



Clinical trial results: Evaluation of Safety and Immunogenicity of GARDASIL™ in Healthy Females Between 9 and 26 Years of Age in Sub-Saharan Africa Summary

EudraCT number	2017-000110-35
Trial protocol	Outside EU/EEA
Global end of trial date	15 April 2013

Results information

Result version number	v1 (current)
This version publication date	24 March 2017
First version publication date	24 March 2017

Trial information

Trial identification

Sponsor protocol code	V501-046
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01245764
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	15 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2013
Global end of trial reached?	Yes
Global end of trial date	15 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was designed to determine the safety, tolerability and immunogenicity of a 3-dose regimen of GARDASIL™ administered to healthy females between 9 and 26 years of age in Sub-Saharan Africa. Data from the current study are needed in order to complement existing extensive safety data from the GARDASIL™ clinical trials program, and confirm that GARDASIL™ may be administered safely and will induce immune responses in populations from and living in Sub-Saharan Africa, as GARDASIL™ has not previously been studied in this region of the world. In Phase A of the study, healthy females between 9 and 12 years of age were randomized (4:1) to receive the 3-dose regimen of GARDASIL™ or placebo, and those between 13 and 26 years old received GARDASIL™. In Phase B of the study, participants who received placebo in Phase A had the option to receive the 3-dose regimen of GARDASIL™.

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	21 March 2011
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	Ghana: 30
Country: Number of subjects enrolled	Kenya: 90
Country: Number of subjects enrolled	Senegal: 130
Worldwide total number of subjects	250
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

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

Children (2-11 years)	75
Adolescents (12-17 years)	70
Adults (18-64 years)	105
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy female participants between 9 and 26 years of age in sub-Saharan Africa were enrolled into the study.

Pre-assignment

Screening details:

A total of 257 participants were screened and 250 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Gardasil 9 to 12 Years Old
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Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Arm type	Experimental
Investigational medicinal product name	GARDASIL™
Investigational medicinal product code	
Other name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A

Arm title	Gardasil 13 to 15 Years Old
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Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Arm type	Experimental
Investigational medicinal product name	GARDASIL™
Investigational medicinal product code	
Other name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A

Arm title	Gardasil 16 to 26 Years Old
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Arm description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Arm type	Experimental
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Investigational medicinal product name	GARDASIL™
Investigational medicinal product code	
Other name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A	
Arm title	Placebo 9 to 12 Years Old

Arm description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months)

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 injection at the Day 1, Month 2, and Month 6 visits in study Phase A

Number of subjects in period 1	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Gardasil 16 to 26 Years Old
Started	80	30	120
Completed Vaccinations in Study Phase A	77	28	117
Completed	71	25	110
Not completed	9	5	10
Unknown	3	2	3
Lost to follow-up	-	-	5
Protocol deviation	6	3	2

Number of subjects in period 1	Placebo 9 to 12 Years Old
Started	20
Completed Vaccinations in Study Phase A	19
Completed	17
Not completed	3
Unknown	1
Lost to follow-up	-
Protocol deviation	2

Period 2

Period 2 title	Study Phase B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Placebo 9 to 12 Years Old (Gardasil in Phase B)
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Arm description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. After database lock and unblinding for study Phase A, participants accepted the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B.

Arm type	Catch-up vaccination
Investigational medicinal product name	GARDASIL™
Investigational medicinal product code	
Other name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, V501
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B

Number of subjects in period 2^[1]	Placebo 9 to 12 Years Old (Gardasil in Phase B)
Started	17
Completed	17

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: Phase B was voluntary.

Baseline characteristics

Reporting groups

Reporting group title	Gardasil 9 to 12 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Gardasil 13 to 15 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Gardasil 16 to 26 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Placebo 9 to 12 Years Old
Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months)	

Reporting group values	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Gardasil 16 to 26 Years Old
Number of subjects	80	30	120
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	10.7	13.8	21.3
standard deviation	± 1	± 0.8	± 2.9
Gender Categorical Units: Subjects			
Female	80	30	120
Male	0	0	0
Age Units: Subjects			
<9 years	0	0	0
9 to 12 years	80	0	0
13 to 15 years	0	30	0
16 to 26 years	0	0	120
>26 years	0	0	0
Race/Ethnicity Units: Subjects			
Black	80	30	119
Native Hawaiian or Other Pacific Island	0	0	1

Reporting group values	Placebo 9 to 12 Years Old	Total	
Number of subjects	20	250	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	10.5 ± 1.1	-	
Gender Categorical Units: Subjects			
Female	20	250	
Male	0	0	
Age Units: Subjects			
<9 years	0	0	
9 to 12 years	20	100	
13 to 15 years	0	30	
16 to 26 years	0	120	
>26 years	0	0	
Race/Ethnicity Units: Subjects			
Black	20	249	
Native Hawaiian or Other Pacific Island	0	1	

End points

End points reporting groups

Reporting group title	Gardasil 9 to 12 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Gardasil 13 to 15 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Gardasil 16 to 26 Years Old
Reporting group description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.	
Reporting group title	Placebo 9 to 12 Years Old
Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months)	
Reporting group title	Placebo 9 to 12 Years Old (Gardasil in Phase B)
Reporting group description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. After database lock and unblinding for study Phase A, participants accepted the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B.	
Subject analysis set title	Gardasil 9 to 26 Years Old
Subject analysis set type	Per protocol
Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). This subject analysis set includes randomized participants who received at least one vaccination in Study Phase A.	
Subject analysis set title	Placebo 9 to 12 Years Old
Subject analysis set type	Per protocol
Subject analysis set description: Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. This subject analysis set includes randomized participants who received at least one vaccination in Study Phase A.	
Subject analysis set title	Gardasil 9 to 12 Years Old
Subject analysis set type	Safety analysis
Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.	
Subject analysis set title	Gardasil 13 to 15 Years Old
Subject analysis set type	Safety analysis
Subject analysis set description: GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.	
Subject analysis set title	Gardasil 16 to 26 Years Old
Subject analysis set type	Safety analysis

Subject analysis set description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.

Subject analysis set title	Placebo 9 to 12 Years Old
Subject analysis set type	Safety analysis

Subject analysis set description:

Placebo 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. This subject analysis set includes participants who received at least one vaccination in Study Phase A.

Primary: Number of Participants Who Seroconvert to Human Papillomavirus (HPV) Type 6

End point title	Number of Participants Who Seroconvert to Human Papillomavirus (HPV) Type 6 ^[1]
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End point description:

Seroconversion was defined as achieving an anti-HPV Type 6 competitive Luminex Immunoassay (cLIA) level of ≥ 20 milli Merck U/mL. The dilution-corrected limit of detection for the Type 6 cLIA was 4.2 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

End point type	Primary
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End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

Notes:

[1] - 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 conducted for this endpoint.

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147	13		
Units: Participants	147	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 11

End point title	Number of Participants Who Seroconvert to HPV Type 11 ^[2]
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End point description:

Seroconversion was defined as achieving an anti-HPV Type 11 cLIA level of ≥ 16 milli Merck U/mL. The dilution-corrected limit of detection for the Type 11 cLIA was 3.9 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

End point type	Primary
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End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

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 conducted for this endpoint

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147	13		
Units: Participants	147	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 16

End point title	Number of Participants Who Seroconvert to HPV Type 16 ^[3]
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End point description:

Seroconversion was defined as achieving an anti-HPV Type 16 cLIA level of ≥ 20 milli Merck U/mL. The dilution-corrected limit of detection for the Type 16 cLIA was 9.7 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

End point type	Primary
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End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

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 conducted for this endpoint

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	14		
Units: Participants	160	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Seroconvert to HPV Type 18

End point title	Number of Participants Who Seroconvert to HPV Type 18 ^[4]
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End point description:

Seroconversion was defined as achieving an anti-HPV Type 18 cLIA level of ≥ 24 milli Merck U/mL. The dilution-corrected limit of detection for the Type 18 cLIA was 5.8 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.

End point type	Primary
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End point timeframe:

Month 7 (1 month postdose 3 in Study Phase A)

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 conducted for this endpoint

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156	14		
Units: Participants	156	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Injection-site Adverse Experiences

End point title	Number of Participants With Injection-site Adverse
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End point description:

Participants were prompted to report injection-site experiences of pain, erythema, or swelling and were also asked to report any other injection-site adverse experiences. The analysis included all participants receiving at least 1 vaccination in study Phase A and who had postvaccination follow-up.

End point type	Primary
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End point timeframe:

Up to Day 5 after any vaccination in Study Phase A

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was conducted for this endpoint.

End point values	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Gardasil 16 to 26 Years Old	Placebo 9 to 12 Years Old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	79	29	119	19
Units: Participants	54	21	88	9

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Elevated Temperature (Oral Temperature ≥ 100 °F)

End point title	Number of Participants With Elevated Temperature (Oral Temperature ≥ 100 °F)
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End point description:

The analysis included all participants receiving at least 1 vaccination in study Phase A and who had temperature data

End point type	Primary
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End point timeframe:

Up to Day 5 after any vaccination in Study Phase A

End point values	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Gardasil 16 to 26 Years Old	Placebo 9 to 12 Years Old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	79	29	119	19
Units: Participants	9	6	7	5

Statistical analyses

Statistical analysis title	Analysis of Maximum Temperatures
Statistical analysis description:	
Analysis compared the difference in percentage of participants with elevated temperature	
Comparison groups	Gardasil 9 to 12 Years Old v Placebo 9 to 12 Years Old
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.097
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	-14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.4
upper limit	2.2

Primary: Number of Participants With Serious Adverse Experiences

End point title	Number of Participants With Serious Adverse Experiences ^[6]
End point description:	
A serious adverse experience is any adverse experience that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is an overdose, or is another important medical event that may jeopardize the participant and may require medical or surgical intervention. The analysis included all participants receiving at least 1 vaccination in study Phase A or B and who had postvaccination follow-up.	
End point type	Primary
End point timeframe:	
From the time informed consent is signed through the last study visit (up to 19 months)	

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 statistical analysis was conducted for this endpoint.

End point values	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Gardasil 16 to 26 Years Old	Placebo 9 to 12 Years Old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	79	29	119	19
Units: Participants	0	0	1	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Geometric Mean Titer (GMT) of Anti-HPV Type 6 Antibody
End point description: Anti-HPV Type 6 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <10 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.	
End point type	Secondary
End point timeframe: Month 7 (1 month postdose 3 in Study Phase A)	

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147	13		
Units: Milli Merck U/mL				
geometric mean (confidence interval 95%)	602 (526 to 689)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 11 Antibody

End point title	GMT of Anti-HPV Type 11 Antibody
End point description: Anti-HPV Type 11 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 16 milli Merck U/mL. A value of 9999 indicates that the GMT was <7 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.	
End point type	Secondary
End point timeframe: Month 7 (1 month postdose 3 in Study Phase A)	

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147	13		
Units: Milli Merck U/mL				
geometric mean (confidence interval 95%)	626 (545 to 718)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 16 Antibody

End point title	GMT of Anti-HPV Type 16 Antibody
End point description: Anti-HPV Type 16 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 20 milli Merck U/mL. A value of 9999 indicates that the GMT was <9 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL and compared these with results for participants receiving placebo.	
End point type	Secondary
End point timeframe: Month 7 (1 month postdose 3 in Study Phase A)	

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	14		
Units: Milli Merck U/mL				
geometric mean (confidence interval 95%)	3786 (3360 to 4265)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMT of Anti-HPV Type 18 Antibody

End point title	GMT of Anti-HPV Type 18 Antibody
End point description: Anti-HPV Type 18 antibodies were measured by cLIA. The seropositive cut-off threshold for this assay is defined as 24 milli Merck U/mL. A value of 9999 indicates that the GMT was <15 milli Merck U/mL. Participants analyzed included those who received all 3 vaccinations in study Phase A and provided a sample for Month 7 serology testing. This analysis pooled results for participants receiving GARDASIL	

and compared these with results for participants receiving placebo.

End point type	Secondary
End point timeframe:	
Month 7 (1 month postdose 3 in Study Phase A)	

End point values	Gardasil 9 to 26 Years Old	Placebo 9 to 12 Years Old		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156	14		
Units: Milli Merck U/mL				
geometric mean (confidence interval 95%)	811 (708 to 928)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events were assessed up to 19 months from study start. Other adverse events were assessed up to 15 days after each vaccination in study Phase A.

Adverse event reporting additional description:

The analysis included all participants receiving at least one vaccination and had at least one postvaccination follow-up visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Gardasil 9 to 12 Years Old
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Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Reporting group title	Gardasil 13 to 15 Years Old
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Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Reporting group title	Placebo 9 to 12 Years Old
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Reporting group description:

Placebo to GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A. After database lock and unblinding for study Phase A, participants had the option to receive GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase B. Safety evaluation continued to Month 7 of study Phase B (total study duration up to 19 months).

Reporting group title	Gardasil 16 to 26 Years Old
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Reporting group description:

GARDASIL™ 0.5 mL injection at the Day 1, Month 2, and Month 6 visits in study Phase A. Immunogenicity was assessed at Month 7 of study Phase A and safety evaluation continued to Month 12 (total study duration up to 12 months). Participants did not continue to study Phase B.

Serious adverse events	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Placebo 9 to 12 Years Old
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 29 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Foetal distress syndrome			
subjects affected / exposed	0 / 79 (0.00%)	0 / 29 (0.00%)	0 / 19 (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	Gardasil 16 to 26 Years Old		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 119 (0.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Pregnancy, puerperium and perinatal conditions			
Foetal distress syndrome			
subjects affected / exposed	1 / 119 (0.84%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Gardasil 9 to 12 Years Old	Gardasil 13 to 15 Years Old	Placebo 9 to 12 Years Old
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 79 (77.22%)	22 / 29 (75.86%)	15 / 19 (78.95%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 79 (1.27%)	1 / 29 (3.45%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Headache			
subjects affected / exposed	27 / 79 (34.18%)	12 / 29 (41.38%)	5 / 19 (26.32%)
occurrences (all)	37	16	7
Somnolence			
subjects affected / exposed	0 / 79 (0.00%)	0 / 29 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 79 (10.13%)	3 / 29 (10.34%)	1 / 19 (5.26%)
occurrences (all)	12	4	1
Injection site pain			
subjects affected / exposed	53 / 79 (67.09%)	20 / 29 (68.97%)	9 / 19 (47.37%)
occurrences (all)	113	46	21
Injection site swelling			

subjects affected / exposed occurrences (all)	23 / 79 (29.11%) 37	8 / 29 (27.59%) 9	4 / 19 (21.05%) 7
Pyrexia subjects affected / exposed occurrences (all)	9 / 79 (11.39%) 12	6 / 29 (20.69%) 7	5 / 19 (26.32%) 8
Eye disorders Eye pain subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	0 / 29 (0.00%) 0	1 / 19 (5.26%) 1
Myopia subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	0 / 29 (0.00%) 0	1 / 19 (5.26%) 1
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 8	2 / 29 (6.90%) 3	1 / 19 (5.26%) 1
Dyspepsia subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	1 / 29 (3.45%) 1	1 / 19 (5.26%) 1
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	1 / 29 (3.45%) 1	0 / 19 (0.00%) 0
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	0 / 29 (0.00%) 0	1 / 19 (5.26%) 1
Malaria subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 3	2 / 29 (6.90%) 2	1 / 19 (5.26%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2	1 / 29 (3.45%) 2	0 / 19 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	0 / 29 (0.00%) 0	1 / 19 (5.26%) 1

Non-serious adverse events	Gardasil 16 to 26 Years Old		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 119 (86.55%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 119 (2.52%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	41 / 119 (34.45%)		
occurrences (all)	58		
Somnolence			
subjects affected / exposed	0 / 119 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	15 / 119 (12.61%)		
occurrences (all)	21		
Injection site pain			
subjects affected / exposed	88 / 119 (73.95%)		
occurrences (all)	188		
Injection site swelling			
subjects affected / exposed	31 / 119 (26.05%)		
occurrences (all)	48		
Pyrexia			
subjects affected / exposed	9 / 119 (7.56%)		
occurrences (all)	10		
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 119 (0.00%)		
occurrences (all)	0		
Myopia			
subjects affected / exposed	0 / 119 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	8 / 119 (6.72%) 8 2 / 119 (1.68%) 4		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	11 / 119 (9.24%) 16		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Malaria subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0 2 / 119 (1.68%) 2 13 / 119 (10.92%) 14 3 / 119 (2.52%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported