Clinical trial results:
An Immunogenicity and Safety Study of GARDASIL™ in Chinese Female Subjects Aged 9 to 45 Years and Male Subjects Aged 9 to 15 Years

Summary

EudraCT number	2014-004581-16
Trial protocol	Outside EU/EEA
Global end of trial date	28 February 2009

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	V501-030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00496626
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	28 February 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2009
Global end of trial reached?	Yes
Global end of trial date	28 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a China registration study. A randomized, double-blind, placebo-controlled immunogenicity and safety study in Chinese female participants aged 9 to 45 years and male participants aged 9 to 15 years. Approximately 600 participants will be randomized in a 1:1 ratio to receive either vaccine or aluminum-containing placebo. Each participant received one injection at each visit at Day 1, Month 2, and Month 6. Vaccine or placebo was given as a 0.5-mL intramuscular injection. Serum will be collected from all participants to evaluate immune response against anti-Human Papillomavirus (HPV) 6/11/16/18 with Luminex Assay. At Month 2, Month 6, Month 7, subjects will be evaluated for any new medical condition or health concerns and Serious Adverse Experiences throughout the study. The primary objective is to evaluate the vaccine-induced serum anti-HPV 6, 11, 16 and 18 antibody titers following 3-dose regimen of Gardasil® 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	20 July 2008
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	China: 600
Worldwide total number of subjects	600
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)	95

Adolescents (12-17 years)	122
Adults (18-64 years)	383
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy Chinese participants aged 9 to 45 years (females) or 9 to 15 years (males) were enrolled. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

A total of 610 participants were screened and 600 were enrolled.

Period 1

Period 1 title	Vaccination and Follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Vaccine (GARDASIL™) Group

Arm description:

Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

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

Dosage and administration details:

Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

Arm title	Placebo Group

Arm description:

Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

Arm type	Placebo
Investigational medicinal product name	Placebo to GARDASIL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

Number of subjects in period 1	Vaccine (GARDASIL™) Group	Placebo Group
Started	302	298
Completed	296	292
Not completed	6	6
Consent withdrawn by subject	5	4
Lost to follow-up	-	1
Relocated	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Vaccine (GARDASIL™) Group
Reporting group description:	
Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.	
Reporting group title	Placebo Group
Reporting group description:	
Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.	

Reporting group values	Vaccine (GARDASIL™) Group	Placebo Group	Total
Number of subjects	302	298	600
Age categorical Units: Subjects			
9 to 15 years of age	101	99	200
16 to 26 years of age	76	74	150
27 to 34 years of age	63	62	125
35 to 45 years of age	62	63	125
Age continuous Units: years			
arithmetic mean	24.5	24.8	
standard deviation	± 10.9	± 11	-
Gender categorical Units: Subjects			
Female	251	249	500
Male	51	49	100
Body Temperature Units: ° C			
arithmetic mean	36.5	36.5	
standard deviation	± 0.31	± 0.31	-
Pulse Rate Units: Beats per minute			
arithmetic mean	74.4	74.6	
standard deviation	± 11.2	± 11.2	-

End points

End points reporting groups

Reporting group title	Vaccine (GARDASIL™) Group
Reporting group description:	
Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.	
Reporting group title	Placebo Group
Reporting group description:	
Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.	
Subject analysis set title	Vaccine (GARDASIL™) Group Day 1
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. This Subject Analysis Set is for Day 1 immunogenicity results.	
Subject analysis set title	Vaccine (GARDASIL™) Group Month 7
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. This Subject Analysis Set is for Month 7 immunogenicity results.	
Subject analysis set title	Placebo Group Day 1
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. This Subject Analysis Set is for Day 1 immunogenicity results.	
Subject analysis set title	Placebo Group Month 7
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. This Subject Analysis Set is for Month 7 immunogenicity results.	

Primary: Geometric Mean Titer (GMT) of Anti-HPV 6, 11, 16, and 18

End point title	Geometric Mean Titer (GMT) of Anti-HPV 6, 11, 16, and 18
End point description:	
Measured GMT of anti-HPV 6, 11, 16 and 18 at Day 1 and Month 7 (1 month after completion of administration of a 6-month 3-dose regimen of vaccines). GMT at Day 1 was used to define per-protocol population. Antibody titers were tested with Luminex array (cLIA). The numeric values for the Day 1 (Vaccine and Placebo groups) and the Month 7 (Placebo groups) are the threshold of detection for the cLIA assays. The reported values are all below the lower limit of qualification, ([less than] <7, <8, <11, <10 respectively). Per-protocol population, defined as all participants who received all 3 dose vaccinations within acceptable day ranges, had at least 1 valid serology result after the third injection, and adhered to protocol guidelines. To be included in the immunogenicity analysis for given HPV type, participants must be seronegative to that HPV type at baseline.	
End point type	Primary
End point timeframe:	
Day 1 before vaccination and Month 7	

End point values	Vaccine (GARDASIL™) Group Day 1	Vaccine (GARDASIL™) Group Month 7	Placebo Group Day 1	Placebo Group Month 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	302	302	298	298
Units: milli Merck units/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 (N=269, 269, 275, 275)	7 (7 to 7)	426 (369.5 to 491)	7 (7 to 7)	7 (7 to 7)
Anti-HPV 11 (N=279, 279, 281, 281)	8 (8 to 8)	665 (589.4 to 750.3)	8 (8 to 8)	8 (8 to 8)
Anti-HPV 16 (N=277, 277, 277, 277)	11 (11 to 11)	2336.9 (2023.1 to 2699.3)	11 (11 to 11)	11 (11 to 11)
Anti-HPV 18 (N=287, 287, 282, 282)	10 (10 to 10)	535.6 (461.8 to 621.2)	10 (10 to 10)	10 (10 to 10)

Statistical analyses

Statistical analysis title	Superiority Analysis for All HPV Types: Month 7

Statistical analysis description:

An Analysis of Covariance (ANCOVA) model was used for each HPV type, based on the pooled data from all age groups and genders. The natural-log-transformed titer was the response variable, and vaccination group, gender and age group were covariates. The null hypothesis was that the GMT ratio (Gardasil/Placebo) was equal to 1.

Comparison groups	Vaccine (GARDASIL™) Group Month 7 v Placebo Group Month 7
Number of subjects included in analysis	600
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	GMT Ratio (Gardasil/Placebo)
Point estimate	101.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	88.1
upper limit	117.2

Notes:

[1] - Superiority of GARDASIL™ to placebo was claimed if, for each of the four HPV types, the lower bound of the two-sided 95% CI on the GMT ratio [GARDASIL™/placebo] being >1, or equivalently, the two-sided p-value <0.05. The ANCOVA models showed the lower bounds of two-sided 95% CI on the GMT ratio [GARDASIL™/placebo] were greater than 1 for each HPV type, so the null hypothesis was rejected. The CI reported is for HPV18, the type with the smallest CI lower bound.

Secondary: Number of Participants Who Were Seronegative at Baseline and Developed Seropositive at Month 7

End point title	Number of Participants Who Were Seronegative at Baseline and Developed Seropositive at Month 7

End point description:

Anti-HPV 6, 11, 16, 18 Seroconversion Rate, i.e., the Number of participants who were seronegative at baseline and developed seropositive at Month 7. Seroconversion for HPV 6, 11, 16, and 18 was defined as achieving an anti-HPV cLIA level of at least 20, 16, 20 and 24 mill Merck units/mL, respectively.

Seroconversion rate = (number of participants with seronegative at baseline and developed seropositive

at Month 7)/(number of participants with seronegative at baseline regardless relevant HPV serum status at Month 7). Measure serum anti-HPV 6, 11, 16, 18 titers at Day 1 prior to vaccination and at Month 7.

Per-protocol population, defined as all participants who received all 3 dose vaccinations within acceptable day ranges, had at least 1 valid serology result after the third injection, and adhered to protocol guidelines. To be included in the immunogenicity analysis for given HPV type, participants must be seronegative to that HPV type at baseline.

End point type	Secondary

End point timeframe:

Day 1 before vaccination and Month 7

End point values	Vaccine (GARDASIL™) Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	298		
Units: Number of participants				
Anti-HPV 6 (N=269, 275)	260	2		
Anti-HPV 11 (N=279, 281)	277	2		
Anti-HPV 16 (N=277, 277)	275	0		
Anti-HPV 18 (N=287, 282)	284	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Adverse Experience Categories

End point title	Number of Participants by Adverse Experience Categories

End point description:

All adverse experiences were collected through 14 days following each vaccination. All participants were requested to record injection-site adverse experiences and monitor the participant's temperature daily on the Vaccination Report Card for Day 1 thereafter for 4 additional calendar days, and record all systemic adverse experiences that occurred during the 14-day period after each injection.

Safety population, defined as all participants who were vaccinated with at least one dose and had safety follow-up data.

End point type	Secondary

End point timeframe:

Serious adverse experiences and systemic adverse experiences: up to 14 days after each vaccination; injection-site adverse experiences: up to 5 days after each vaccination

End point values	Vaccine (GARDASIL™) Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	298		
Units: Number of participants				
Clinical Adverse Experiences	153	131		

Injection-site Adverse Experiences	66	40		
Systemic Adverse Experiences	129	119		
Vaccine-related Adverse Experiences	123	100		
Vaccine-related Injection-site Adverse Experiences	66	40		
Vaccine-related Systemic Adverse Experiences	87	82		
Serious Adverse Experiences	0	1		
Vaccine-related Serious Adverse Experiences	0	0		
Adverse Experiences Leading to Discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse experiences and systemic adverse experiences: up to 14 days after each vaccination; injection-site adverse experiences: up to 5 days after each vaccination

Assessment type	Systematic

Dictionary used

Dictionary name	WHOART
Dictionary version	2000Q4

Reporting groups

Reporting group title	Vaccine (GARDASIL™) Group

Reporting group description:

Participants received 0.5 mL intramuscular injection of GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

Reporting group title	Placebo Group

Reporting group description:

Participants received 0.5 mL intramuscular injection of placebo to GARDASIL™ on Day 1, Month 2, and Month 6. Immunogenicity was assessed on Day 1 and at Month 7 and safety was assessed through Month 7.

Serious adverse events	Vaccine (GARDASIL™) Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 302 (0.00%)	1 / 298 (0.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Acute suppurative tonsillitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.25 %

Non-serious adverse events	Vaccine (GARDASIL™) Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	260 / 302 (86.09%)	215 / 298 (72.15%)	
Nervous system disorders			

Headache			
subjects affected / exposed	16 / 302 (5.30%)	18 / 298 (6.04%)	
occurrences (all)	20	20	
General disorders and administration site conditions			
Allergic reaction			
subjects affected / exposed	8 / 302 (2.65%)	2 / 298 (0.67%)	
occurrences (all)	9	2	
Fatigue			
subjects affected / exposed	17 / 302 (5.63%)	22 / 298 (7.38%)	
occurrences (all)	24	25	
Fever			
subjects affected / exposed	71 / 302 (23.51%)	70 / 298 (23.49%)	
occurrences (all)	83	85	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 302 (2.98%)	10 / 298 (3.36%)	
occurrences (all)	11	10	
Nausea			
subjects affected / exposed	8 / 302 (2.65%)	12 / 298 (4.03%)	
occurrences (all)	9	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 302 (3.64%)	10 / 298 (3.36%)	
occurrences (all)	12	16	
Skin and subcutaneous tissue disorders			
Injection site redness			
subjects affected / exposed	3 / 302 (0.99%)	2 / 298 (0.67%)	
occurrences (all)	3	2	
Injection site pain			
subjects affected / exposed	61 / 302 (20.20%)	39 / 298 (13.09%)	
occurrences (all)	94	46	
Injection site induration			
subjects affected / exposed	6 / 302 (1.99%)	1 / 298 (0.34%)	
occurrences (all)	6	1	
Injection site swelling			

subjects affected / exposed	9 / 302 (2.98%)	2 / 298 (0.67%)	
occurrences (all)	9	3	
Injection site pruritus			
subjects affected / exposed	12 / 302 (3.97%)	2 / 298 (0.67%)	
occurrences (all)	16	3	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	11 / 302 (3.64%)	12 / 298 (4.03%)	
occurrences (all)	16	12	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	18 / 302 (5.96%)	13 / 298 (4.36%)	
occurrences (all)	21	14	

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