Vaccine 34 (2016) 4205–4212

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men

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ARTICLE INFO

Article history:
Received 14 April 2016
Received in revised form 13 June 2016
Accepted 17 June 2016
Available online 25 June 2016

Keywords:
Human papilloma virus
Anogenital cancers
Anogenital warts
Immunogenicity
Safety
Nine-valent human papilloma virus vaccine

ABSTRACT

Background: A nine-valent human papilloma virus (9vHPV) vaccine has been developed to prevent infections and diseases related to HPV 6/11/16/18 (as per the licensed quadrivalent HPV (qHPV) vaccine) as well as to five additional oncogenic HPV types (HPV 31/33/45/52/58). The 9vHPV vaccine has the potential to prevent 90% of cervical cancers, HPV-related anal, vaginal and vulval cancers and anogenital warts. We compared the immunogenicity and safety of the 9vHPV vaccine versus the qHPV vaccine in 16–26-year-old men.

Methods: Participants ($N = 500$) were randomised to receive 9vHPV or qHPV vaccines on day 1, month 2 and month 6. Serology testing was performed on day 1 and month 7. HPV type-specific antibody titres (anti-HPV 6/11/16/18/31/33/45/52/58) were determined by competitive Luminex immunoassay and expressed as geometric mean titres and seroconversion rates. Vaccine safety was also assessed.

Results: The HPV 6/11/16/18 immune responses elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine. All participants receiving the 9vHPV vaccine seroconverted for HPV 31/33/45/52/58. The 9vHPV and qHPV vaccines showed comparable safety profiles.

Conclusions: In addition to immune responses to HPV 31/33/45/52/58, a three-dose regimen of the 9vHPV vaccine elicited a similar immune response to HPV 6/11/16/18 when compared with the qHPV vaccine in men aged 16–26 years. The safety profile was also similar for the two vaccines. The results from this study support extending the efficacy findings with qHPV vaccine to 9vHPV vaccine in men aged 16–26 years.

NCT02114385

1. Introduction

A nine-valent human papilloma virus (types 6/11/16/18/31/33/45/52/58) (9vHPV) vaccine (Gardasil 9, Merck & Co. Inc., Kenilworth, NJ, USA) was developed to provide protection against the HPV types already covered by the quadrivalent HPV (types 6/11/16/18) (qHPV) vaccine and the next five most common oncogenic types associated with cervical cancer worldwide (types 31/33/45/52/58) [1]. The 9vHPV vaccine could potentially prevent approximately 90% of cervical cancers, 90% of HPV-related vulval, vaginal and anal cancers and 90% of genital warts worldwide [2–7]. The 9vHPV vaccine was licensed in 2014 in the USA, and in 2015 in Canada, the EU and Australia.

In clinical trials in women aged 16–26 years, the qHPV vaccine prevented infection and cervical/vaginal/vulval dysplasia caused by HPV 6/11/16/18 as well as HPV 6/11-related condyloma. In a clinical trial in men aged 16–26 years, the qHPV vaccine prevented genital and anal infection and anal dysplasia caused by HPV

Abbreviations: 9vHPV vaccine, 9-valent HPV vaccine; AE, adverse event; ANOVA, analysis of variance; CI, confidence interval; cLIA, competitive Luminex immunoassay; EU, European Union; GMTs, geometric mean titres; HPV, human papilloma virus; qHPV vaccine, quadrivalent HPV vaccine; SAE, serious adverse event; USA, United States of America; VLP, virus-like particle; VRC, vaccination report card.

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http://dx.doi.org/10.1016/j.vaccine.2016.06.056
0264-410X/

6/11/16/18 as well as HPV 6/11-related condyloma [8,9]. Based on these results, the qHPV vaccine has been widely licensed for use in both genders.

In a clinical trial conducted in women aged 16–26 years, the 9vHPV vaccine prevented infection and disease caused by HPV 31/33/45/52/58. It also induced anti-HPV 6/11/16/18 antibody responses that were non-inferior to responses induced by the qHPV vaccine; efficacy of the 9vHPV vaccine against infection and disease caused by HPV 6/11/16/18 in women aged 16–26 years was inferred based on these results [10].

In another clinical trial, the 9vHPV vaccine induced non-inferior anti-HPV antibody responses to HPV 6/11/16/18/31/33/45/52/58 in men aged 16–26 years versus women aged 16–26 years. Efficacy of the 9vHPV vaccine against infection and disease caused by the nine vaccine HPV types in men aged 16–26 years was inferred based on these results [11].

In this report, we compare the safety and immunogenicity of the 9vHPV and qHPV vaccines in men aged 16–26 years, and assess whether the 9vHPV vaccine induced non-inferior anti-HPV 6/11/16/18 antibody responses compared with the qHPV vaccine. The study aims at supporting the extension of the efficacy findings with qHPV vaccine to 9vHPV vaccine in men aged 16–26 years.

2. Materials and methods

We conducted a double-blind, randomized, controlled, with qHPV vaccine, immunogenicity and safety study of the 9vHPV vaccine in young men 16–26 years of age. Participants were enrolled from seven centres located in three countries (Belgium, Germany, and the Netherlands). The study was conducted in accordance with the principles of Good Clinical Practice, as well as the Declaration of Helsinki, the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, and national and local relevant guidelines and requirements regarding ethical committee review. This trial is registered with Clinicaltrials.gov number NCT02114385.

2.1. Population

The study was designed to enrol 500 males aged ⩾16 to <27 years who were in good physical health and had a history of no more than five lifetime female and no male sexual partners (the immunogenicity of the 9vHPV vaccine in men having sex with men (MSM) was assessed in another study [11]; see Section 4 for further information). Reasons for exclusion from the study included known allergy to any component of the vaccine, a previous history of a severe allergic reaction, thrombocytopenia, coagulation disorder, or a positive HPV test, concurrent participation in any other clinical trial of an investigational medicinal product, and previous vaccination with a marketed HPV vaccine or participation in a previous HPV vaccine clinical trial (active agent or placebo). Individuals who were immunocompromised (including those who had a splenectomy), received immunosuppressive therapy in the previous year, received immunoglobulin or a blood-derived product within the previous 6 months, or had a history of any condition that could confound study results or interfere with participation in the study were also excluded.

2.2. Randomization

An Interactive Web Response System (IWRS) was used to allocate participants to 9vHPV or qHPV vaccine in a blinded manner. The system assigned an allocation number from a randomized, age-stratified (16–17 years and 18–26 years) allocation schedule. The IWRS ensured that at least 75 participants (15%) aged 16–17 years were randomized in order to avoid underrepresentation of minor participants; whenever necessary, randomization of participants aged 18 years or older was stopped when 425 of these participants had been randomized in the study. Participants were randomized in a 1:1 ratio using blocks of randomization (size 8) within each age stratum to 9vHPV or qHPV vaccine.

2.3. Study vaccination

All participants were administered a 3-dose regimen of 9vHPV or qHPV vaccine at day 1, month 2, and month 6. Each vaccine dose was administered as a 0.5-mL intramuscular injection. Vaccination was deferred if a participant had an oral temperature ⩾37.8 °C for 24 h prior to vaccination.

2.4. Vaccine immunogenicity

Blood samples were drawn at day 1 (immediately before vaccination) and at month 7. Serum collected from all participants at day 1 and month 7 was analyzed for antibodies to the nine vaccine HPV types by competitive Luminex immunoassay (cLIA; HPV-9 cLIA Version 2.0; performed by PPD Vaccines and Biologics Lab, Wayne, PA, USA) [12]. Because antibody titres to each individual HPV type were determined using type-specific monoclonal antibodies, it is not possible to directly compare assay results across HPV types.

The primary immunogenicity objective was to show that geometric mean titres (GMTs) at month 7 for anti-HPV 6/11/16/18 in the 9vHPV vaccine group would be non-inferior to the GMTs at month 7 in the qHPV vaccine group. The secondary immunogenicity objectives were to provide a summary of GMTs and seroconversion rates at month 7 for all nine HPV types (HPV 6/11/16/18/31/33/45/52/58).

Serology results at day 1 were part of the criteria to define the per-protocol analysis populations. Participants who were seropositive to a vaccine HPV type at day 1 were excluded from the per-protocol immunogenicity analysis for the corresponding HPV type.

2.5. Vaccine safety and tolerability

Following each vaccination, participants were observed for ⩾30 min for any untoward effects, including allergic reactions. All participants received a vaccination report card (VRC) at each vaccination visit. They were asked to record their oral temperature on the VRC from day 1 to day 5 after each vaccination (starting on the evening after vaccination), and any injection-site and systemic adverse events (AEs) for a total of 15 days including the day of vaccination. The study site personnel reviewed the VRC for completeness and could not alter the original information recorded by the participants on the VRC. The investigator determined the causality of systemic AEs reported on the VRC, and classified each AE reported on the VRC as a serious or non-serious AE.

An oral temperature ⩾37.8 °C during the follow-up period was considered an elevated temperature (fever). For each AE, 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); injection-site AEs of swelling and erythema were rated by size. Investigators were instructed to assign causality to AEs on the basis of exposure, time course, likely cause, and consistency with the vaccine's known profile.

Serious AEs (SAEs) were predefined as any AE that resulted in death, deemed by the investigator to be life-threatening, or that

resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing in-patient hospitalization, or was a congenital anomaly, a cancer, or an 'other important medical event'. SAEs were collected for the entire duration of the study irrespective of cause.

2.6. Statistical methods

HPV specific per-protocol sets were to comprise participants who received all three vaccinations, had a month 7 serology result, were seronegative for the corresponding HPV type at day 1, and had no protocol violations that could interfere with immune responses. It was estimated that there would be approximately a 25% exclusion rate from each per-protocol set, leaving 185/250 evaluable participants per vaccine group for the primary analysis.

The non-inferiority margin was set at 0.5, the true GMT ratio was estimated to be 1.0 for HPV6, 16 and 18 and 0.75 for HPV11, and the standard deviation (natural log scale) was estimated at 1.2 (for HPV 16,18, 6 and 11 post-vaccination titres). Based on these parameters, the study has greater than 90% power to demonstrate the non-inferiority of the HPV 6/11/16/18 GMTs following vaccination with the 9vHPV vaccine versus the qHPV vaccine.

Immunogenicity results are presented for the per-protocol sets. Non-inferiority of anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 GMTs was demonstrated by four one-sided tests (one for each HPV type) conducted at $\alpha = 0.025$ level (one-sided). Non-inferiority was achieved if the lower bound of the two-sided 95% CI for the GMT ratio (post-dose 3 9vHPV vaccine GMT/post-dose 3 qHPV vaccine GMT) was greater than 0.5. Each test was conducted using an analysis of variance (ANOVA) model with a response of log individual titres and a fixed effect for group and age strata (as per randomisation). Descriptive statistics were used for all other immunogenicity analyses. Confidence intervals for seroconversion rates were calculated using the exact method for binary variables as proposed by Collett [13].

Safety analyses are described for the safety set (all participants who received at least one study vaccine dose and for whom safety follow-up data were available).

3. Results

Overall, 502 individuals were screened for inclusion in the study (between 24 March 2014 and 17 September 2014), of whom 500 (the randomized set) were included in the study and randomized to the 9vHPV or qHPV vaccine groups (Fig. 1). The baseline characteristics of randomized participants were generally similar between vaccine groups (Table 1). The mean age at the first vaccination visit was 21.0 years. The most common reason for exclusion from the per-protocol immunogenicity (PPI) sets was having a month 7 serum sample or result missing or being seropositive at day 1 for one of the vaccine HPV types (Table 2).

3.1. Immunogenicity

As seen in Table 3, anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 GMTs elicited by the 9vHPV vaccine were non-inferior to those elicited by the qHPV vaccine (the lower bound of the two-sided 95% CI for the GMT ratio [9vHPV vaccine/qHPV vaccine] was $\geqslant 0.5$, $P < 0.001$; Table 3).

Anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 GMTs were numerically higher in the younger age stratum (16–17 years) than the older age stratum (18–26 years) and comparable within each age stratum for both vaccines (Table 3).

All participants seroconverted for HPV 6/11/16/18 after receiving three doses of the 9vHPV vaccine or qHPV vaccine, except for seven participants who did not seroconvert to HPV 6 (four having received the 9vHPV vaccine and three the qHPV vaccine), and two participants who did not convert to HPV 18 (one in each group). These participants who were all in the 18–26 year stratum, had no relevant medical history reported at baseline, except for one participant with a medical history of seronegative rheumatoid arthritis reported at baseline, and prior/concomitant treatment with Plaquenil starting the previous year and ending nine days after dose 2, and one participant who received concomitant treatment with Decortin H, 40 mg/day for eight days ending seven days before dose 3 to treat obstructive bronchitis. These participants also had low immune responses to the other HPV types, with antibody titres generally 2–47-fold lower than the GMTs.

As shown in Table 3, marked HPV 31/33/45/52/58 antibody responses were measured post-dose 3 in the 9vHPV vaccine group. Anti-HPV 31/33/45/52/58 GMTs post-dose 3 were numerically greater by at least twofold and up to 15-fold in the 9vHPV vaccine group compared with the qHPV vaccine group. Numerically higher anti-HPV 31/33/45/52/58 GMTs were observed in 16–17 year olds compared with 18–26 year olds. Seroconversion rates after dose 3 were 100% for HPV 31/33/45/52/58 among participants who received three doses of the 9vHPV vaccine. Anti-HPV 31/33/45/52/58 GMTs post-dose 3 were low in the qHPV vaccine group. Nonetheless, the qHPV vaccine induced measurable levels immune response to the HPV types not included in the vaccine (post-dose 3 GMTs can be seen in Table 3), including seroconversion rates after dose 3 as high as 61.6% for HPV 31 and 36.1% for HPV 58 (Table 4).

3.2. Safety/tolerability

Most participants reported at least one AE over the course of the study, including 81.5% and 79.0% of participants in the 9vHPV and qHPV vaccine groups, respectively, who experienced vaccine-related AEs from day 1 to day 15 following any vaccination (Table 5).

Most participants reported at least one injection-site reaction from day 1 to day 5 following either vaccination (9vHPV vaccine: 79.0%; qHPV vaccine: 72.2%). Although more participants reported injection-site pain and swelling after receiving the 9vHPV vaccine (77.8% and 14.5%, respectively) compared with the qHPV vaccine (70.2% and 9.3%, respectively), these differences did not reach statistical significance ($P = 0.053$ and $P = 0.072$, respectively). Moreover, no participant reported severe injection-site pain, and severe injection-site swelling (>5 cm) was reported in a similar proportion of participants in each vaccine group (9vHPV vaccine: 1.2%; qHPV vaccine: 1.6%).

Comparable percentages of participants in each vaccine group reported vaccine-related systemic AEs (23.0% and 21.8% of participants in the 9vHPV and qHPV vaccine groups, respectively). The most common vaccine related systemic AEs in the 9vHPV vaccine group were headache (8.1%), lymphadenopathy (2.4%), pyrexia (2.0%), fatigue (2.0%), nausea (2.0%), diarrhea (2.0%), nasopharyngitis (1.6%), myalgia (1.6%), dizziness (1.2%) and oropharyngeal pain (1.2%). Among participants receiving the qHPV vaccine, the most frequent vaccine-related systemic AEs were headache (8.9%), fatigue (3.2%), pyrexia (2.8%), diarrhoea (2.4%), nasopharyngitis (1.6%) and nausea (1.2%).

No vaccine-related SAEs and no discontinuations due to an AE were reported. Six SAEs were reported for six participants (all in the qHPV vaccine group), including joint dislocation (left shoulder dislocation during sport activities) 21 days post-dose 1, ligament injury (trauma to the cruciate ligaments of the left knee during sport activities) 34 days post-dose 2, ligament rupture (rupture of the anterior cruciate ligament of the right knee during sport activities) 44 days post-dose 2, foot fracture (tarsometatarsal

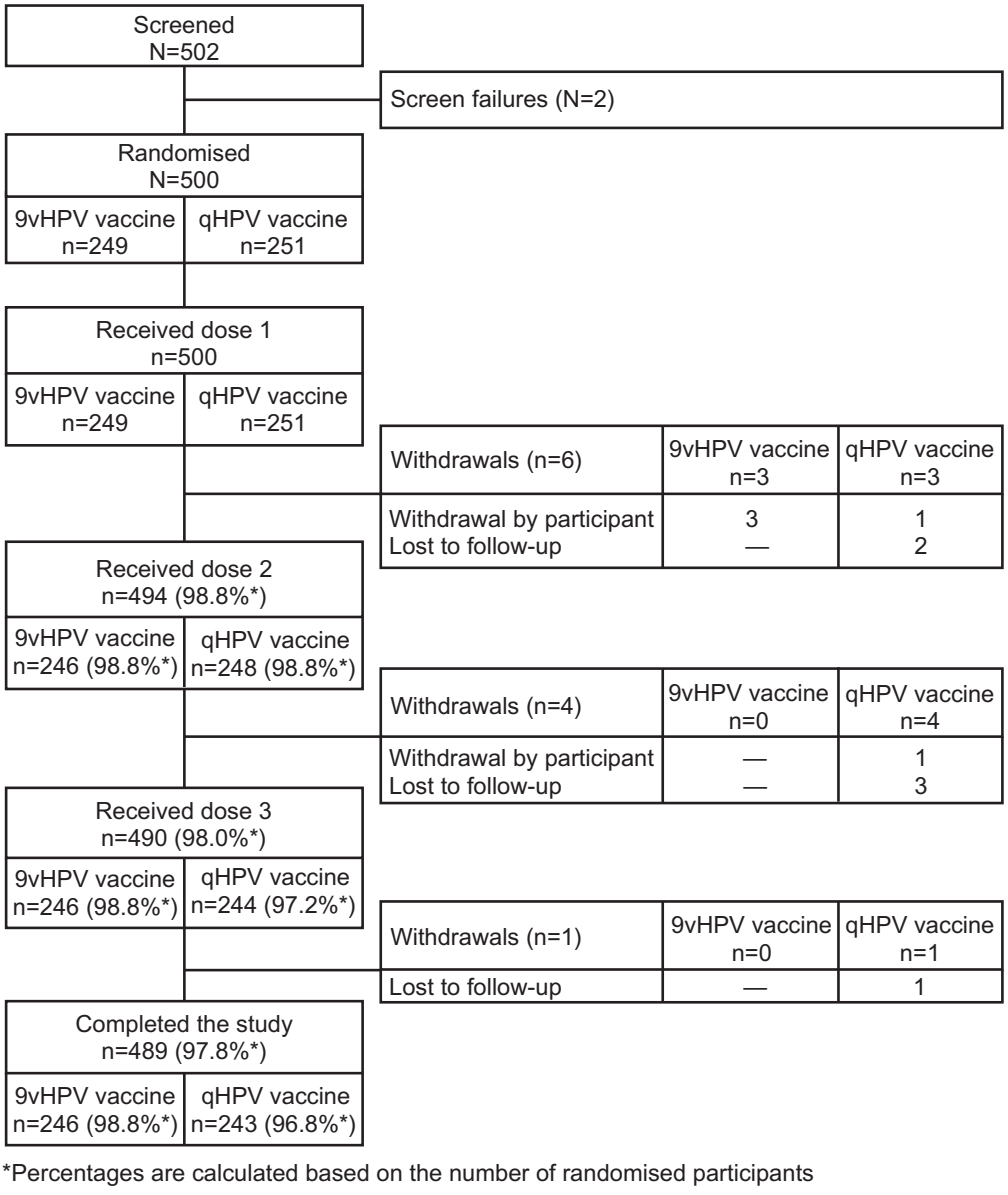

Fig. 1. A summary of the disposition of participants throughout the study, from screening to study completion.

fracture of the right foot following a traffic accident) 17 days post-dose 3, concussion (head injury following a traffic accident) 28 days post-dose 3, and cytomegalovirus infection (with subsequent hospitalization due to high fever) 32 days post-dose 3.

Table 1
Demographic characteristics – randomised set ($N = 500$).

		9vHPV vaccine $N = 249$	qHPV vaccine $N = 251$	All $N = 500$
Age at first dose	Mean (SD)	20.8 (2.7)	21.3 (3.0)	21.0 (2.8)
	Range	16.0–26.0	16.0–26.0	16.0–26.0
16–17 years old	*n*	37	38	75
	Mean (SD)	16.4 (0.5)	16.4 (0.5)	16.4 (0.5)
18–26 years old	*n*	212	213	425
	Mean (SD)	21.6 (2.1)	22.1 (2.3)	21.8 (2.2)
Weight (kg)	Mean (SD)	75.2 (10.9)	74.2 (11.0)	74.7 (11.0)
	Range	50–111	47–115	47–115
Height (cm)	Mean (SD)	181.9 (7.6)	181.7 (7.1)	181.8 (7.3)
	Range	161–202	160–204	160–204

N, number of randomised participants in the respective vaccination group; *n*, number of participants contributing to the analysis; SD, standard deviation.

4. Discussion

We have compared the immunogenicity of the 9vHPV and qHPV vaccines in young men aged 16–26 years. We found that administration of a three-dose regimen of 9vHPV vaccine generated similar antibody responses to HPV types 6/11/16/18 compared with a three-dose regimen of the qHPV vaccine. HPV 6/11/16/18 antibody responses at 1 month after dose 3 were non-inferior in the 9vHPV vaccine group compared with the qHPV vaccine group. Thus, the primary objective of the study was met. Based on these results, the efficacy of the 9vHPV vaccine can be inferred to be comparable to that of the qHPV vaccine for preventing infection and disease related to HPV 6/11/16/18.

The AE profile was generally similar for both vaccines. Injection-site reactions were more common in the 9vHPV vaccine than in the qHPV vaccine group. This may be a consequence of the higher dose

Table 2
Summary of exclusions from the per-protocol analyses.

	9vHPV vaccine (N = 249)	qHPV vaccine (N = 251)
Participants who received ⩾1 injection	249	251
Per-protocol immunogenicity sets (PPI)		
PPI for HPV 6	228	226
PPI for HPV 11	228	226
PPI for HPV 16	234	237
PPI for HPV 18	234	236
PPI for HPV 31	234	237
PPI for HPV 33	236	236
PPI for HPV 45	232	236
PPI for HPV 52	235	236
PPI for HPV 58	232	233
Reasons for exclusion		
Participants with protocol deviations	13	11
Administration of incorrect clinical material	1	0
Incomplete vaccination schedule	3	7
Month 7 serum sample outside of acceptable day range	3	2
Month 7 serum sample or results missing	3	8
Received non-study live vaccine	1	0
Received non-study inactivated/ recombinant vaccine[a]	2	0
Vaccination out of the acceptable day ranges[b]	3	1
Day 1 seropositive[c]		
HPV 6	5	12
HPV 11	3	6
HPV 16	2	3
HPV 18	2	5
HPV 31	2	4
HPV 33	0	5
HPV 45	4	5
HPV 52	1	5
HPV 58	4	8

Participants are counted once in each applicable category. A participant may appear in more than one category.
[a] Includes any live vaccine received 21 days prior to or 14 days following study vaccine.
[b] Includes any inactivated or recombinant vaccine received within 14 days of study vaccine.
[c] Seropositive at day 1 to the relevant HPV type(s) applies to the PPI set for the relevant HPV type(s) only.

of VLPs and adjuvant contained in the 9vHPV vaccine compared with the qHPV vaccine. It should be noted that HBVaxPro® 10 μg (Sanofi Pasteur MSD, Lyon, France, manufactured by Merck & Co., Kenilworth, NJ, USA), which contains the same quantity of the same adjuvant as the 9vHPV vaccine, has been widely administered to children and young adults and has a proven favourable safety profile [14]. Furthermore, no participant withdrew from the study due to injection-site reactions; thus, we do not anticipate that injection-site reactions would have a significant impact on vaccine uptake. Overall, these results are consistent with the results of previous studies which showed similar AE profiles for 9vHPV vaccine and qHPV vaccine in 16–26-year-old women and 9–15-year-old girls [10,15].

A 9vHPV vaccine dose formulation was selected in Phase II studies conducted in 16–26-year-old women based on the induction of non-inferior anti-HPV 6/11/16/18 antibody responses compared with qHPV vaccine [16]. This result was confirmed in Phase III studies in 16–26-year-old women and 9–15-year-old girls [10,15]. A similar analysis in 9–15-year-old boys was not deemed necessary because the immunogenicity of 9vHPV vaccine and qHPV vaccine are similar in 9–15-year-old boys and girls [17,18], and the two vaccines have similar immunogenicity in 9–15-year-old girls [15]. The current study demonstrates non-inferior anti-HPV 6/11/16/18 antibody responses in 16–26-year-old men. Collectively, these results support the conclusion that in males and females aged 9–26 years, 9vHPV vaccine and qHPV vaccine have similar immunogenicity profiles with respect to HPV 6/11/16/18.

There are several limitations to our study. The clinical efficacy of 9vHPV vaccine was not assessed in males. Since the licensed qHPV vaccine prevents anal pre-cancers due to HPV 16/18, using a placebo would not be acceptable in an efficacy study. Thus an efficacy study would require a comparison between the investigational 9vHPV vaccine and the licensed qHPV vaccine. Since both qHPV vaccine and 9vHPV vaccine are highly efficacious against HPV 6/11/16/18, a low incidence of HPV 6/11/16/18-associated disease is expected with both vaccines. For this reason, an efficacy comparison of the 9vHPV versus qHPV vaccine would require a prohibitively large sample size [19]. The clinical efficacy of 9vHPV vaccine with respect to HPV 6/11/16/18-related infection and disease was inferred in 16–26-year-old women based on the demonstration of non-inferior immunogenicity compared with qHPV vaccine [10]. Using the same approach, efficacy findings with qHPV vaccine in 16–26-year-old men can be extended to 9vHPV vaccine based on the results from this study. The clinical efficacy of the 9vHPV vaccine in preventing HPV 31/33/45/52/58-related infection and disease was demonstrated in a clinical study in 16–26-year-old women [10]; these efficacy findings were extended to 16–26-year-old men based on the demonstration of non-inferior immunogenicity compared with 16–26-year-old women in another study [11].

Our study was conducted in heterosexual men (HM): the immunogenicity of HPV vaccines is lower in MSM than in HM [11,20]. Therefore, analyses of HPV vaccine immunogenicity should be conducted separately in HM and MSM. The immunogenicity of 9vHPV vaccine and qHPV vaccine in HM and MSM were extensively assessed in previous studies; the GMT ratios between HM and MSM were found to be similar with 9vHPV vaccine and qHPV vaccine [11,20]. Thus it was not deemed necessary to conduct an assessment of immunogenicity in MSM in this study.

5. Conclusion

In conclusion, a three-dose regimen of the 9vHPV vaccine elicited a similar antibody response to HPV 6/11/16/18 as did the qHPV vaccine in men aged 16–26 years. The safety and tolerability profile was also generally similar for the two vaccines. Based on these results, the efficacy of the 9vHPV vaccine is inferred to be comparable with that of the qHPV vaccine. Furthermore, the 9vHPV vaccine could offer additional benefits by targeting HPV types 31/33/45/52/58, which are responsible for 8% of HPV-related anal cancers and 15% of HPV-related penile cancers [4,21].

Disclosures and contributions

Disclosures

AL is employee of Merck & Co., Inc., and may own stock and/or stock options in the company. PVD acts as coordinating and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers; speakers fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. PVD receives no personal remuneration for this work. CJLM received speakers fees from GSK, Qiagen, SPMSD/Merck, Roche, Menarini and Seegene, served occasionally on the scientific advisory board (expert meeting) of GSK, Qiagen,

Table 3
Summary of month 7 GMTs in the 9vHPV vaccine and qHPV vaccine groups; HPV-specific per-protocol immunogenicity set.

Assay	9vHPV vaccine *N* = 249			qHPV vaccine *N* = 251			Estimated GMT ratio 9vHPV/qHPV (95% CI)
	n	GMT (mMU/mL)	95% CI	*n*	GMT (mMU/mL)[a]	95% CI[a]	
Anti-HPV 6							
All	228	758.3	665.9; 863.4	226	618.4	554.0; 690.3	1.23 (1.04; 1.45)[b]
16–17 y	36	1284.5	1009.0; 1635.2	36	1012.7	794.0; 1291.6	
18–26 y	192	686.9	594.8; 793.2	190	563.2	500.2; 634.2	
Anti-HPV 11							
All	228	681.7	608.9; 763.4	226	769.1	683.5; 865.3	0.89 (0.76; 1.04)[b]
16–17 y	36	1138.6	889.4; 1457.5	36	1119.3	859.7; 1457.2	
18–26 y	192	619.2	548.1; 699.7	190	716.3	629.3; 815.3	
Anti-HPV 16							
All	234	3924.1	3513.8; 4382.3	237	3787.9	3378.4; 4247.0	1.04 (0.89; 1.21)[b]
16–17 y	36	5868.0	4486.1; 7675.6	37	6045.7	4445.0; 8222.9	
18–26 y	198	3647.2	3237.5; 4108.7	200	3474.0	3079.9; 3918.6	
Anti-HPV 18							
All	234	884.3	766.4; 1020.4	236	790.9	683.0; 915.7	1.12 (0.91; 1.37)[b]
16–17 y	36	1390.4	989.6; 1953.6	36	1346.2	951.1; 1905.4	
18–26 y	198	814.5	696.9; 951.8	200	718.7	613.1; 842.3	
Anti-HPV 31							
All	234	794.4	694.2; 909.2	237	14.8	12.5; 17.5	
16–17 y	36	1441.9	999.1; 2080.9	36	22.0	13.8; 35.1	
18–26 y	198	712.8	619.1; 820.8	201	13.8	11.5; 16.5	
Anti-HPV 33							
All	236	460.5	410.6; 516.4	236	3.4	3.1; 3.7	
16–17 y	36	778.8	586.0; 1035.1	37	4.4	3.4; 5.7	
18–26 y	200	418.9	371.0; 473.1	199	3.2	2.9; 3.5	
Anti-HPV 45							
All	232	262.9	226.2; 305.5	236	2.5	2.3; 2.8	
16–17 y	34	479.1	321.9; 713.3	37	3.3	2.4; 4.6	
18–26 y	198	237.1	202.3; 278.1	199	2.4	2.1; 2.6	
Anti-HPV 52							
All	235	430.7	377.8; 491.0	236	1.9	1.8; 2.1	
16–17 y	36	773.6	551.7; 1084.7	37	2.5	2.0; 3.1	
18–26 y	199	387.4	337.4; 444.8	199	1.9	1.7; 2.0	
Anti-HPV 58							
All	232	691.0	614.9; 776.5	233	5.7	5.0; 6.5	
16–17 y	35	1259.1	938.1; 1690.1	36	9.0	6.0; 13.4	
18–26 y	197	621.1	549.8; 701.8	197	5.2	4.6; 6.0	

CI, confidence interval; GMT, geometric mean titres; mMU, milli-Merck units; *N*, number of randomised participants in the respective vaccination group; *n*, number of participants contributing to the analysis; y, years.
[a] The estimated GMT ratio and associated CI are based on an analysis of variance (ANOVA) model including group and age strata as independent variables.
[b] Non-inferiority was achieved if the lower bound of the 2-sided 95% CI for the GMT ratio was greater than 0.50.

SPMSD/Merck, Roche and Genticel, and on occasion as consultant for Qiagen and Genticel. He is minority stockholder of Diassay b. v. and of Self-Screen b.v., a spin off company of Free University Medical Center, Amsterdam, the Netherlands. Until 2014 he held a small number of certificates of shares in Delphi Biosciences, which went into receivership in 2014. He received research funding via his institution from Gen Probe and Abbott. DK has obtained grants from Sanofi Pasteur MSD, Lyon, France to conduct the study. MB, ST and AS are/were employees of Sanofi-Pasteur MSD at the time the study was conducted.

Contributors

AL contributed to protocol design and development, drafted the initial manuscript, critically reviewed and/or revised the manuscript and approved the final version of the manuscript. PVD contributed to revising the protocol, in data collection, data analysis and interpretation; provided comments on the first draft, and approved the final version of the manuscript. CJLMM contributed in data collection, data interpretation and commented/approved final version of the manuscript. DK has contributed to data acquisition, data analysis and interpretation, has provided critical comments on manuscript draft and approved the final version of the manuscript. MB contributed to protocol design and development, data analysis and interpretation, approved the first draft of the manuscript, provided critical comments on manuscripts drafts and approved the final version of the manuscript. ST contributed to protocol design and development, data analysis and interpretation, approved the first draft of the manuscript, provided critical comments on manuscripts drafts and approved the final version of the manuscript. AS contributed to protocol design and development, data analysis and interpretation, approved the first draft of the manuscript, provided critical comments on manuscripts drafts and approved the final version of the manuscript.

All authors were involved in data interpretation, writing the paper, and approval of the final version and decision to submit to Vaccine for publication.

Role of the funding source

Sanofi Pasteur MSD provided financial support for the conduct of the research and preparation of the article and were involved in the study design, in the collection, analysis and interpretation of data and in the writing of the trial report.

Table 4
Summary of month 7 seropositivity rates in the 9vHPV vaccine and qHPV vaccine groups; HPV-specific per-protocol immunogenicity set.

Assay	9vHPV vaccine $N = 249$				qHPV vaccine $N = 251$			
	n	m	%	95% CI	n	m	%	95% CI*
Anti-HPV 6	228	224	98.2	95.6; 99.5	226	223	98.7	96.2; 99.7
Anti-HPV 11	228	228	100	98.4; 100	226	226	100	98.4; 100
Anti-HPV 16	234	234	100	98.4; 100	237	237	100	98.5; 100
Anti-HPV 18	234	233	99.6	97.6; 100	236	235	99.6	97.7; 100
Anti-HPV 31	234	234	100	98.4; 100	237	146	61.6	55.1; 67.8
Anti-HPV 33	236	236	100	98.4; 100	236	40	16.9	12.4; 22.4
Anti-HPV 45	232	232	100	98.4; 100	236	22	9.3	5.9; 13.8
Anti-HPV 52	235	235	100	98.4; 100	236	6	2.5	0.9; 5.5
Anti-HPV 58	232	232	100	98.4; 100	233	84	36.1	29.9; 42.6

CI, confidence interval; N, number of randomised participants in the respective vaccination group; n, number of participants contributing to the analysis; m, number of participants changing serostatus from seronegative to seropositive; seropositive represents the percent of participants with anti-HPV serum levels $\geqslant$30, 16, 20, 24, 10, 8, 8, 8, and 8 milli-Merck units/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.

Table 5
Summary of safety for days 1–15 following either vaccination; safety set.

	9vHPV vaccine $N = 248$ n (%)	qHPV vaccine $N = 248$ n (%)
No adverse events	44 (17.7)	45 (18.1)
One or more adverse events	204 (82.3)	203 (81.9)
One or more vaccine-related adverse reactions	202 (81.5)	196 (79.0)
Injection-site adverse reaction	196 (79.0)	179 (72.2)
Solicited injection-site adverse reaction	195 (78.6)	177 (71.4)
Injection site erythema	38 (15.3)	43 (17.3)
Injection site swelling	36 (14.5)	23 (9.3)
Injection site pain	193 (77.8)	174 (70.2)
Other injection-site adverse reaction	24 (9.7)	23 (9.3)
Severe injection-site adverse reaction	3 (1.2)	4 (1.6)
Systemic adverse events	101 (40.7)	100 (40.3)
Vaccine-related systemic adverse event	57 (23.0)	54 (21.8)
Serious adverse events	0 (0)	0 (0)
Vaccine-related serious adverse event at any time	0 (0)	0 (0)
Serious adverse events leading to death	0 (0)	0 (0)
Withdrawn due to an adverse event	0 (0)	0 (0)

CI, confidence interval; N, number of participants in the respective vaccination group; n, number of participants reporting at least one event.

Acknowledgements

The authors take full responsibility for the content of this contribution and thank Graham Joint, Synercom Limited, Macclesfield, UK (supported by Sanofi Pasteur MSD) for preparing the manuscript for submission.

The authors would like to thank the participants who participated in the trial, as well as the investigators and their study-site personnel for their contribution to the study: Geert Leroux-Roels, Annelies Aerssens, Cathy Maes, Fien De Boever, Jan de Hoon, Corinne Vandermeulen, Ruud Bekkers, Marjolein van Zummeren, Nicole Polman, Roosmarijn Luttmer, Maarten Schim van der Loeff, Titia Heijman, Annick Hens and Katrin Steul. They also would like to thank Patrick Richard (former Sanofi Pasteur MSD statistician) and Joshua Chen (former statistician at Merck) for their contribution to study design as well as Xavier Cornen (Sanofi Pasteur MSD) for data management.

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