Clinical trial results:
A Phase II Double-Blind Comparative Study of V501 in Females Aged 9 to 17 Years

Summary

EudraCT number	2017-000112-42
Trial protocol	Outside EU/EEA
Global end of trial date	18 September 2009

Results information

Result version number	v1 (current)
This version publication date	25 March 2017
First version publication date	25 March 2017

Trial information

Trial identification

Sponsor protocol code	V501-028

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00411749
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Study Number: 2006_052

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, 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	18 September 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the serum antibody titers to the vaccine human papilloma virus (HPV) types at 1 month Postdose 3 in the participants who received the quadrivalent HPV (Types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine compared with placebo.

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	11 December 2006
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	Japan: 107
Worldwide total number of subjects	107
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)	37
Adolescents (12-17 years)	70
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 8 sites in Japan from 2006 to 2009.

Pre-assignment

Screening details:

Girls between the ages of 9 years and 17 years who had not yet had coitarche and did not plan on becoming sexually active through the course of the study were enrolled in Part I. Participants randomly assigned to receive V501 and received all 3 vaccination in Part I were followed for an additional 2 years.

Period 1

Period 1 title	Treatment - Day 1 to Month 7
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	V501

Arm description:

Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine. Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).

Arm type	Experimental
Investigational medicinal product name	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine
Investigational medicinal product code	
Other name	Gardasil
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).

Arm title	Placebo

Arm description:

Total of three 0.5 mL intramuscular injections (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:

Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).

Number of subjects in period 1	V501	Placebo
Started	82	25
Completed	82	25

Period 2	
Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	V501

Arm description:

Participants who received V501 in treatment period and were followed for 2 years after last vaccination

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	V501
Started	82
Completed	82

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: Only participants from V501 arm were enrolled in follow-up. Participants from placebo arm did not continue.

Baseline characteristics

Reporting groups	
Reporting group title	V501
Reporting group description:	
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine. Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).	
Reporting group title	Placebo
Reporting group description:	
Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).	

Reporting group values	V501	Placebo	Total
Number of subjects	82	25	107
Age Categorical			
Units: Subjects			
Children (2-11 years)	28	9	37
Adolescents (12-17 years)	54	16	70
Age Continuous			
Units: years			
arithmetic mean	12.8	12.6	
standard deviation	± 2.4	± 2.6	-
Gender Categorical			
Units: Subjects			
Female	82	25	107
Male	0	0	0
Body Weight			
Units: kg			
arithmetic mean	45.5	45.2	
standard deviation	± 10.8	± 9.6	-

End points

End points reporting groups

Reporting group title	V501
Reporting group description:	
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine. Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).	
Reporting group title	Placebo
Reporting group description:	
Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).	
Reporting group title	V501
Reporting group description:	
Participants who received V501 in treatment period and were followed for 2 years after last vaccination	
Subject analysis set title	V501- Part I
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received 3 doses of Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (V501) and who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type, and a Month 7 serum sample collected within an acceptable time range.	
Subject analysis set title	Placebo - Part I
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received 3 doses of placebo and who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type, and a Month 7 serum sample collected within an acceptable time range.	
Subject analysis set title	V501- Part II
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received all 3 doses of V501 in Part I and were followed from Month 7 to Month 31 (24 months post last dose of V501) and had available data for endpoint	

Primary: Human Papilloma Virus (HPV) 6 Serum Antibody Titer at Month 7

End point title	Human Papilloma Virus (HPV) 6 Serum Antibody Titer at Month 7
End point description:	
Antibodies to HPV virus-like particles (VLP) type 6 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 7 mMU/ml. Geometric mean titers (GMTs) and confidence limits below the limit of detection are shown as "7.0".	
End point type	Primary
End point timeframe:	
Month 7 (1 month after last vaccination)	

End point values	V501- Part I	Placebo - Part I		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[1]	25		
Units: mMU/mL				
geometric mean (confidence interval 95%)	674.5 (528.6 to 860.8)	7 (7 to 8.4)		

Notes:

[1] - Data not available for 2 participants

Statistical analyses

Statistical analysis title	Between Group Comparison
Comparison groups	V501- Part I v Placebo - Part I
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Human Papilloma Virus (HPV) 11 Serum Antibody Titer at Month 7

End point title	Human Papilloma Virus (HPV) 11 Serum Antibody Titer at Month 7

End point description:

Antibodies to HPV virus-like particles (VLP) type 11 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 8 mMU/ml. Geometric mean titers (GMTs) and confidence limits below the limit of detection are shown as "8.0".

End point type	Primary

End point timeframe:

Month 7 (1 month after last vaccination)

End point values	V501- Part I	Placebo - Part I		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[2]	25		
Units: mMU/ml				
geometric mean (confidence interval 95%)	944.5 (755.3 to 1181)	8 (8 to 8.5)		

Notes:

[2] - Data not available for 2 participants

Statistical analyses

Statistical analysis title	Between Group Comparison
Comparison groups	V501- Part I v Placebo - Part I

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Human Papilloma Virus (HPV) 16 Serum Antibody Titer at Month 7

End point title	Human Papilloma Virus (HPV) 16 Serum Antibody Titer at Month 7

End point description:

Antibodies to HPV virus-like particles (VLP) type 16 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 11 mMU/ml. Geometric mean titers (GMTs) and confidence limits below the limit of detection are shown as "11.0".

End point type	Primary

End point timeframe:

Month 7 (1 month after last vaccination)

End point values	V501- Part I	Placebo - Part I		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	25		
Units: mMU/mL				
geometric mean (confidence interval 95%)	4275.4 (3375.4 to 5415.4)	11 (11 to 13.5)		

Statistical analyses

Statistical analysis title	Between Group Comparison
Comparison groups	V501- Part I v Placebo - Part I
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Human Papilloma Virus (HPV) 18 Serum Antibody Titer at Month 7

End point title	Human Papilloma Virus (HPV) 18 Serum Antibody Titer at Month 7

End point description:

Antibodies to HPV virus-like particles (VLP) type 18 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 10 mMU/ml. Geometric mean titers (GMTs) and confidence limits below the limit of detection are shown as "10.0".

End point type	Primary

End point timeframe:

Month 7 (1 month after last vaccination)

End point values	V501- Part I	Placebo - Part I		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	25		
Units: mMU/mL				
geometric mean (confidence interval 95%)	829.2 (642.3 to 1070.5)	10 (10 to 10.1)		

Statistical analyses

Statistical analysis title	Between Group Comparison
Comparison groups	V501- Part I v Placebo - Part I
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Human Papilloma Virus (HPV) 6 Serum Antibody Titer at Month 30

End point title	Human Papilloma Virus (HPV) 6 Serum Antibody Titer at Month 30

End point description:

Antibodies to HPV virus-like particles (VLP) type 6 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 7 mMU/ml.

End point type	Secondary

End point timeframe:

Month 30 (24 months post last dose of vaccine)

End point values	V501- Part II			
Subject group type	Subject analysis set			
Number of subjects analysed	79[3]			
Units: mMU/mL				
geometric mean (confidence interval 95%)	155.2 (126.2 to 190.9)			

Notes:

[3] - Data not available for 3 participants

Statistical analyses

No statistical analyses for this end point

Secondary: Human Papilloma Virus (HPV) 11 Serum Antibody Titer at Month 30

End point title	Human Papilloma Virus (HPV) 11 Serum Antibody Titer at Month 30

End point description:

Antibodies to HPV virus-like particles (VLP) type 11 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 8 mMU/ml.

End point type	Secondary

End point timeframe:

Month 30 (24 months post last dose of vaccine)

End point values	V501- Part II			
Subject group type	Subject analysis set			
Number of subjects analysed	80[4]			
Units: mMU/mL				
geometric mean (confidence interval 95%)	198.2 (160.9 to 244.2)			

Notes:

[4] - Data not available for 2 participants

Statistical analyses

No statistical analyses for this end point

Secondary: Human Papilloma Virus (HPV) 16 Serum Antibody Titer at Month 30

End point title	Human Papilloma Virus (HPV) 16 Serum Antibody Titer at Month 30

End point description:

Antibodies to HPV virus-like particles (VLP) type 16 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 11 mMU/ml.

End point type	Secondary

End point timeframe:

Month 30 (24 months post last dose of vaccine)

End point values	V501- Part II			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: mMU/mL				
geometric mean (confidence interval 95%)	617.1 (491.7 to 774.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Human Papilloma Virus (HPV) 18 Serum Antibody Titer at Month 30

End point title	Human Papilloma Virus (HPV) 18 Serum Antibody Titer at Month 30

End point description:

Antibodies to HPV virus-like particles (VLP) type 18 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). The limit of detection of the assay was 10 mMU/ml.

End point type	Secondary

End point timeframe:

Month 30 (24 months post last dose of vaccine)

End point values	V501- Part II			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: mMU/mL				
geometric mean (confidence interval 95%)	90 (68.8 to 117.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days post each of the 3 vaccinations for non-serious adverse events. Serious adverse events were collected during the entire study.

Adverse event reporting additional description:

Population included all enrolled participants who received at least 1 injection and had available safety data.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	V501

Reporting group description:

Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine. Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).

Reporting group title	Placebo

Reporting group description:

Total of three 0.5 mL intramuscular injections (Day 1, Month 2, and Month 6).

Serious adverse events	V501	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 82 (2.44%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Strabismus congenital			
subjects affected / exposed	1 / 82 (1.22%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	V501	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 82 (92.68%)	23 / 25 (92.00%)	
Investigations			
Platelet count increased			
subjects affected / exposed	3 / 82 (3.66%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Protein urine present			
subjects affected / exposed	4 / 82 (4.88%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 82 (10.98%)	1 / 25 (4.00%)	
occurrences (all)	10	1	
General disorders and administration site conditions			
Injection site discomfort			
subjects affected / exposed	1 / 82 (1.22%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Injection site erythema			
subjects affected / exposed	35 / 82 (42.68%)	5 / 25 (20.00%)	
occurrences (all)	55	5	
Injection site haemorrhage			
subjects affected / exposed	0 / 82 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	69 / 82 (84.15%)	19 / 25 (76.00%)	
occurrences (all)	158	42	
Injection site pruritus			
subjects affected / exposed	12 / 82 (14.63%)	1 / 25 (4.00%)	
occurrences (all)	18	1	
Injection site swelling			
subjects affected / exposed	38 / 82 (46.34%)	4 / 25 (16.00%)	
occurrences (all)	57	4	
Malaise			
subjects affected / exposed	2 / 82 (2.44%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Pyrexia			

subjects affected / exposed	4 / 82 (4.88%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 82 (7.32%)	2 / 25 (8.00%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	2 / 82 (2.44%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Upper respiratory tract inflammation			
subjects affected / exposed	4 / 82 (4.88%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 82 (2.44%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	0 / 82 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 82 (10.98%)	5 / 25 (20.00%)	
occurrences (all)	10	6	

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