Clinical trial results:
A Randomized, Double-Blinded, Controlled with GARDASIL® (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase 3 Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in 16- to 26-year-old men.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-003399-10
Trial protocol	DE BE NL
Global end of trial date	22 April 2015

Results information

Result version number	v1 (current)
This version publication date	23 April 2016
First version publication date	23 April 2016

Trial information

Trial identification

Sponsor protocol code	GDS07C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02114385
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)	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	22 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2015
Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that administration of the 9-valent HPV L1 VLP (9vHPV) vaccine induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 6, 11, 16, and 18, compared to GARDASIL® (qHPV) in 16- to 26-year-old men.

Protection of trial subjects:

Healthy men 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 (Types 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 tolerability of the 9vHPV vaccine versus qHPV vaccine in young men, 16 to 26 years of age.

Actual start date of recruitment	24 March 2014
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	Netherlands: 155
Country: Number of subjects enrolled	Belgium: 276
Country: Number of subjects enrolled	Germany: 69
Worldwide total number of subjects	500
EEA total number of subjects	500

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)	75
Adults (18-64 years)	425
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled in 7 active centres in 3 European countries (Belgium, Germany, and The Netherlands) between 24 March 2014 and 17 September 2014.

Pre-assignment

Screening details:

502 subjects were screened.
500 subjects were randomised.
490 subjects received all 3 doses of 9vHPV or qHPV vaccine.
489 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 were presented in the same sealed outer packaging.
The subjects, investigators (and his/her staff), laboratory staff, and the 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, GARDASIL®9
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	249	251
Completed	246	243
Not completed	3	8
Consent withdrawn by subject	3	2
Lost to follow-up	-	6

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	249	251	500
Age categorical Units: Subjects			
16-17 years old	37	38	75
18-26 years old	212	213	425
Age continuous			
Age at 1st dose			
Units: years			
arithmetic mean	20.8	21.3	
standard deviation	± 2.7	± 3	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	249	251	500

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 6, 11, 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 6, 11, 16 and 18 antibodies (Abs) Post-Dose 3 (V4) of 9vHPV versus qHPV vaccine
End point description:	
Anti-HPV types 6, 11, 16 and 18 Ab titres were measured by competitive Luminex ImmunoAssay (cLIA) 3 to 7 weeks Post-Dose 3 of 9vHPV versus 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", respectively.	
End point type	Primary
End point timeframe:	
3 to 7 weeks Post-Dose 3 of 9vHPV versus qHPV vaccine.	

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	237		
Units: mMU/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 6 GMT (N=228, 226)	758.3 (665.9 to 863.4)	618.4 (554 to 690.3)		
Anti-HPV 11 GMT (N=228, 226)	681.7 (608.9 to 763.4)	769.1 (683.5 to 865.3)		
Anti-HPV 16 GMT (N=234, 237)	3924.1 (3513.8 to 4382.3)	3787.9 (3378.4 to 4247)		

Anti-HPV 18 GMT (N=234, 236)	884.3 (766.4 to 1020.4)	790.9 (683 to 915.7)		

Statistical analyses

Statistical analysis title	Non-inferiority for HPV 6

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 6 was calculated with its P-value and its 2-sided 95% confidence interval (CI) using an ANOVA model including group and age strata as independent variables.
If the lower bound of the 95% CI was greater than 0.5 (i.e., the non-inferiority margin), it was concluded that 9vHPV GMT was non-inferior to qHPV GMT.
Analysis was done on the HPV 6 specific PPS. N= 454 (9vHPV vaccine: 228, qHPV vaccine: 226).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.45

Statistical analysis title	Non-inferiority for HPV 11

Statistical analysis description:

The estimate of the 9vHPV vaccine/qHPV vaccine GMT ratio for HPV 11 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 0.5 (i.e., the non-inferiority margin), it was concluded that 9vHPV GMT was non-inferior to qHPV GMT.
Analysis was done on the HPV 11 specific PPS. N= 454 (9vHPV vaccine: 228, qHPV vaccine: 226).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.04

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 0.5 (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= 471 (9vHPV vaccine: 234, qHPV vaccine: 237).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.21

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 0.5 (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= 470 (9vHPV vaccine: 234, qHPV vaccine: 236).

Comparison groups	9vHPV vaccine v qHPV vaccine
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.37

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 versus qHPV vaccine.

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	237		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-HPV 6 ≥30 mMU/mL (N=228, 226)	98.2 (95.6 to 99.5)	98.7 (96.2 to 99.7)		
Anti-HPV 11 ≥16 mMU/mL (N=228, 226)	100 (98.4 to 100)	100 (98.4 to 100)		
Anti-HPV 16 ≥20 mMU/mL (N=234, 237)	100 (98.4 to 100)	100 (98.5 to 100)		
Anti-HPV 18 ≥24 mMU/mL (N=234, 236)	99.6 (97.6 to 100)	99.6 (97.7 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 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	Secondary

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV versus qHPV vaccine.

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: mMU/mL				
geometric mean (confidence interval 95%)				
Anti-HPV 31 GMT (N=234, 237)	794.4 (694.2 to 909.2)	14.8 (12.5 to 17.5)		
Anti-HPV 33 GMT (N=236, 236)	460.5 (410.6 to 516.4)	3.4 (3.1 to 3.7)		
Anti-HPV 45 GMT (N=232, 236)	262.9 (226.2 to 305.5)	2.5 (2.3 to 2.8)		
Anti-HPV 52 GMT (N=235, 236)	430.7 (377.8 to 491)	1.9 (1.8 to 2.1)		
Anti-HPV 58 GMT (N=232, 233)	691 (614.9 to 776.5)	5.7 (5 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: 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, anti-HPV 45, anti-HPV 52, and anti HPV 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	Secondary

End point timeframe:

3 to 7 weeks Post-Dose 3 of 9vHPV versus qHPV vaccine.

End point values	9vHPV vaccine	qHPV vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-HPV 31 ≥10 mMU/mL (N=234, 237)	100 (98.4 to 100)	61.6 (55.1 to 67.8)		

Anti-HPV 33 ≥8 mMU/mL (N=236, 236)	100 (98.4 to 100)	16.9 (12.4 to 22.4)		
Anti-HPV 45 ≥8 mMU/mL (N=232, 236)	100 (98.4 to 100)	9.3 (5.9 to 13.8)		
Anti-HPV 52 ≥8 mMU/mL (N=235, 236)	100 (98.4 to 100)	2.5 (0.9 to 5.5)		
Anti-HPV 58 ≥8 mMU/mL (N=232, 233)	100 (98.4 to 100)	36.1 (29.9 to 42.6)		

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 Analysis 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	248	248		
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 AE (D1-D15)	82.3 (76.9 to 86.8)	81.9 (76.5 to 86.4)		
At least 1 vaccine-related AE (D1-D15)	81.5 (76 to 86.1)	79 (73.4 to 83.9)		
At least 1 ISR (D1-D5)	79 (73.4 to 83.9)	72.2 (66.2 to 77.7)		
At least 1 solicited ISR (D1-D5)	78.6 (73 to 83.6)	71.4 (65.3 to 76.9)		
At least 1 other ISR (D1-D5)	9.7 (6.3 to 14.1)	9.3 (6 to 13.6)		
At least 1 severe ISR (D1-D5)	1.2 (0.3 to 3.5)	1.6 (0.4 to 4.1)		
At least 1 systemic AE (D1-D15)	40.7 (34.6 to 47.1)	40.3 (34.2 to 46.7)		

At least 1 vaccine-related systemic AE (D1-D15)	23 (17.9 to 28.7)	21.8 (16.8 to 27.4)		

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 Analysis 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	248	248		
Units: Percentage of subjects				
number (not applicable)				
Solicited injection-site erythema	15.3	17.3		
Solicited injection-site swelling	14.5	9.3		
Solicited injection-site pain	77.8	70.2		
Unsolicited injection-site movement impairment	2	3.6		
Unsolicited injection-site induration	1.6	2.4		
Unsolicited injection-site pruritus	1.6	2		
Unsolicited injection-site haematoma	1.6	0.8		
Unsolicited injection-site haemorrhage	0.8	0.4		
Unsolicited injection-site bruising	0.4	0.4		
Unsolicited injection-site joint pain	0.4	0.4		
Unsolicited injection-site reaction	0	0.8		
Unsolicited injection-site lymphadenopathy	0.4	0		
Unsolicited injection-site paraesthesia	0.4	0		
Unsolicited injection-site urticaria	0.4	0		
Unsolicited injection-site warmth	0.4	0		

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 temperature [37.8°C-38.9°C[and [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 Analysis 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	248	248		
Units: Percentage of subjects				
number (not applicable)				
Oral temperature [37.8°C-38.9°C[	2.8	2		
Oral temperature [38.9°C-39.9°C[	0	0.4		

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 Analysis 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	17.1

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, 101 (40.7%) subjects reported at least 1 unsolicited systemic AE, and 57 (23%) 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, 100 (40.3%) subjects reported at least 1 unsolicited systemic AE, and 54 (21.8%) 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	0 / 248 (0.00%)	6 / 248 (2.42%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
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	101 / 248 (40.73%)	100 / 248 (40.32%)	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 248 (11.69%)	37 / 248 (14.92%)	
occurrences (all)	43	51	
Dizziness			
subjects affected / exposed	5 / 248 (2.02%)	1 / 248 (0.40%)	
occurrences (all)	5	1	
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	6 / 248 (2.42%)	0 / 248 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 248 (3.63%)	8 / 248 (3.23%)	
occurrences (all)	12	11	
Fatigue			
subjects affected / exposed	8 / 248 (3.23%)	9 / 248 (3.63%)	
occurrences (all)	8	9	
Hangover			
subjects affected / exposed	1 / 248 (0.40%)	5 / 248 (2.02%)	
occurrences (all)	1	8	
Influenza like illness			
subjects affected / exposed	3 / 248 (1.21%)	2 / 248 (0.81%)	
occurrences (all)	4	2	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 248 (1.21%)	1 / 248 (0.40%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 248 (2.82%)	12 / 248 (4.84%)	
occurrences (all)	8	12	
Nausea			
subjects affected / exposed	6 / 248 (2.42%)	5 / 248 (2.02%)	
occurrences (all)	7	7	
Abdominal pain upper			
subjects affected / exposed	3 / 248 (1.21%)	2 / 248 (0.81%)	
occurrences (all)	3	3	
Abdominal pain			
subjects affected / exposed	3 / 248 (1.21%)	1 / 248 (0.40%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed	8 / 248 (3.23%)	9 / 248 (3.63%)	
occurrences (all)	8	10	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	3 / 248 (1.21%)	0 / 248 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	5 / 248 (2.02%)	2 / 248 (0.81%)	
occurrences (all)	5	2	
Musculoskeletal stiffness			
subjects affected / exposed	3 / 248 (1.21%)	2 / 248 (0.81%)	
occurrences (all)	4	2	
Pain in extremity			
subjects affected / exposed	3 / 248 (1.21%)	1 / 248 (0.40%)	
occurrences (all)	4	1	
Back pain			
subjects affected / exposed	3 / 248 (1.21%)	0 / 248 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 248 (4.44%)	14 / 248 (5.65%)	
occurrences (all)	13	16	
Upper respiratory tract infection			
subjects affected / exposed	3 / 248 (1.21%)	7 / 248 (2.82%)	
occurrences (all)	4	7	
Rhinitis			
subjects affected / exposed	5 / 248 (2.02%)	4 / 248 (1.61%)	
occurrences (all)	5	5	
Gastroenteritis			
subjects affected / exposed	4 / 248 (1.61%)	4 / 248 (1.61%)	
occurrences (all)	4	4	
Influenza			
subjects affected / exposed	2 / 248 (0.81%)	3 / 248 (1.21%)	
occurrences (all)	2	3	
Oral herpes			

subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 3	1 / 248 (0.40%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2014	Country-specific protocol amendment for the Netherlands: - at the EC's request, the withdrawal criteria were clarified to specify that subjects could be withdrawn for any event likely to affect the safety of the subject, or any serious GCP issue (previously "administrative reasons"), - the phone number for immediate reporting of adverse events was corrected, - the instructions to Investigators for immediate reporting of adverse events were clarified, - reporting of medical errors to the Sponsor was added.
04 March 2014	Country-specific protocol amendment for Germany: - the address for the Sponsor Sanofi Pasteur MSD was updated, as their offices had moved, - the Coordinating Investigator and instructions for immediate reporting of adverse events for France were removed, as the clinical trial application was withdrawn in France, - a justification of the choice of non-inferiority margin was added to the statistical methods and the sample size and power calculations section.
31 March 2014	Protocol amendment applicable to all countries: Same as Protocol Amendment 2 (issued on 4 March 2014) which was only applicable to Germany.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported