16, and 18 at Month 120 Assessed by IgG LIA ^[22]
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End point description:

Antibodies to HPV types were measured using IgG LIA. Thresholds for seropositive were ≥ 9 , 6, 5, and 5 IgG LIA mMU/mL for HPV Types 6, 11, 16, and 18, respectively. The per-protocol population included all participants who 1) were seronegative at Day 1 and PCR negative to the relevant HPV type(s) at Day 1 through Month 7, 2) received all 3 vaccinations within pre-specified day ranges, and 3) did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point type	Secondary
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End point timeframe:

Month 120

Notes:

[22] - 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: Assessment of immunogenicity was planned and conducted only for participants who received qHPV vaccine in the Base Study.

End point values	qHPV Vaccine in Base Study			
Subject group type	Reporting group			
Number of subjects analysed	2025			
Units: Percentage of participants				
number (confidence interval 95%)				
HPV Type 6 (n=278)	91.7 (87.8 to 94.7)			
HPV Type 11 (n=274)	92.0 (88.1 to 94.9)			
HPV Type 16 (n=291)	99.7 (98.1 to 100)			
HPV Type 18 (n=305)	92.1 (88.5 to 94.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Base Study: Sub-study to Evaluate the Incidence of HPV Type 6/11/16/18-related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in Men Having Sex with Men (MSM)

End point title	Base Study: Sub-study to Evaluate the Incidence of HPV Type 6/11/16/18-related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in Men Having Sex with Men (MSM)
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End point description:

Participants with HPV 6/11/16/18-related AIN or anal cancer per 100 person-years of follow-up was assessed. Only a subset of the enrolled population was used for the analysis of this sub-study. Per protocol population: participants must have received 3 doses of qHPV vaccine or placebo within 1 year, must have no protocol violations that could interfere with evaluation of vaccine efficacy, must be seronegative to the relevant HPV type (as measured by cLIA) at Day 1 and PCR negative to the relevant HPV type Day 1 through Month 7, and must provide follow-up data after Month 7.

End point type	Other pre-specified
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End point timeframe:

Base study: through Month 36

End point values	qHPV Vaccine in Base Study	Placebo in Base Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	208		
Units: Incidence per 100 person-years				
number (not applicable)	1.3	5.8		

Statistical analyses

Statistical analysis title	Percent Relative Risk Reduction
Comparison groups	qHPV Vaccine in Base Study v Placebo in Base Study
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	77.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.6
upper limit	93.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Base study: all AEs through Month 36 of Base Study. EXT1: SAEs through Month 7 of EXT1. LTFU (EXT2): SAEs and deaths through 7 years of LTFU (EXT2). Non-serious AEs were not solicited during EXT1 or LTFU (EXT2).

Adverse event reporting additional description:

Analysis population: Base Study: all participants vaccinated in Base Study excluding 6 participants who received non-compliant mixed regimens of qHPV vaccine and placebo; EXT1: all participants who received qHPV vaccine in EXT1 and had follow-up data; LTFU (EXT2): all participants enrolled in LTFU (EXT2).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	qHPV Vaccine in Base Study
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Reporting group description:

The Vaccination Period for the Base Study encompassed Day 1 through Month 7, during which time participants received qHPV vaccine at Day 1, Month 2 and Month 6.

Reporting group title	Placebo in Base Study
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Reporting group description:

The Vaccination Period for the Base Study encompassed Day 1 through Month 7, during which time participants received placebo at Day 1, Month 2 and Month 6.

Reporting group title	qHPV Vaccine in EXT1
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Reporting group description:

Participants who received placebo and participants who received only 1 dose of qHPV vaccine in the Base Study were offered a complete 3-dose qHPV vaccine regimen (administered at EXT1 Day 1, Month 2 and Month 6). Participants who received only 2 doses of qHPV vaccine in the base Study were offered a single additional dose of qHPV vaccine (administered at EXT1 Day 1).

Reporting group title	LTFU (EXT2)
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Reporting group description:

Participants received ≥ 1 dose of qHPV vaccine in Base Study, or received placebo in Base Study and qHPV vaccine in EXT1.

Serious adverse events	qHPV Vaccine in Base Study	Placebo in Base Study	qHPV Vaccine in EXT1
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 2020 (0.40%)	11 / 2029 (0.54%)	3 / 1084 (0.28%)
number of deaths (all causes)	3	10	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroma			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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

Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	1 / 1084 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chemical poisoning			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Contusion			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (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	1 / 2020 (0.05%)	3 / 2029 (0.15%)	1 / 1084 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Head injury			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple drug overdose			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 2020 (0.05%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Traumatic brain injury			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blast injury			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Burns second degree			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Craniocerebral injury			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial haemorrhage			

subjects affected / exposed	0 / 2020 (0.00%)	1 / 2029 (0.05%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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			
Completed suicide			
subjects affected / exposed	0 / 2020 (0.00%)	2 / 2029 (0.10%)	0 / 1084 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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
Cellulitis			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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
Varicella			
subjects affected / exposed	1 / 2020 (0.05%)	0 / 2029 (0.00%)	0 / 1084 (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 / 2020 (0.00%)	0 / 2029 (0.00%)	1 / 1084 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HIV infection			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	0 / 2020 (0.00%)	0 / 2029 (0.00%)	0 / 1084 (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	LTFU (EXT2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 1803 (0.39%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroma			

subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chemical poisoning			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gun shot wound			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Head injury			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple drug overdose			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			

subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Traumatic brain injury			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blast injury			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Burns second degree			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Craniocerebral injury			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			

subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial haemorrhage			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	0 / 1803 (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 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	0 / 1803 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
HIV infection			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	1 / 1803 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	qHPV Vaccine in Base Study	Placebo in Base Study	qHPV Vaccine in EXT1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1277 / 2020 (63.22%)	1183 / 2029 (58.30%)	0 / 1084 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	179 / 2020 (8.86%)	207 / 2029 (10.20%)	0 / 1084 (0.00%)
occurrences (all)	222	275	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	118 / 2020 (5.84%)	125 / 2029 (6.16%)	0 / 1084 (0.00%)
occurrences (all)	131	149	0
Injection-site erythema			
subjects affected / exposed	304 / 2020 (15.05%)	275 / 2029 (13.55%)	0 / 1084 (0.00%)
occurrences (all)	446	384	0
Injection-site pain			
subjects affected / exposed	1116 / 2020 (55.25%)	992 / 2029 (48.89%)	0 / 1084 (0.00%)
occurrences (all)	2087	1767	0
Injection-site pruritus			
subjects affected / exposed	23 / 2020 (1.14%)	24 / 2029 (1.18%)	0 / 1084 (0.00%)
occurrences (all)	27	29	0
Injection-site swelling			
subjects affected / exposed	219 / 2020 (10.84%)	187 / 2029 (9.22%)	0 / 1084 (0.00%)
occurrences (all)	318	270	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	19 / 2020 (0.94%)	23 / 2029 (1.13%)	0 / 1084 (0.00%)
occurrences (all)	21	23	0
Diarrhoea			
subjects affected / exposed	40 / 2020 (1.98%)	36 / 2029 (1.77%)	0 / 1084 (0.00%)
occurrences (all)	44	38	0
Nausea			
subjects affected / exposed	27 / 2020 (1.34%)	16 / 2029 (0.79%)	0 / 1084 (0.00%)
occurrences (all)	30	16	0
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	38 / 2020 (1.88%) 38	37 / 2029 (1.82%) 37	0 / 1084 (0.00%) 0
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	42 / 2020 (2.08%) 43	44 / 2029 (2.17%) 47	0 / 1084 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	44 / 2020 (2.18%) 46	50 / 2029 (2.46%) 59	0 / 1084 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	22 / 2020 (1.09%) 23	20 / 2029 (0.99%) 21	0 / 1084 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	27 / 2020 (1.34%) 28	20 / 2029 (0.99%) 22	0 / 1084 (0.00%) 0

Non-serious adverse events	LTFU (EXT2)		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 1803 (0.00%)		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Injection-site erythema subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Injection-site pain subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Injection-site pruritus subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		

Injection-site swelling subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Pharyngitis subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 1803 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2005	Amendment 2: clarified terms for external genital endpoints, changed enrollment to 3700, added wording that participants who do not complete the 3-dose series will be allowed to continue in the study, clarified timing of retention contact visits, revised criteria for the clinical impression of external genital lesions, revised procedures for high-resolution anoscopy
13 March 2006	Amendment 3: changed enrollment to 3870, clarified that participants who test positive for HIV will not be discontinued, clarified wording as to management of lesions observed on Day 1 as to etiology, assumed vaccine efficacy for MSM endpoint changed to 85%.
21 May 2007	Amendment 4: adopted registered trademark name, GARDASIL™, updated planned enrollment numbers, clarified sexual history information, updated competitive Luminex immunoassay information, clarified or corrected details for sample handling, notifications, and other technical matters.
21 May 2009	Amendment 10: provided for the vaccination of placebo recipients, clarified the MSM sub-study endpoint, described the Type 1 Error adjustment for testing the MSM sub-study hypothesis, clarified the visit schedule to finalize efficacy phase, added and clarified criteria to unblind participants, added information on eligibility of participants to receive the vaccination series in the Study Vaccination Extension.
29 March 2010	Amendment 20: provided for long term evaluation of vaccine effectiveness in males, through active follow-up of study participants for up to 10 years from the day of enrollment into the Base Study.
01 December 2010	Amendment 21: clarified definitions of AE relationship to study vaccine, added or clarified details for sample collection and study visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported