Clinical trial results:
A Randomized, Double-Blinded, Controlled with GARDASIL® (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase III Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescent and Adolescent Girls (9- to 15-year-olds)

Summary

EudraCT number	2010-023393-39
Trial protocol	FI BE SE ES DK IT
Global end of trial date	20 December 2011

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	GDS01C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01304498
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur MSD S.N.C.
Sponsor organisation address	162 avenue Jean Jaurès - CS 50712, Lyon Cedex 07, France, 69367
Public contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com
Scientific contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000654-PIP01-09
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	20 December 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2011
Global end of trial reached?	Yes
Global end of trial date	20 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that administration of the 9-valent HPV L1 VLP (9vHPV) vaccine induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 16 and anti-HPV 18 compared to GARDASIL® (qHPV) in preadolescent and adolescent girls 9 to 15 years of age.

Protection of trial subjects:

Healthy girls with known allergy to any vaccine component were excluded.
Vaccines were administered by qualified study personnel.
After each vaccination, subjects were kept under observation for at least 30 minutes to ensure their safety.

Background therapy: -

Evidence for comparator:

9vHPV vaccine (= V503) is a prophylactic 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine that is composed of VLPs of the 4 HPV types (Type 6, 11, 16, and 18) contained in qHPV vaccine (= GARDASIL®, a quadrivalent prophylactic HPV vaccine), plus the VLPs of 5 additional oncogenic HPV types (Types 31, 33, 45, 52, and 58).
qHPV vaccine has been approved by the European Medicines Agency (EMA) in September 2006 and is currently approved and marketed in over 100 countries.
This study was designed to provide a direct comparison of immunogenicity and safety/tolerability of the 9vHPV vaccine versus qHPV vaccine in preadolescent and adolescent girls, 9 to 15 years of age.

Actual start date of recruitment	23 February 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	Spain: 89
Country: Number of subjects enrolled	Sweden: 122
Country: Number of subjects enrolled	Belgium: 96
Country: Number of subjects enrolled	Denmark: 69
Country: Number of subjects enrolled	Finland: 150
Country: Number of subjects enrolled	Italy: 74
Worldwide total number of subjects	600
EEA total number of subjects	600

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)	246
Adolescents (12-17 years)	354
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled in 24 active centres in 6 European countries (Belgium, Denmark, Finland, Italy, Spain, and Sweden) between 23 February 2011 and 11 May 2011.

Pre-assignment

Screening details:

603 subjects were screened.
600 subjects were randomised.
592 subjects received all 3 doses of 9vHPV or qHPV vaccine.
589 subjects completed the study.

Period 1

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

Blinding implementation details:

Blinded vaccines had visually identical presentations and were presented in an indistinguishable packaging.
The subjects, investigators (and his/her staff), laboratory staff, and sponsor remained blinded to subject vaccine allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	9vHPV vaccine

Arm description:

Subjects received 3 doses of 9vHPV vaccine* by intramuscular (IM) route: dose 1 at Visit 1 (V1, Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks).
Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3.
*9vHPV vaccine = V503 = 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine (recombinant, absorbed)

Arm type	Experimental
Investigational medicinal product name	9-valent HPV VLP
Investigational medicinal product code	9vHPV
Other name	V503
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM route (deltoid muscle of the nondominant arm), 3 doses: dose 1 at V1 (Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks).

Arm title	qHPV vaccine

Arm description:

Subjects received 3 doses of qHPV vaccine* by intramuscular (IM) route: dose 1 at V1 (Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks).
Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3.
*qHPV vaccine = GARDASIL® = 4-valent HPV (Types 6, 11, 16 and 18) L1 virus-like particle (VLP) vaccine (Recombinant, absorbed)

Arm type	Active comparator

Investigational medicinal product name	GARDASIL®
Investigational medicinal product code	qHPV
Other name	SILGARD®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM route (deltoid muscle of the nondominant arm), 3 doses: dose 1 at V1 (Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks).

Number of subjects in period 1	9vHPV vaccine	qHPV vaccine
Started	300	300
Completed	294	295
Not completed	6	5
Consent withdrawn by subject	2	3
Adverse event, non-fatal	1	1
Lost to follow-up	2	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	9vHPV vaccine
Reporting group description:	
# Subjects received 3 doses of 9vHPV vaccine* by intramuscular (IM) route: dose 1 at Visit 1 (V1, Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks). # Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3. *9vHPV vaccine = V503 = 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine (recombinant, absorbed)	
Reporting group title	qHPV vaccine
Reporting group description:	
# Subjects received 3 doses of qHPV vaccine* by intramuscular (IM) route: dose 1 at V1 (Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks). # Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3. *qHPV vaccine = GARDASIL® = 4-valent HPV (Types 6, 11, 16 and 18) L1 virus-like particle (VLP) vaccine (Recombinant, absorbed)	

Reporting group values	9vHPV vaccine	qHPV vaccine	Total
Number of subjects	300	300	600
Age categorical Units: Subjects			
9-12 years old	150	150	300
13-15 years old	150	150	300
Age continuous			
Age at 1st dose			
Units: years			
arithmetic mean	12.6	12.6	
standard deviation	± 1.9	± 1.9	-
Gender categorical Units: Subjects			
Female	300	300	600

End points

End points reporting groups

Reporting group title	9vHPV vaccine
Reporting group description:	
# Subjects received 3 doses of 9vHPV vaccine* by intramuscular (IM) route: dose 1 at Visit 1 (V1, Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks). # Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3. *9vHPV vaccine = V503 = 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine (recombinant, absorbed)	
Reporting group title	qHPV vaccine
Reporting group description:	
# Subjects received 3 doses of qHPV vaccine* by intramuscular (IM) route: dose 1 at V1 (Day 1), dose 2 at V2 (2 months after Day 1, ±3 weeks), and dose 3 at V3 (6 months after Day 1, ±4 weeks). # Subjects were blood sampled (i) before vaccination (V1), and (ii) at V4, i.e., 3 to 7 weeks after V3 = Post-Dose 3. *qHPV vaccine = GARDASIL® = 4-valent HPV (Types 6, 11, 16 and 18) L1 virus-like particle (VLP) vaccine (Recombinant, absorbed)	

Primary: Non-inferiority of Geometric Mean Titres (GMTs) of anti-HPV types 16 and 18 antibodies (Abs) Post-Dose 3 (V4) of 9vHPV versus qHPV vaccine

End point title	Non-inferiority of Geometric Mean Titres (GMTs) of anti-HPV types 16 and 18 antibodies (Abs) Post-Dose 3 (V4) of 9vHPV versus qHPV vaccine
End point description:	
Anti-HPV types 16 and 18 Ab titres were measured by competitive Luminex ImmunoAssay (cLIA) 3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4). Ab titres are expressed in milli Merck units (mMU)/mL. Analysis was done on the HPV specific Per Protocol Sets (PPS), i.e., subjects who received all 3 vaccinations, and seronegative to the relevant HPV type at Day 1, excluding those with protocol deviation which could interfere with the immunogenicity evaluation. Note: (N=***, ***) represents the number of assessed subjects in the "9vHPV vaccine" and "qHPV vaccine" groups, respectively.	
End point type	Primary
End point timeframe:	
3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).	

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	270		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-HPV 16 GMT (N=276, 270)	6739.5 (6134.5 to 7404.1)	6887.4 (6220.8 to 7625.5)		
Anti-HPV 18 GMT (N=276, 269)	1956.6 (1737.3 to 2203.7)	1795.6 (1567.2 to 2057.3)		

Statistical analyses

Statistical analysis title	Non-inferiority for HPV 16

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 16 was calculated with its P-value and its 2-sided 95% confidence interval (CI) using an ANOVA model including group and age stratum as independent variables.
If the lower bound of the 95% CI was greater than 0.67 (i.e., the non-inferiority margin), it was concluded that 9vHPV GMT was non-inferior to qHPV GMT.
Analysis was done on the HPV 16 specific PPS. N= 546 (9vHPV vaccine: 276, qHPV vaccine: 270).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	546
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.11

Statistical analysis title	Non-inferiority for HPV 18

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 18 was calculated with its P-value and its 2-sided 95% confidence interval (CI) using an ANOVA model including group and age stratum as independent variables.
If the lower bound of the 95% CI was greater than 0.67 (i.e., the non-inferiority margin), it was concluded that 9vHPV GMT was non-inferior to qHPV GMT.
Analysis was done on the HPV 18 specific PPS. N= 545 (9vHPV vaccine: 276, qHPV vaccine: 269).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	546
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.29

Secondary: Comparison of GMTs of anti-HPV types 6 and 11 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point title	Comparison of GMTs of anti-HPV types 6 and 11 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point description:

Anti-HPV types 6 and 11 Ab titres were measured by cLIA 3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).
Ab titres are expressed in mMU/mL.
Analysis was done on the HPV specific Per Protocol Sets (PPS), i.e., subjects who received all 3 vaccinations, and seronegative to the relevant HPV type at Day 1, excluding those with protocol deviation which could interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "9vHPV vaccine" and "qHPV vaccine" groups, respectively.

End point type	Secondary

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	261		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-HPV 6 GMT (N=273, 261)	1679.4 (1518.9 to 1856.9)	1565.9 (1412.2 to 1736.3)		
Anti-HPV 11 GMT (N=273, 261)	1315.6 (1183.8 to 1462)	1417.3 (1274.2 to 1576.5)		

Statistical analyses

Statistical analysis title	9vHPV/qHPV GMT ratio for HPV 6

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 6 was calculated with its 2-sided 95% confidence interval (CI) using an ANOVA model including group and age stratum as independent variables.
Analysis was done on the HPV 6 specific PPS. N= 534 (9vHPV vaccine: 273, qHPV vaccine: 261).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.23

Statistical analysis title	9vHPV/qHPV GMT ratio for HPV 11

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 11 was calculated with its 2-sided 95% confidence interval (CI) using an ANOVA model including group and age stratum as independent variables.
Analysis was done on the HPV 11 specific PPS. N= 534 (9vHPV vaccine: 273, qHPV vaccine: 261).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.08

Secondary: Seroconversion rates for anti-HPV types 6, 11, 16, and 18 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point title	Seroconversion rates for anti-HPV types 6, 11, 16, and 18 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point description:

The seroconversion rates to HPV types 6, 11, 16, and 18 defined as Ab titres ≥30 mMU/mL for anti-HPV 6, ≥16 mMU/mL for anti-HPV 11, ≥20 mMU/mL for anti-HPV 16, and ≥24 mMU/mL for anti-HPV 18 were determined 3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).
Ab titres were measured by cLIA.
Analysis was done on the HPV specific Per Protocol Sets (PPS), i.e., subjects who received all 3 vaccinations, and seronegative to the relevant HPV type at Day 1, excluding those with protocol deviation which could interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "9vHPV vaccine" and "qHPV vaccine" groups, respectively.

End point type	Secondary

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	270		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-HPV 6 ≥30 mMU/mL (N=273, 261)	100 (98.7 to 100)	100 (98.6 to 100)		
Anti-HPV 11 ≥16 mMU/mL (N=273, 261)	100 (98.7 to 100)	100 (98.6 to 100)		
Anti-HPV 16 ≥20 mMU/mL (N=276, 270)	100 (98.7 to 100)	100 (98.6 to 100)		
Anti-HPV 18 ≥24 mMU/mL (N=276, 269)	100 (98.7 to 100)	100 (98.6 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global summary of safety from D1 to D15 after any vaccination (3 doses of 9vHPV or qHPV)

End point title	Global summary of safety from D1 to D15 after any vaccination (3 doses of 9vHPV or qHPV)

End point description:

Adverse events (AEs) were recorded as follows.
1/ From D1 to D5 after each vaccination: # oral temperature ≥37.8°C, # solicited (erythema, pain, and swelling at injection-site) and # other injection-site adverse reactions (ISRs).
2/ From D1 to D15 after each vaccination: systemic AEs.
AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.
The percentage of subjects presenting at least once the considered events after any vaccination is reported hereafter.
Analyses following any doses were based on the vaccines corresponding to the highest number of doses received by the subject.
Analysis was done on the Safety Set, i.e., all subjects who received at least 1 dose of the study vaccines and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D15 after any vaccination (3 doses of 9vHPV or qHPV).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Percentage of subjects				
number (not applicable)				
At least 1 AE (D1-D15)	96	93.7		
At least 1 vaccine-related AE (D1-D15)	93.3	90.3		
At least 1 ISR (D1-D5)	91.6	88.3		
At least 1 solicited ISR (D1-D5)	91.6	88.3		
At least 1 other ISR (D1-D5)	11.7	14		
At least 1 systemic AE (D1-D15)	47.5	52		

At least 1 vaccine-related systemic AE (D1-D15)	20.7	24.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting ISRs from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV)

End point title	Percentage of subjects reporting ISRs from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV)

End point description:

The percentage of subjects presenting at least once solicited (erythema, pain, and swelling) or other ISRs from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV) is reported hereafter.
AEs at injection-site were always considered as related to vaccine (ISRs).
Analyses following any doses were based on the vaccines corresponding to the highest number of doses received by the subject.
Analysis was done on the Safety Set, i.e., all subjects who received at least 1 dose of the study vaccines and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D5 after any vaccination (3 doses of 9vHPV or qHPV).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Percentage of subjects				
number (not applicable)				
Solicited injection-site erythema	34.1	29.3		
Solicited injection-site pain	89.3	88.3		
Solicited injection-site swelling	47.8	36		
Unsolicited injection-site haematoma	3.7	4.7		
Unsolicited injection-site pruritus	4	2.7		
Unsolicited injection-site haemorrhage	1	2		
Unsolicited injection-site induration	2	1		
Unsolicited injection-site warmth	0.7	1.7		
Unsolicited injection-site reaction	0.3	1		
Unsolicited injection-site discomfort	0.7	0.3		
Unsolicited injection-site paraesthesia	0.3	0.7		
Unsolicited injection-site discolouration	0.3	0.3		
Unsolicited injection-site lymphadenopathy	0.3	0.3		
Unsolicited injection-site nodule	0.3	0.3		
Unsolicited injection-site papule	0	0.7		
Unsolicited injection-site rash	0	0.7		
Unsolicited injection-site movement impairment	0	0.3		
Unsolicited injection-site scar	0	0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting oral temperature [37.8°C-38.9°C[or [38.9°C-39.9°C[from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV)

End point title	Percentage of subjects reporting oral temperature [37.8°C-38.9°C[or [38.9°C-39.9°C[from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV)

End point description:

Maximum oral temperatures recorded daily were reported from D1 to D5 after any vaccination (3 doses of 9vHPV or qHPV).
The percentage of subjects presenting at least once oral temperature [37.8°C-38.9°C[or [38.9°C-39.9°C[is presented hereafter.
Analyses following any doses were based on the vaccines corresponding to the highest number of doses received by the subject.
Analysis was done on the Safety Set, i.e., all subjects who received at least 1 dose of the study vaccines and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D5 after any vaccination (3 doses of 9vHPV or qHPV).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	300		
Units: Percentage of subjects				
number (not applicable)				
Oral temperature [37.8°C-38.9°C[	5.4	2.7		
Oral temperature [38.9°C-39.9°C[	1.3	0.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: GMTs of anti-HPV types 31, 33, 45, 52, and 58 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point title	GMTs of anti-HPV types 31, 33, 45, 52, and 58 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point description:

Anti-HPV types 31, 33, 45, 52, and 58 Ab titres were measured by cLIA 3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).
Ab titres are expressed in mMU/mL.
Analysis was done on the HPV specific Per Protocol Sets (PPS), i.e., subjects who received all 3 vaccinations, and seronegative to the relevant HPV type at Day 1, excluding those with protocol

deviation which could interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "9vHPV vaccine" and "qHPV vaccine" groups, respectively.

End point type	Other pre-specified

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	271		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-HPV 31 GMT (N=276, 268)	1770.4 (1585.7 to 1976.6)	22.2 (18.9 to 26.1)		
Anti-HPV 33 GMT (N=275, 269)	937.1 (845.3 to 1038.9)	4 (3.6 to 4.5)		
Anti-HPV 45 GMT (N=275, 271)	622.4 (545.4 to 710.2)	3.2 (2.8 to 3.6)		
Anti-HPV 52 GMT (N=276, 269)	927.3 (837.5 to 1026.9)	1.9 (1.8 to 2.1)		
Anti-HPV 58 GMT (N=267, 261)	1348.8 (1218.3 to 1493.2)	9.4 (8.1 to 10.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Seroconversion rates for anti-HPV types 31, 33, 45, 52, and 58 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point title	Seroconversion rates for anti-HPV types 31, 33, 45, 52, and 58 Abs Post-Dose 3 (V4) of 9vHPV or qHPV vaccine

End point description:

The seroconversion rates to HPV types 31, 33, 45, 52, and 58 defined as Ab titres ≥10 mMU/mL for anti-HPV 31, and ≥8 mMU/mL for anti-HPV 33, 45, 52, and 58 were determined 3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).
Ab titres were measured by cLIA.
Analysis was done on the HPV specific Per Protocol Sets (PPS), i.e., subjects who received all 3 vaccinations, and seronegative to the relevant HPV type at Day 1, excluding those with protocol deviation which could interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "9vHPV vaccine" and "qHPV vaccine" groups, respectively.

End point type	Other pre-specified

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV or qHPV vaccine (V4).

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	271		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-HPV 31 ≥10 mMU/mL (N=276, 268)	100 (98.7 to 100)	73.5 (67.8 to 78.7)		
Anti-HPV 33 ≥8 mMU/mL (N=275, 269)	100 (98.7 to 100)	20.4 (15.8 to 25.8)		
Anti-HPV 45 ≥8 mMU/mL (N=275, 271)	99.6 (98 to 100)	21 (16.3 to 26.4)		
Anti-HPV 52 ≥8 mMU/mL (N=276, 269)	100 (98.7 to 100)	3.3 (1.5 to 6.3)		
Anti-HPV 58 ≥8 mMU/mL (N=267, 261)	100 (98.6 to 100)	54.8 (48.5 to 60.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Systemic adverse events (AEs) were collected from D1 to D15 after each dose of 9vHPV or qHPV vaccine.
Serious AEs and deaths were collected throughout the study.

Adverse event reporting additional description:

Analysis of AEs was done on the Safety Set, i.e., all subjects who received at least 1 dose of the study vaccines and who had safety follow-up data.
Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence ≥1% are presented hereafter.
None of the serious AEs were vaccine-related.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	9vHPV vaccine

Reporting group description:

Subjects received 3 doses of 9vHPV vaccine (V503) by IM route: dose 1 at Visit 1 (Day 1), dose 2 at Visit 2 (2 months after Day 1, ±3 weeks), and dose 3 at Visit 3 (6 months after Day 1, ±4 weeks).
Respectively, 142 (47.5%) subjects reported at least 1 unsolicited systemic AE, and 62 (20.7%) subjects reported at least 1 vaccine-related unsolicited systemic AE within 15 days after any vaccination (3 doses of 9vHPV vaccine).

Reporting group title	qHPV vaccine

Reporting group description:

Subjects received 3 doses of qHPV vaccine (GARDASIL®) by IM route: dose 1 at Visit 1 (Day 1), dose 2 at Visit 2 (2 months after Day 1, ±3 weeks), and dose 3 at Visit 3 (6 months after Day 1, ±4 weeks).
Respectively, 156 (52.0%) subjects reported at least 1 unsolicited systemic AE, and 73 (24.3%) subjects reported at least 1 vaccine-related unsolicited systemic AE within 15 days after any vaccination (3 doses of qHPV vaccine).

Serious adverse events	9vHPV vaccine	qHPV vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 299 (0.33%)	2 / 300 (0.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Partial complex epilepsy	Additional description: Event of severe intensity that occurred 36 days after qHPV vaccine dose 1. This subject received the 2 other doses of qHPV vaccine without experiencing further adverse event.		
subjects affected / exposed	0 / 299 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Event of moderate intensity diagnosed approximately 2 months after 9vHPV vaccine dose 2, experienced by the same subject who experienced pulmonary vasculitis.		

subjects affected / exposed	1 / 299 (0.33%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary vasculitis	Additional description: Event of moderate intensity diagnosed approximately 2 months after 9vHPV vaccine dose 2, experienced by the same subject who experienced anaemia.		
subjects affected / exposed	1 / 299 (0.33%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura	Additional description: Event of moderate intensity that occurred 46 days after qHPV vaccine dose 2.		
subjects affected / exposed	0 / 299 (0.00%)	1 / 300 (0.33%)	
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 %

Non-serious adverse events	9vHPV vaccine	qHPV vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 299 (47.49%)	156 / 300 (52.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	57 / 299 (19.06%)	57 / 300 (19.00%)	
occurrences (all)	84	93	
Dizziness			
subjects affected / exposed	4 / 299 (1.34%)	7 / 300 (2.33%)	
occurrences (all)	4	7	
Syncope			
subjects affected / exposed	2 / 299 (0.67%)	3 / 300 (1.00%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 299 (7.36%)	17 / 300 (5.67%)	
occurrences (all)	23	17	
Fatigue			

subjects affected / exposed	1 / 299 (0.33%)	10 / 300 (3.33%)	
occurrences (all)	1	12	
Malaise			
subjects affected / exposed	4 / 299 (1.34%)	2 / 300 (0.67%)	
occurrences (all)	4	2	
Feeling cold			
subjects affected / exposed	2 / 299 (0.67%)	3 / 300 (1.00%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 299 (5.35%)	16 / 300 (5.33%)	
occurrences (all)	17	17	
Abdominal pain upper			
subjects affected / exposed	11 / 299 (3.68%)	12 / 300 (4.00%)	
occurrences (all)	12	17	
Abdominal pain			
subjects affected / exposed	4 / 299 (1.34%)	4 / 300 (1.33%)	
occurrences (all)	5	4	
Diarrhoea			
subjects affected / exposed	4 / 299 (1.34%)	3 / 300 (1.00%)	
occurrences (all)	4	3	
Vomiting			
subjects affected / exposed	3 / 299 (1.00%)	3 / 300 (1.00%)	
occurrences (all)	3	3	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	9 / 299 (3.01%)	12 / 300 (4.00%)	
occurrences (all)	11	15	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	16 / 299 (5.35%)	17 / 300 (5.67%)	
occurrences (all)	17	18	
Cough			
subjects affected / exposed	9 / 299 (3.01%)	4 / 300 (1.33%)	
occurrences (all)	9	4	
Skin and subcutaneous tissue disorders			

Urticaria			
subjects affected / exposed	2 / 299 (0.67%)	3 / 300 (1.00%)	
occurrences (all)	2	3	
Eczema			
subjects affected / exposed	1 / 299 (0.33%)	3 / 300 (1.00%)	
occurrences (all)	1	6	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	4 / 299 (1.34%)	2 / 300 (0.67%)	
occurrences (all)	4	2	
Myalgia			
subjects affected / exposed	3 / 299 (1.00%)	2 / 300 (0.67%)	
occurrences (all)	4	2	
Pain in extremity			
subjects affected / exposed	3 / 299 (1.00%)	1 / 300 (0.33%)	
occurrences (all)	3	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 299 (1.67%)	16 / 300 (5.33%)	
occurrences (all)	7	18	
Upper respiratory tract infection			
subjects affected / exposed	9 / 299 (3.01%)	11 / 300 (3.67%)	
occurrences (all)	10	13	
Rhinitis			
subjects affected / exposed	3 / 299 (1.00%)	5 / 300 (1.67%)	
occurrences (all)	3	5	
Gastroenteritis			
subjects affected / exposed	1 / 299 (0.33%)	5 / 300 (1.67%)	
occurrences (all)	1	5	
Pharyngitis			
subjects affected / exposed	2 / 299 (0.67%)	3 / 300 (1.00%)	
occurrences (all)	2	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