Clinical trial results:
A Phase IV Open-label, Descriptive Study to Evaluate the Safety and Effectiveness on the Incidence of HPV 6, 11, 16 and 18 Related CIN 2/3 or worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in 16- to 26-Year-Old Japanese Women

Summary

EudraCT number	2015-002932-42
Trial protocol	Outside EU/EEA
Global end of trial date	01 December 2016

Results information

Result version number	v1 (current)
This version publication date	13 May 2017
First version publication date	13 May 2017

Trial information

Trial identification

Sponsor protocol code	V501-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01544478
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	27 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the long term safety of quadrivalent Human Papillomavirus (HPV) types 6, 11, 16, 18 vaccine (V501) and its effectiveness in the prevention of cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ, and cervical cancer related to HPV in Japanese women.

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	22 November 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	Japan: 1030
Worldwide total number of subjects	1030
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)	2
Adults (18-64 years)	1028
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were healthy Japanese females 16 to 26 years of age.

Pre-assignment

Screening details:

A total of 1036 participants were screened and 1030 were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	V501

Arm description:

Participants received a 0.5 mL vaccination by intramuscular injection of V501 on Day 1, Month 2, and Month 6

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

Dosage and administration details:

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

Number of subjects in period 1	V501
Started	1030
Vaccination 1	1030
Vaccination 2	1026
Vaccination 3	1019
Completed	912
Not completed	118
Physician decision	15
Consent withdrawn by subject	52
Adverse event, non-fatal	1
Death	1
Pregnancy	1
Lost to follow-up	48

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Participants received a 0.5 mL vaccination by intramuscular injection of V501 on Day 1, Month 2, and Month 6	

Reporting group values	Overall Study	Total	
Number of subjects	1030	1030	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	1028	1028	
Age Continuous Units: years			
arithmetic mean	22.9		
standard deviation	± 2.2	-	
Gender Categorical Units: Subjects			
Female	1030	1030	
Male	0	0	
Race Units: Subjects			
Asian	1030	1030	

End points

End points reporting groups

Reporting group title	V501

Reporting group description:

Participants received a 0.5 mL vaccination by intramuscular injection of V501 on Day 1, Month 2, and Month 6

Primary: Combined incidence of Cervical Intraepithelial Neoplasia (CIN) 2/3 or worse related to HPV type 6, 11, 16, or 18

End point title	Combined incidence of Cervical Intraepithelial Neoplasia (CIN) 2/3 or worse related to HPV type 6, 11, 16, or 18[1]

End point description:

The endpoint included pathology panel consensus diagnosis of CIN 2 or 3, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, and HPV type 6, 11, 16, or 18 detected in an adjacent section from the same tissue block. The population analyzed included participants who received the full vaccination series, had at least 1 visit after Month 7, had no general protocol violations, and were seronegative at Baseline and polymerase chain reaction-negative from Baseline through Month 7 for the relevant HPV type. The point estimates and exact 95% confidence intervals for incidence rate were based on the Poisson distribution.

End point type	Primary

End point timeframe:

Up to Month 48

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 hypothesis testing was planned or conducted for this endpoint

End point values	V501			
Subject group type	Reporting group			
Number of subjects analysed	967[2]			
Units: Cases per 100 person-years at risk				
number (confidence interval 95%)	0 (0 to 0.1)			

Notes:

[2] - A total of 3034.6 person-years was evaluated

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Month 48	
Adverse event reporting additional description:	
Participants at risk included all who received at least 1 vaccination and had safety follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	V501
Reporting group description:	
Participants received a 0.5 mL vaccination by intramuscular injection of V501 on Day 1, Month 2, and Month 6	

Serious adverse events	V501		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 1029 (0.78%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 1029 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	4 / 1029 (0.39%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1029 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foetal malpresentation			

subjects affected / exposed	1 / 1029 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Peritonsillitis			
subjects affected / exposed	1 / 1029 (0.10%)		
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	V501		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 1029 (16.42%)		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	118 / 1029 (11.47%)		
occurrences (all)	168		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	61 / 1029 (5.93%)		
occurrences (all)	67		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	Amendment 1: change in the handling of relocated participants, and minor changes to the Regimen for Triage: Investigator Aids for Colposcopy and Definitive Therapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported