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Key words: human papillomavirus (HPV), vaccine, safety, male, adult, adolescent

Background: Prophylactic vaccination with a quadrivalent HPV (types 6, 11, 16, 18) vaccine (qHPV) has been shown to prevent infection with HPV 6/11/16/18 and associated disease in women and more recently, in men. Here we report on the safety and reactogenicity of the qHPV vaccine in males. A total of 4,065 healthy males aged 16–26 years were enrolled into a randomized, placebo-controlled, double-blind trial. Subjects were randomized 1:1 to receive qHPV vaccine or placebo at day 1, month 2 and month 6. Safety and tolerability were assessed via the collection of reported adverse experiences (AEs). All serious AEs (vaccine- or procedure-related or not) and all deaths occurring during the study were recorded. Safety analyses were conducted in all subjects who received at least one dose of vaccine or placebo. The proportion of subjects who reported at least one injection-site AE was higher in the qHPV vaccine group versus the placebo group (60.1% vs. 53.7%, respectively), however most of these AEs were mild/moderate in intensity. The incidence of at least one systemic AE was comparable between the vaccine and placebo groups (31.7% vs. 31.4%, respectively). There were no vaccine-related serious AEs or deaths. The occurrence of AEs did not increase with each successive injection, and among trial participants who were seropositive for at least one vaccine HPV type at enrollment, the profile of adverse events was similar to that of the entire study cohort. The qHPV vaccine was generally well tolerated in males aged 16–26 years and had a favorable safety profile.

Introduction

Infection with human papillomaviruses (HPVs) is common; the lifetime risk of becoming infected with HPV exceeds 50%.[1] Approximately 35–40 HPV types are capable of infecting the genital epithelium, although not all of these types are oncogenic. While HPV infections can be transient in nature and largely clinically inapparent, HPV infection can also result in genital warts[2] and a variety of premalignant and malignant anogenital lesions in both males[2,3] and females.[4-7] The epidemiology of genital HPV infection in men is likely similar to that of women. In a 12-month period, the probability of acquiring a new genital HPV infection in men is estimated to be between 0.29–0.39;[13-15] comparable to estimates reported for women. The duration of genital HPV infection in men appears similar to that of females, with approximately 70% of both sexes clearing infections in a 12-month period.[16]

Two large pivotal clinical trials have demonstrated that a prophylactic quadrivalent HPV (qHPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine was highly effective in preventing HPV 6, 11, 16 or 18-related cervical, vulvar or vaginal intraepithelial neoplasia, as well as adenocarcinoma in situ in females aged 16 to 26.[17,18] These trials have also shown that the qHPV vaccine is generally well tolerated in young women,[17,18] although a slightly higher occurrence of overall adverse experiences (AEs) and vaccine-related AEs were reported by those receiving the qHPV vaccine when compared with placebo. This is largely due to the higher incidence of overall and vaccine-related injection-site AEs reported by vaccinees. Combined data from both key clinical trials in women 16–26 years old show that

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Table 1A. Summary of adverse experiences among all subjects during days 1–15 following vaccination

	qHPV (N = 2020)		Placebo (N = 2029)		Risk difference qHPV-placebo	95% confidence interval	p value[§]
	n	(%)	n	(%)			
Subjects in analysis population	2020		2029				
Subjects with follow-up	1945		1950				
Number (%) of subjects:							
with no adverse experience	600	(30.8)	706	(36.2)			
with one or more adverse experiences	1345	(69.2)	1244	(63.8)	5.357	(2.39, 8.32)	<0.001
injection-site adverse experiences	1169	(60.1)	1047	(53.7)	6.411	(3.30, 9.51)	<0.001
systemic adverse experiences	616	(31.7)	613	(31.4)	0.235	(-2.69, 3.16)	0.875
with vaccine-related* adverse experiences	1242	(63.9)	1134	(58.2)	5.702	(2.63, 8.76)	<0.001
injection-site adverse experiences	1169	(60.1)	1046	(53.6)	6.462	(3.35, 9.56)	<0.001
systemic adverse experiences	275	(14.1)	283	(14.5)	-0.374	(-2.58, 1.83)	0.739
with serious adverse experiences[†]	5	(0.3)	1	(0.1)	0.206	(-0.06, 0.56)	0.102
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000
who died	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000
discontinued[‡] due to an adverse experience	2	(0.1)	4	(0.2)	-0.102	(-0.44, 0.20)	0.416
discontinued due to a vaccine-related adverse experience	2	(0.1)	3	(0.2)	-0.051	(-0.36, 0.24)	0.657
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000

*Determined by the investigator to be possibly, probably, or definitely related to the vaccine. †1 subject enrolled more than once and was excluded from this table. ‡Discontinued = Subject discontinued from therapy. §p-values are unadjusted for multiple comparisons.

pain at the injection site was the most common AE, reported by 83.9% of vaccine recipients and 75.4% of aluminum-containing placebo recipients within 5 days after receiving an injection.[19] Mild to moderate swelling and erythema were also reported more frequently among qHPV recipients when compared with placebo recipients. Importantly, systemic AEs such as fever (≥100°F) and nausea (occurring 1–15 days after vaccination) were relatively rare and balanced between the vaccine and placebo groups; being reported by 10.3% and 4.2% of qHPV vaccine recipients and 8.6% and 4.1% of placebo recipients, respectively.

Recently, data from a large clinical study of the qHPV vaccine in males 16–26 years of age (protocol V501-020) showed that prophylactic administration of qHPV vaccine was highly efficacious in preventing HPV 6/11/16/18-related external genital lesions (EGLs).[20] The vaccine reduced the incidence of HPV 6/11/16/18-related EGLs by 90.4% (95% CI: 69.2, 98.1) in an HPV naïve population. Efficacy against condyloma acuminata (external genital warts) was high at 89.4% (95% CI: 65.5, 97.9). In addition, qHPV vaccine was efficacious against HPV 6/11/16/18-related persistent infection as well as DNA detection at one or more visits.

While this previous publication contained a brief overview of safety data gathered throughout the trial, a more thorough review of these data is warranted. Therefore, in the current report we analyze detailed data from protocol V501-020 in order to better characterize the safety and reactogenicity (i.e., the capacity to produce localized adverse reactions) of the qHPV vaccine in a population of males 16–26 years of age.

Results

A total of 4,065 men were enrolled. Ten subjects who were randomized in error and did not receive vaccination were excluded from the safety analyses. In addition, six subjects (five subjects who were randomized to receive qHPV vaccine and 1 subject who was randomized to receive placebo) received protocol non-compliant vaccination regimens (mixed regimens of vaccine and placebo) and were also excluded from the current report. A total of 4,049 males who received at least one dose of qHPV vaccine or placebo were included in this report. The safety profile of the qHPV vaccine was generally comparable in MSM and HM subjects; safety data are therefore presented for the overall study population.

Compliance in returning diary cards was high for vaccine and placebo groups, n = 1,945 (96.3%) and n = 1,950 (96.1%), respectively. On days 1–15 following vaccination the proportion of subjects who reported at least one clinical AE or at least one injection-site AE was slightly higher in the qHPV vaccine group than in the placebo group (69.2% vs. 63.8% and 60.1% vs. 53.7%, respectively; $p < 0.001$) (**Table 1A**). In addition, the proportion of subjects who reported at least one systemic AE was

Table 1B. Summary of adverse experiences among all subjects during the entire study period

	qHPV (N = 2020)		Placebo (N = 2029)		Risk difference qHPV-placebo	95% confidence interval	p-value[§]
	n	(%)	n	(%)			
Subjects in analysis population	2020		2029				
Subjects with follow-up	1945		1950				
Number (%) of subjects:							
with no adverse experience	599	(30.8)	698	(35.8)			
with one or more adverse experiences	1346	(69.2)	1252	(64.2)	4.998	(2.03, 7.95)	0.001
injection-site adverse experiences	1169	(60.1)	1047	(53.7)	6.411	(3.30, 9.51)	<0.001
systemic adverse experiences	617	(31.7)	622	(31.9)	-0.175	(-3.10, 2.76)	0.907
with vaccine-related* adverse experiences	1242	(63.9)	1134	(58.2)	5.702	(2.63, 8.76)	<0.001
injection-site adverse experiences	1169	(60.1)	1046	(53.6)	6.462	(3.35, 9.56)	<0.001
systemic adverse experiences	275	(14.1)	283	(14.5)	-0.374	(-2.58, 1.83)	0.739
with serious adverse experiences[†]	8	(0.4)	11	(0.6)	-0.153	(-0.65, 0.32)	0.494
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000
who died	3	(0.2)	10	(0.5)	-0.359	(-0.81, 0.01)	0.052
discontinued[‡] due to an adverse experience	5	(0.3)	14	(0.7)	-0.461	(-0.98, -0.02)	0.039
discontinued due to a vaccine-related adverse experience	2	(0.1)	3	(0.2)	-0.051	(-0.36, 0.24)	0.657
discontinued due to a serious adverse experience	3	(0.2)	10	(0.5)	-0.359	(-0.81, 0.01)	0.052
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(-0.20, 0.20)	1.000

*Determined by the investigator to be possibly, probably or definitely related to the vaccine. †Three subjects enrolled more than once and were excluded from this table. Serious adverse experiences in the qHPV vaccine group included appendicitis, cellulitis, non-cardiac chest pain, hypersensitivity (peanut allergy), chickenpox-related seizure, traffic accident (2-both resulted in death) and gun shot wound (resulted in death); serious adverse experiences in the placebo group included contusion related to traffic accident and the following cases of death: gun shot wound, 3; drug overdose, 2; suicide, 2; traffic accident, chemical poisoning and myocardial ischemia. Three additional subjects were considered to have serious adverse experiences as they received more than 3 doses of vaccine or placebo; none of these subjects reported adverse experiences after any of the injections they received. ‡Discontinued = Subject discontinued from therapy. §P-values are unadjusted for multiple comparisons.

generally comparable between the vaccine and placebo groups (31.7% vs. 31.4%, respectively) (**Table 1A**). As seen in **Table 1B**, AEs reported at any time during the study were comparable to those observed on days 1–15 following vaccination. Few subjects who received qHPV vaccine or placebo discontinued the study due to an AE (0.3% vs. 0.7%, respectively) (**Table 1B**). Five males in the vaccine group discontinued the trial or did not receive all three vaccinations; only two of the five men's reasons for discontinuation were deemed related to vaccination (malaise and headache). The other reasons included vertebral fracture, gun shot wound, traumatic brain injury and road traffic accident. Fourteen males in the placebo group discontinued the trial or did not receive all three vaccinations. There were no vaccine-related SAEs.

AE data following each injection of qHPV vaccine or placebo indicate that the occurrence of AEs did not increase with each successive injection (**Table 2**). After the first dose of qHPV vaccine 53.6% of subjects reported at least one AE. After doses 2 and 3 this number fell to 42.4% and 39.3%, respectively.

A total of 13 subjects died during the study (**Tables 1 and 2**). Causes of death for the 10 participants in the placebo group included accidental illicit drug overdose,[2] suicide,[2] motor vehicle accident, gun shot wound,[3] poisoning and ischemic heart disease. Causes of death for the three participants in the qHPV vaccine group included motor vehicle accident[2] and gun shot wound. None of the deaths were vaccine-related.

A summary of the number and percentage of subjects with injection-site AEs and fever within five days following any vaccination visit can be seen in **Table 3**. Vaccine recipients (59.9%) were more likely than placebo recipients (53.6%) to report injection-site AEs, the most common of these being pain at the site (risk difference, 6.4%; 95% CI 3.3 to 9.5). Injection-site erythema, swelling and pruritus were less common and similar proportions of vaccine and placebo recipients reported them. Among trial participants who were seropositive for one or more of the four HPV types at day 1, the profile of adverse events was similar to that of the entire study cohort (data not shown).

In **Table 4**, we provide a summary of the number and percentage of subjects who reported systemic clinical AEs by system organ class (incidence ≥1%) within 15 days following any vaccination visit. The percentage of subjects who reported one or more systemic AEs was comparable between the qHPV vaccine group

Table 2. Clinical adverse experience summary for days 1–15 following each vaccination

	After dose 1				After dose 2				After dose 3			
	qHPV		Placebo		qHPV		Placebo		qHPV		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2020		2029		1931		1928		1855		1845	
Subjects with follow-up	1945		1950		1860		1854		1806		1799	
Number (%) of subjects:												
With no adverse experiences	902	(46.4)	946	(48.5)	1071	(57.6)	1177	(63.5)	1097	(60.7)	1205	(67.0)
With one or more adverse experiences	1043	(53.6)	1004	(51.5)	789	(42.4)	677	(36.5)	709	(39.3)	594	(33.0)
Injection-site adverse experiences	863	(44.4)	813	(41.7)	698	(37.5)	558	(30.1)	628	(34.8)	500	(27.8)
Systemic adverse experiences	398	(20.5)	423	(21.7)	199	(10.7)	213	(11.5)	182	(10.1)	162	(9.0)
With vaccine-related† adverse experiences	924	(47.5)	877	(45.0)	738	(39.7)	611	(33.0)	653	(36.2)	538	(29.9)
Injection-site adverse experiences	862	(44.3)	812	(41.6)	698	(37.5)	558	(30.1)	628	(34.8)	500	(27.8)
Systemic adverse experiences	161	(8.3)	169	(8.7)	89	(4.8)	101	(5.4)	70	(3.9)	65	(3.6)
With serious adverse experiences	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.2)	1	(0.1)
With serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued‡ due to an adverse experience	2	(0.1)	1	(0.1)	0	(0.0)	3	(0.2)	0	(0.0)	0	(0.0)
Discontinued due to a vaccine-related adverse experience	2	(0.1)	1	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

†Determined by the investigator to be possibly, probably or definitely related to the vaccine. ‡Discontinued = Subject discontinued from therapy. Percentages are calculated based on the number of subjects with follow-up.

(31.7%) and the placebo group (31.4%). The most common individual clinical AEs reported was headache (9.2% in the vaccine group and 10.6% in the placebo group), followed by pyrexia oral temperature ≥37.8°C (100°F). The number of subjects who reported an oral temperature ≥37.8°C (100°F) was similar in the qHPV vaccine and placebo groups (6.2% vs. 6.4%, respectively).

The majority of both injection-site and systemic AEs were mild or moderate in intensity (as judged by maximum intensity rating) from days 1–15 following injection of qHPV vaccine or placebo (**Table 5A and B**). Approximately 80% and 50% of the reported injection-site and systemic AEs among qHPV recipients were mild in intensity, respectively.

The most common new medical conditions reported during the vaccination period (day 1 to month 7) were nasopharyngitis and pharyngitis. The proportion of subjects reporting new medical conditions during the vaccination period remained generally comparable between the vaccination groups (24.7% vs. 22.8% in the qHPV vaccine and placebo groups respectively) (data not shown). The most commonly reported new medical conditions during the follow-up (post month 7) period were upper respiratory infections and pharyngitis. The proportion of subjects reporting new medical conditions during follow-up remained generally comparable between the vaccination groups (28.2% vs. 30.0% in the vaccine and placebo groups respectively) (data not shown).

Discussion

We have shown that administration of qHPV vaccine was generally well-tolerated in males 16–26 years of age. The proportions of subjects who reported SAEs, or who discontinued due to an AE were low and comparable between vaccination groups. To ensure that this study would provide a high level of confidence in the safety and reactogenicity of the qHPV vaccine, we enrolled a diverse population of young males in several countries from different areas of the world. In addition, data on SAEs, whether considered vaccine-related or not, were collected for the entire follow-up period.

As anticipated, the most commonly reported AEs were injection site reactions; most of these AEs were mild or moderate in intensity. These local AEs were more common among subjects who received qHPV vaccine compared with placebo subjects. Injection site reactions in women receiving saline placebo in other qHPV trials were even less frequent (48.6%), this gradient suggests that the adjuvant may contribute to local reactogenicity.[21] This finding is consistent with those of other studies of inactivated or subunit vaccines.[22,23] However, most of these AEs were mild or moderate in intensity. In addition, the frequency of erythema, swelling and pruritus at the site of injection was comparable in both vaccine and placebo groups. Notably, there was no evidence that the incidence of these solicited local symptoms (or other clinical AEs) increased with each subsequent doses of

Table 3. Summary of specific injection-site adverse experiences (days 1–5 following any vaccination visit)

	qHPV vaccine (N = 2,020)		Placebo (N = 2,029)		Risk difference (qHPV vaccine-Placebo)	95% confidence interval
	n	(%)	n	(%)		
All subjects						
Number of subjects with follow-up	1945		1950			
Number of subjects without follow-up	75		79			
Number (%) of subjects with one or more injection-site adverse experiences	1166	(59.9)	1046	(53.6)	6.30	(3.2, 9.4)
Injection Site Pain	1113	(57.2)	991	(50.8)	6.40	(3.3, 9.5)
Injection Site Erythema	304	(15.6)	275	(14.1)	1.50	(-0.7, 3.8)
Injection Site Swelling	219	(11.3)	187	(9.6)	1.70	(-0.3, 3.6)
Injection Site Pruritus	22	(1.1)	24	(1.2)	-0.10	(-0.8, 0.6)
Number (%) of subjects with one or more injection-related systemic adverse experiences						
Fever						
<37.8°C	1818	(94.0)	1826	(94.2)		
37.8 to <38.9°C	89	(4.6)	86	(4.4)		
38.9 to <39.9°C	22	(1.1)	23	(1.2)		
39.9 to <40.9°C	4	(0.2)	3	(0.2)		
≥40.9°C	1	(0.1)	1	(0.1)		
Subjects seropositive for one or more of vaccine HPV types at day 1						
Number of subjects with follow-up	148		145			
Number of subjects without follow-up	6		7			
Number (%) of subjects with one or more injection-site adverse experiences	87	(58.8)	71	(49.0)	9.80	(-1.6, 21.0)
Injection Site Pain	28	(18.9)	21	(14.5)	4.40	(-4.2, 13.1)
Injection Site Erythema	82	(55.4)	68	(46.9)	8.50	(-3.0, 19.8)
Injection Site Swelling	1	(0.7)	3	(2.1)	-1.40	(-5.3, 1.9)
Injection Site Pruritus	19	(12.8)	15	(10.3)	2.50	(-5.0, 10.1)

qHPV vaccine or among trial participants who were seropositive for one or more of the four HPV types at day 1.

In our study, the proportion of males reporting injection-site AEs during the first five days after vaccination (59.9% in vaccinees and 53.6% in the placebo group) was somewhat lower than those reported in a large phase III trial of the qHPV vaccine among females (87% and 77%, in the respective groups).[17] Among other reasons, these differences may result from young males being less willing to express pain, or the fact that, on average, males have larger deltoid muscle than females and thus may experience less pain at the injection site.

The incidence of SAEs and systemic AEs, categorized according to organ system, was comparable across the vaccine and placebo groups. Consistent with the low reactogenicity and favorable safety profile of the qHPV in young males, most AEs reported by participants in this study were mild or moderate in severity, no vaccine-related SAE were reported, and no subject withdrew from the trial due to a SAE. In addition, most deaths were reported as accidental and none was considered attributable to the vaccine.

Despite the differences in monitoring and defining AEs between studies, the frequency of AEs in our trial was similar to those reported in trials of other recently licensed investigational vaccines.[22,23] Moreover, the rates of AEs reported by a diverse population of young males in the present qHPV vaccine trial are comparable to, or even somewhat lower than those reported by females in recent large qHPV vaccine phase III trials.[17,18,24]

This study has demonstrated that the qHPV vaccine was generally well tolerated in a large sample of young males, consistent with previous findings from studies in 16- to 45-year-old females[17,18,24] and preadolescent and adolescent girls and boys.[25] Additional data from either continued active follow-up of participants in phase III trials or from active safety assessment in post-licensure phase IV trials, as well as post-licensure safety surveillance will be important to our understanding of the long-term safety of the qHPV vaccine and to assess potentially rare AEs.

Methods

Study population. Between September 3, 2004 and August 29, 2008, 4,065 healthy males [3,463 heterosexual males (HM) and 602 men who have sex with men (MSM)] were enrolled from 71 sites in 18 countries into a randomized, placebo-controlled, double-blind safety, immunogenicity and efficacy study (protocol 020; NCT00090285). The current report represents a

Table 4. Summary of systemic clinical adverse experiences (≥1%) among participants with detailed safety data (days 1–15 following vaccination)

	qHPV (N = 2020)				Placebo (N = 2029)			
	All adverse experiences		VR		All adverse experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2020				2029			
Subjects with follow-up	1945				1950			
Number (%) of Subjects with one or more systemic adverse experiences	616	(31.7)			613	(31.4)		
Gastrointestinal Disorders	**125**	**(6.4)**	**35**	**(1.8)**	**120**	**(6.2)**	**33**	**(1.7)**
Diarrhoea	40	(2.1)	10	(0.5)	36	(1.8)	13	(0.7)
Nausea	27	(1.4)	16	(0.8)	16	(0.8)	7	(0.4)
Abdominal pain upper	19	(1.0)	5	(0.3)	23	(1.2)	7	(0.4)
General Disorders	**161**	**(8.3)**	**110**	**(5.7)**	**169**	**(8.7)**	**122**	**(6.3)**
Pyrexia	120	(6.2)	93	(4.8)	125	(6.4)	98	(5.0)
Fatigue	13	(0.7)	6	(0.3)	19	(1.0)	15	(0.8)
Infections and Infestations	**182**	**(9.4)**	**18**	**(0.9)**	**187**	**(9.6)**	**20**	**(1.0)**
Influenza	42	(2.2)	9	(0.5)	44	(2.3)	7	(0.4)
Nasopharyngitis	44	(2.3)	3	(0.2)	50	(2.6)	5	(0.3)
Pharyngitis	22	(1.1)	1	(0.1)	20	(1.0)		
Upper respiratory tract infection	27	(1.4)	3	(0.2)	20	(1.0)	4	(0.2)
Injury, Poisoning and Procedural Complications	**30**	**(1.5)**			**24**	**(1.2)**		
Musculoskeletal and Connective Tissue Disorders	**61**	**(3.1)**	**21**	**(1.1)**	**50**	**(2.6)**	**15**	**(0.8)**
Nervous System Disorders	**207**	**(10.6)**	**121**	**(6.2)**	**231**	**(11.8)**	**137**	**(7.0)**
Headache	179	(9.2)	107	(5.5)	207	(10.6)	119	(6.1)
Dizziness	19	(1.0)	12	(0.6)	18	(0.9)	14	(0.7)
Respiratory, Thoracic And Mediastinal Disorders	**70**	**(3.6)**	**25**	**(1.3)**	**68**	**(3.5)**	**8**	**(0.4)**
Oropharyngeal pain	38	(2.0)	14	(0.7)	37	(1.9)	2	(0.1)
Skin And Subcutaneous Tissue Disorders	**26**	**(1.3)**	**10**	**(0.5)**	**31**	**(1.6)**	**14**	**(0.7)**

VR, vaccine related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably or definitely related to the vaccine. Percentages are calculated based on the number of subjects with follow-up. Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories. Adverse experience terms are from MedDRA Version 12.0.

median follow-up time of 2.9 years following first dose of vaccine or placebo.

The institutional review board at each participating center approved the protocol and informed consent was obtained from all subjects. Studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Vaccine and randomization. The quadrivalent HPV (type 6/11/16/18) L1 VLP vaccine [qHPV (GARDASIL®/SILGARD®, Merck & Co., Inc.,)] with amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant and a visually indistinguishable AAHS-containing placebo have been described previously in reference 26. Subjects were randomized 1:1 to receive qHPV vaccine or placebo at day 1, month 2 (±3 weeks), and month 6 (±4 weeks). Vaccine or placebo was administered as a 0.5 mL injection into the deltoid muscle.

A computer-generated allocation schedule was produced by the Sponsor. Following informed consent and determination that all entry criteria were met, eligible subjects were randomized to a vaccination group. All investigators and site personnel, subjects, monitors and laboratory personnel remained blinded to treatment allocation throughout the study. Staff of the Sponsor was blinded from the study onset through the database lock for this analysis.

Objectives and safety measurements. The primary objective was to assess the safety and tolerability of the qHPV vaccine, in addition to its efficacy. Clinical safety and tolerability were assessed using the collection of AEs reported throughout the study. Serious adverse experiences (SAEs) were predefined as any AE that resulted in death, was deemed by the investigator to be life threatening or resulted in a persistent or severe disability or incapacity. Investigators were instructed to assign causality to AEs on the basis of exposure, time course, likely cause and consistency with the test vaccine's known profile. Vaccine-related AEs

Table 5A. Summary of injection-site experiences by maximum intensity rating (days 1–15 following vaccination)

	qHPV (N = 2020)		Placebo (N = 2029)	
	n	(%)	n	(%)
Number of subjects with follow-up	1945		1950	
Number (%) of subjects with injection-site adverse experiences	1166	(59.9)	1046	(53.6)
Number (%) of subjects by maximum intensity rating				
Mild	936	(48.1)	868	(44.5)
Moderate	199	(10.2)	155	(7.9)
Severe	25	(1.3)	19	(1.0)
Unknown	6	(0.3)	4	(0.2)

Percentages are calculated based on the number of subjects with follow-up. N, Number of subjects who received only the clinical material indicated in the given column. For the measured adverse experiences of redness and swelling, Mild = 0 to 1 inch, Moderate >1 to <2 inches, and Severe >2 inches. Subjects were counted by their worst severity rating.

Table 5B. Summary of systemic adverse experiences by maximum intensity rating (days 1–15 following vaccination)

	qHPV (N= 2020)		Placebo (N=2029)	
	n	(%)	n	(%)
Number of subjects with follow-up	1945		1950	
Number (%) of subjects with Systemic adverse experiences	616	(31.7)	613	(31.4)
Number (%) of subjects by maximum intensity rating				
Mild	308	(15.8)	286	(14.7)
Moderate	256	(13.2)	274	(14.1)
Severe	51	(2.6)	53	(2.7)
Unknown	1	(0.1)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up. N = Number of subjects who received only the clinical material indicated in the given column. Subjects were counted by their worst severity rating.

were those that were determined by the investigator to be possibly, probably or definitely vaccine related. Pre-specified safety-related end points were collected as described subsequently.

After each injection, subjects were requested to remain at the study site for 30 min and were observed for any immediate adverse experiences. Subjects were instructed to record their daily body temperature for 5 days after each vaccination and to record any AEs for 14 days after each vaccination using diary cards. For each AE, including injection-site reactions, participants were asked to rate the symptom as mild (awareness of sign or symptom but easily tolerated), moderate (discomfort enough to cause interference with usual activities) or severe (incapacitating with inability to work or do usual activity). Each subject was interviewed at months 2, 6 and 7 and every 6 months thereafter to collect reports of AEs that may have occurred. All SAEs, whether considered vaccine- or procedure-related by the investigators or not, and all deaths that occurred during the entire study were also recorded.

Statistical analyses. All subjects who received at least 1 dose of vaccine or placebo were included in the safety analysis. AEs and elevated temperatures [100°F (≥38°C)] were summarized as frequencies and percentages by type of AE and treatment group, by vaccination visit and across all vaccination visits. Pairwise comparisons between each individual vaccine group and placebo were made using the method of Miettinen and Nurminen[27] at a two-sided $\alpha = 0.05$ significance level. No adjustments were made for multiple comparisons. In addition, risk differences and associated 95% CIs were computed comparing vaccine group with placebo. A 95% CI that does not include 0 indicated a nominally significant difference (unadjusted for multiple comparisons) at an alpha level of 0.005 (two-sided).

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Manuscript Contributions

The trial was designed by the sponsor (Merck & Co., Inc.,) in collaboration with external investigators (E.M., A.G., J.P., S.G., C.A., E.V., H.J., R.J.H., F.C., D.F.) and an external data and safety monitoring board. The sponsor collated data (J.M.) monitored the conduct of the trial (R.M.H., D.G., E.G.), performed statistical analyses (J.M.), and coordinated manuscript writing with all authors (S.V.). Authors were actively involved in the collection, analysis and interpretation of the data, creation and revision of the manuscript for intellectual content, and approval of the final manuscript. The first draft was written by E.D.M. and S.V., with contributions from A.G., J.P., D.G. and F.C. All authors vouch for the analyses and manuscript contents. All authors met the ICMJE guidelines for authorship, had access to data (with confidentiality agreements) and took part in the decision on where to submit the manuscript for publication.

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