Clinical trial results:
A Phase III Placebo-controlled Clinical Trial to Study the Tolerability, Immunogenicity and Efficacy of V501 in 16- to 26-year-old Japanese men

Summary

EudraCT number	2015-002931-16
Trial protocol	Outside EU/EEA
Global end of trial date	30 August 2017

Results information

Result version number	v1 (current)
This version publication date	15 August 2018
First version publication date	15 August 2018

Trial information

Trial identification

Sponsor protocol code	V501-122

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01862874
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 132237

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	30 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and tolerability of V501 (quadrivalent Human Papilloma Virus [HPV] [Type 6, 11, 16 and 18] L1 Virus-Like Particle vaccine, GARDASIL™) in healthy, 16- to 26-year old Japanese males. The hypotheses tested are: 1) V501 reduces the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection compared with placebo, and 2) V501 reduces the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia, or penile, perianal, or perineal cancer 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	27 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 1124
Worldwide total number of subjects	1124
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	1121

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1129 participants were screened and 1124 were randomized.

Pre-assignment

Screening details:

Healthy Japanese males age 16 to 26 years were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	V501

Arm description:

Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

Arm type	Experimental
Investigational medicinal product name	Quadrivalent human papillomavirus vaccine
Investigational medicinal product code	
Other name	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine. Formulated with aluminum hydroxyphosphate sulfate (AAHS) adjuvant.
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Arm title	Placebo

Arm description:

Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.

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

Dosage and administration details:

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

Number of subjects in period 1	V501	Placebo
Started	562	562
Vaccination 1	561	562
Vaccination 2	539	542
Vaccination 3	530	532
Completed	483	485
Not completed	79	77
Withdrawn by parent/guardian	1	1
Adverse event, serious fatal	-	1
Physician decision	5	3
Consent withdrawn by subject	46	40
Randomized not treated	1	-
Adverse event, non-fatal	-	3
Lost to follow-up	26	29

Baseline characteristics

Reporting groups	
Reporting group title	V501
Reporting group description:	
Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	

Reporting group values	V501	Placebo	Total
Number of subjects	562	562	1124
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	3	3
Adults (18-64 years)	562	559	1121
Age Continuous Units: Years			
arithmetic mean	22.6	22.6	
standard deviation	± 2.1	± 2.0	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	562	562	1124
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	562	562	1124
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	V501
Reporting group description:	
Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	

Primary: Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection

End point title	Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection
End point description:	
Persistent infection was defined as 1) polymerase chain reaction (PCR) positive to HPV Type 6, 11, 16, or 18 in 2 consecutive anogenital or biopsy samples collected ≥4 months apart, or 2) Pathology Panel consensus diagnosis of condyloma acuminate, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal, or perineal cancer and PCR detection of HPV Type 6, 11, 16, or 18 in an adjacent section and PCR positive for the same HPV type at a separate adjacent visit. The combined incidence of HPV Type 6, 11, 16, or 18 persistent infection detected in samples from ≥2 consecutive visits ≥6 months apart was assessed. The population was participants who were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, received all 3 vaccinations, did not deviate from the study protocol in ways that might interfere with vaccine efficacy, and had ≥1 follow-up visit after Month 7.	
End point type	Primary
End point timeframe:	
Up to Month 36	

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497[1]	498[2]		
Units: Cases per 100 person-years of follow-up				
number (not applicable)	0.3	1.9		

Notes:

[1] - 1137 person-years follow-up

[2] - 1123 person-years follow-up

Statistical analyses

Statistical analysis title	Vaccine Efficacy
Statistical analysis description:	
Vaccine efficacy is defined as the percentage reduction in relative risk for the V501 group versus the placebo group.	
Comparison groups	V501 v Placebo

Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	One-sided exact test
Parameter estimate	Vaccine Efficacy
Point estimate	85.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.7
upper limit	97.3

Notes:

[3] - If the lower bound of the 95% confidence interval for vaccine efficacy excludes 0%, then superiority of the V501 group is demonstrated.

Primary: Percentage of Participants with Maximum Temperature ≥37.5°C Reported on the Vaccination Report Card

End point title	Percentage of Participants with Maximum Temperature ≥37.5°C Reported on the Vaccination Report Card

End point description:

Body temperature (oral or oral equivalent) was recorded on the Vaccination Report Card (VRC). The percentage of participants with a maximum temperature ≥37.5°C was summarized. The population was participants who received ≥1 study vaccination and had follow-up data available.

End point type	Primary

End point timeframe:

Up to 5 days after any vaccination

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	551	557		
Units: Percentage of participants				
number (not applicable)	2.7	3.9		

Statistical analyses

Statistical analysis title	Incidence of elevated temperature
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.256
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	0.9

Notes:

[4] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with an Injection-site Adverse Event Prompted on the Vaccination Report Card

End point title	Percentage of Participants with an Injection-site Adverse Event Prompted on the Vaccination Report Card

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. The percentage of participants with an injection-site AE prompted on the VRC (erythema, pain, and swelling) was summarized. The population was participants who received ≥1 study vaccination and had follow-up data available.

End point type	Primary

End point timeframe:

Up to 5 days after any vaccination

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	559		
Units: Percentage of participants				
number (not applicable)				
Injection-site erythema	24.5	21.6		
Injection-site pain	54.9	48.5		
Injection-site swelling	21.3	14.5		

Statistical analyses

Statistical analysis title	Incidence of injection-site erythema
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1113
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.251
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	7.9

Notes:

[5] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Statistical analysis title	Incidence of injection-site pain
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1113
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.033
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	12.2

Notes:

[6] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Statistical analysis title	Incidence of injection-site swelling
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1113
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.003
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	11.3

Notes:

[7] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with a Systemic Adverse Event

End point title	Percentage of Participants with a Systemic Adverse Event

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. The percentage of participants with a systemic AE was

summarized. The population was participants who received ≥1 study vaccination and had follow-up data available.

End point type	Primary

End point timeframe:

Up to 15 days after any vaccination

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	559		
Units: Percentage of participants				
number (not applicable)	14.4	15.4		

Statistical analyses

Statistical analysis title	Incidence of systemic AEs
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1113
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Risk difference (RD)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	3.3

Notes:

[8] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Primary: Percentage of Participants with a Vaccine-related Systemic Adverse Event

End point title	Percentage of Participants with a Vaccine-related Systemic Adverse Event

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. Vaccine-related AEs are those that were deemed possibly, probably, or definitely related to vaccine administration by the investigator. The percentage of participants with a vaccine-related systemic AE was summarized. The population was participants who received ≥1 study vaccination and had follow-up data available

End point type	Primary

End point timeframe:

Up to 15 days after any vaccination

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	559		
Units: Percentage of participants				
number (not applicable)	3.4	5.0		

Statistical analyses

Statistical analysis title	Incidence of vaccine-related systemic AEs
Comparison groups	V501 v Placebo
Number of subjects included in analysis	1113
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Risk difference (RD)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	0.8

Notes:

[9] - Risk difference (V501 - placebo) was estimated using the Miettinen & Nurminen method.

Secondary: Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection or Disease

End point title	Combined Incidence of HPV Type 6, 11, 16, or 18-related Persistent Infection or Disease

End point description:

Persistent infection was defined as in the first primary endpoint above. Disease was defined as HPV Type 6, 11, 16, or 18-related condyloma acuminate, PIN, penile, perianal, or perineal cancer. The combined incidence of HPV Type 6, 11, 16, or 18 persistent infection or disease was assessed. The population was participants who were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, received all 3 vaccinations, did not deviate from the study protocol in ways that might interfere with vaccine efficacy, and had ≥1 follow-up visit after Month 7.

End point type	Secondary

End point timeframe:

Up to Month 36

End point values	V501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	498[10]	498[11]		
Units: Cases per 100 person-years at risk				
number (not applicable)	0.3	1.9		

Notes:

[10] - 1148 person-years follow-up

[11] - 1132 person-years follow-up

Statistical analyses

Statistical analysis title	Vaccine Efficacy

Statistical analysis description:

Vaccine efficacy is defined as the percentage reduction in relative risk for the V501 versus the placebo group.

Comparison groups	V501 v Placebo
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001
Method	One-sided exact test
Parameter estimate	Vaccine Efficacy
Point estimate	86.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.2
upper limit	97.4

Notes:

[12] - If the lower bound of the 95% confidence interval for vaccine efficacy excludes 0%, superiority of the V501 group is demonstrated.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 36 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received placebo 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	
Reporting group title	V501
Reporting group description: Participants received V501 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36.	

Serious adverse events	Placebo	V501	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 559 (0.18%)	0 / 554 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 559 (0.18%)	0 / 554 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Placebo	V501	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 559 (54.20%)	329 / 554 (59.39%)	
General disorders and administration site conditions			
Injection-site erythema			
subjects affected / exposed	122 / 559 (21.82%)	137 / 554 (24.73%)	
occurrences (all)	179	217	
Injection-site swelling			

subjects affected / exposed	82 / 559 (14.67%)	118 / 554 (21.30%)	
occurrences (all)	121	181	
Injection-site pain			
subjects affected / exposed	271 / 559 (48.48%)	304 / 554 (54.87%)	
occurrences (all)	480	563	

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