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Immunogenicity and safety of a nine-valent human papillomavirus vaccine in women 27–45 years of age compared to women 16–26 years of age: An open-label phase 3 study

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ABSTRACT

Background: Efficacy of the nine-valent human papillomavirus (9vHPV; HPV types 6/11/16/18/31/33/45/52/58) vaccine was demonstrated in a phase 3 study in women 16–26 years of age. We present a phase 3 immunogenicity and safety study of the 9vHPV vaccine in women 27–45 versus 16–26 years of age.

Abbreviations: 2vHPV, bivalent human papillomavirus; 4vHPV, quadrivalent human papillomavirus; 9vHPV, nine-valent human papillomavirus; AE, adverse event; ANOVA, analysis of variance; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HPV, human papillomavirus; mMU, Milli Merck units; PPI, per-protocol immunogenicity; SAE, serious adverse event; SD, standard deviation.

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Methods: This international, open-label study (NCT03158220) was conducted in women 16–45 years of age. Participants (16–26 years, n = 570 and 27–45 years, n = 642) received a three-dose 9vHPV vaccination regimen (day 1, month 2, month 6). Month 7 geometric mean titers (GMTs) and seroconversion percentages to anti-HPV 6/11/16/18/31/33/45/52/58 were assessed. Participants were followed for safety throughout the study.

Results: At month 7, anti-HPV 6/11/16/18/31/33/45/52/58 GMTs in women 27–45 years were compared to those in women 16–26 years of age. The primary hypothesis of non-inferiority of anti-HPV 16/18/31/33/45/52/58 GMTs in older versus younger women was met. The lower bound of the GMT ratio 95% confidence interval (27–45 years to 16–26 years) was 0.60–0.67 depending on HPV type, exceeding the non-inferiority margin of 0.5 for all HPV types. Month 7 seroconversion percentages in women 27–45 years of age were >99% for all HPV types. Injection-site and vaccine-related systemic adverse events (AEs) were observed in 87.5% and 25.1% of women 16–26 years, and 85.2% and 24.1% of women 27–45 years of age, respectively; no vaccine-related serious AEs were reported and no deaths occurred during the study.

Conclusions: The 9vHPV vaccine elicited non-inferior anti-HPV GMTs in women 27–45 years compared with women 16–26 years of age for HPV 16/18/31/33/45/52/58. The vaccine was generally well tolerated with a similar AE profile across the age groups. These data support bridging 9vHPV vaccine efficacy findings in women 16–26 years to women 27–45 years of age.

Clinical trial registration NCT03158220.

1. Introduction

Human papillomavirus (HPV) is responsible annually for approximately 690,000 new cancer cases in women and men worldwide [1]. HPV-related cancers include nearly all cervical cancers and approximately 88% of anal squamous cell carcinomas, 78% of vaginal cancers, 15–48% of vulvar cancers, 51% of penile cancers, and 22–60% of oropharyngeal cancers [1,2].

Three prophylactic HPV vaccines are widely licensed and recommended for use in many countries worldwide for the prevention of HPV-related disease [3,4]. A quadrivalent HPV (4vHPV) vaccine and a bivalent HPV (2vHPV) vaccine were initially licensed in 2006 and 2007, respectively [3,4]. Both vaccines protect against two high-risk types (HPV 16/18) that are responsible for approximately 70% of cervical cancer cases [5]; the 4vHPV vaccine also protects against HPV 6 and 11, responsible for 90% of anogenital warts [6]. Partial cross-protection has been observed against HPV 31 for both vaccines and HPV 45 for 2vHPV vaccine in clinical trials and in real-world public-health programs where high coverage has occurred, although its extent, duration, and public-health significance remain uncertain [4,7–9]. The nine-valent human papillomavirus (9vHPV) vaccine (Gardasil® 9; Merck & Co., Inc., Kenilworth, NJ, USA) was first licensed in 2014 [3]. It was developed to provide protection against the four HPV types covered by the 4vHPV vaccine (HPV 6/11/16/18), plus the five high-risk HPV types that are the most commonly associated with cervical cancer after HPV 16 and HPV 18 (HPV 31/33/45/52/58). The 9vHPV vaccine has the potential to prevent approximately 90% of cervical cancers, and HPV-related vulvar, vaginal, and anal cancers, ≥80% of cervical, and HPV-related vulvar, vaginal, and anal precancers, as well as 90% of genital warts [5,6,10–12]. In addition, an HPV vaccine targeting HPV 16 and 18 was licensed in China in 2019 [13].

Efficacy of the 4vHPV vaccine to prevent cervical, vulvar, and vaginal intraepithelial neoplasia and condyloma related to HPV 6, 11, 16, and 18 was demonstrated in placebo-controlled studies in young women 16–26 years of age [14,15] and adult women 24–45 years of age [16,17]. The 2vHPV vaccine also showed prevention against cervical intraepithelial neoplasia caused by HPV 16 and 18 in a clinical study of women between 15 and 25 years of age [18] as well as a clinical study in women older than 25 years [19,20].

Demonstration of efficacy of the 9vHPV vaccine against disease caused by HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 was based on the results of a 4vHPV vaccine-controlled study conducted in young women 16–26 years of age [21–23]. Efficacy results in young women 16–26 years of age were bridged to girls and boys 9–15 years of age and young men 16–26 years of age through demonstration of non-inferior immune responses (i.e., immunobridging) [3].

Mid-adults remain at risk of acquisition of HPV infection [24]. Approximately 196,000 cases of high-grade cervical dysplasia were diagnosed in the United States in 2016, of which 97,000 were diagnosed in women ≥30 years of age and attributable to HPV types targeted by the 9vHPV vaccine [25,26]. Rates of progression from infection to high-grade cervical dysplasia are similar in young and mid-adult women, and most infections clear or progress within 1 to 3 years [27,28], which suggests that infections occurring during adulthood can cause high-grade cervical lesions. Therefore, it is important that prophylactic HPV vaccination be available for mid-adults to reduce HPV-related morbidity and mortality in that population. As noted, the 4vHPV and 2vHPV vaccines have been extensively assessed not only in young women, but also in mid-adult women. Similarly, it is important to evaluate the 9vHPV vaccine in women 27–45 years of age. Efficacy of the 9vHPV vaccine was demonstrated in women 16–26 years of age. To understand the applicability of these efficacy findings to older women, we report data from an immunogenicity and safety study designed to demonstrate non-inferiority of antibody responses to the 9vHPV vaccine in women aged 27–45 years compared with women aged 16–26 years. This study was conducted as a post-authorization commitment from the European Medicines Agency.

2. Methods

2.1. Study design and participants

The study (Protocol V503-004; NCT03158220) was an international 7-month immunogenicity and safety study of the 9vHPV vaccine in women 16–45 years of age. It was conducted at 24 study sites located in six countries (Austria, Belgium, Finland, Germany, Italy, and Spain).

Participants were healthy women who had never received a prophylactic HPV vaccine, had no history of abnormal Papanicolaou test or cervical biopsy results, no history of genital warts, and no history of a positive test for HPV. Participants were enrolled into the study in two age groups: women aged 16–26 years (this group was sub-stratified into women 16–20 years of age and women aged 21–26 years) and women aged 27–45 years (this group was sub-stratified into women aged 27–36 years and

women aged 37–45 years). Sub-stratification was installed for balanced enrollment purposes.

The study was conducted in accordance with Good Clinical Practice and approved by the appropriate institutional review board prior to initiation at each site. All participants (or for minor participants, their parent/legal guardian and participant) provided written informed consent.

2.2. Vaccination and follow-up

All participants received a three-dose regimen of 9vHPV vaccine on day 1, month 2, and month 6. The vaccine was administered as a 0.5-mL intramuscular injection into the deltoid muscle of the non-dominant arm. Blood collection for immunogenicity testing was performed on day 1 and month 7. Antibodies to HPV 6/11/16/18/31/33/45/52/58 were measured in serum using the competitive Luminex immunoassay (cLIA) [29]. Laboratory personnel conducting HPV assays were blinded to the participant age group.

Participants were monitored for at least 15 min after each study vaccination for any adverse effects including allergic reactions. Safety information (including injection-site and systemic adverse events [AEs]) was collected for 15 days following each vaccination using electronic vaccination report cards. Serious AEs (SAEs) were collected for the entire duration of the study regardless of causality. Pregnancies occurring during the study were followed to outcome.

2.3. Study objectives

The primary objective of the study was to demonstrate that administration of the 9vHPV vaccine in women aged 27–45 years induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 16/18/31/33/45/52/58 compared with women aged 16–26 years at 4 weeks after vaccine Dose 3. Secondary immunogenicity objectives were to demonstrate that the 9vHPV vaccine was immunogenic with respect to HPV 16/18/31/33/45/52/58, based on seroconversion percentages, in women 27–45 years of age and to summarize humoral immune response parameters (GMTs and seroconversion percentages) for HPV 6/11/16/18/31/33/45/52/58 in women 16–26 years of age and women 27–45 years of age. Another secondary objective was to evaluate the safety and tolerability of the 9vHPV vaccine in women 27–45 years of age compared with women 16–26 years of age.

While antibody responses were evaluated for all nine vaccine HPV types, the non-inferiority of antibody responses was not tested for HPV 6 and HPV 11, the HPV types responsible for most genital warts [6]. The peak incidence of genital warts in women is at 14–25 years of age [30,31]. Although the benefit of vaccinating women 27–45 years of age against HPV types 6 and 11 is not negligible, hypothesis testing focused on the seven high-risk HPV types included in the vaccine (HPV 16/18/31/33/45/52/58), since the prevention of precancers and cancers caused by these types is more clinically relevant for this age range.

2.4. Statistical analysis

Per-protocol immunogenicity (PPI) analyses included participants who received all three 9vHPV vaccinations at the correct dose within acceptable day ranges, had evaluable serology within 21–49 days after the third dose, were seronegative to the appropriate HPV types at day 1, and had no protocol deviations that could potentially interfere with evaluation of the participants' immune response to the 9vHPV vaccine.

The primary hypothesis of non-inferiority of anti-HPV 16/18/31/33/45/52/58 GMTs at month 7 in women 27–45 years of age versus women 16–26 years of age was based on one-sided tests comparing month 7 GMTs for each component. An analysis of variance model per HPV type with a response of log individual titers and a fixed effect for age group was used. Hypothesis testing was conducted at $\alpha = 0.025$ level (one-sided). The statistical criterion for non-inferiority required that the lower bound of the 95% confidence intervals (CIs) of the GMT ratio (women aged 27–45 years to women aged 16–26 years) be >0.50 for each HPV type.

The secondary hypothesis of acceptability of anti-HPV 16/18/31/33/45/52/58 seroconversion rates in women aged 27–45 years was based on 95% CIs for the single group proportion calculated using the exact binomial method (Clopper-Pearson method). For each HPV type, acceptability required that the lower bound of the 95% CI for seroconversion rate be >90%. Additional exploratory analyses were conducted to evaluate HPV antibody responses (GMT and seroconversion rates) by age group and their sub-stratifications.

Safety analyses including summaries of counts and percentages of AEs by age group included all participants who received at least one dose of the 9vHPV vaccine and had at least one study visit with safety follow-up.

This study had ≥97% power to demonstrate the non-inferiority of GMTs in women aged 27–45 years compared with women aged 16–26 years, and had >99% power for the acceptability of seroconversion rates in women aged 27–45 years for 7 HPV types (16/18/31/33/45/52/58) at a 1-sided 0.025 alpha-level. This power was calculated based on (1) 600 subjects enrolled per age group (2) an approximately 25–35% exclusion rate from the PPI population (i.e., 450–390 evaluable participants per age group), (3) a non-inferiority margin of 0.5 for the GMT ratio (27–45 years relative to 16–26 years), (4) a true GMT ratio of 0.7, (5) a standard deviation of the natural log concentrations of 1.2, and (6) an assumed true seroconversion rate of >98% for each HPV type.

3. Results

3.1. Participants

Between September 2017 and November 2018, 1212 participants were enrolled, 1210 received at least one vaccination, and 1185 received all three vaccinations (Fig. 1). A total of 32 participants discontinued from the study (women aged 16–26 years, n = 17; women aged 27–45 years, n = 15), most commonly because of loss to follow-up or withdrawal by participant. No participants discontinued from the study because of an AE. Baseline characteristics are presented in Table 1. The older and younger groups of participants were similar in terms of race (mostly white), height, and weight. Baseline HPV seropositivity was slightly higher in the older group compared with the younger group but low in both groups, suggesting limited prior exposure to HPV. The most common reasons for exclusion from PPI analyses were due to the day 1 or month 7 serum samples being collected outside of the acceptable day ranges or missing, or seropositivity at baseline to the relevant HPV type (Table 2).

3.2. Immunogenicity

The 9vHPV vaccine induced anti-HPV responses for all nine HPV types (6/11/16/18/31/33/45/52/58) in both women aged 16–26 years and women aged 27–45 years at month 7. GMTs at month 7 tended to be lower among women aged 27–45 years compared with the women aged 16–26 years (Table 3). In the primary non-inferiority analysis, antibody responses to the seven high-risk HPV types (16/18/31/33/45/52/58) were non-inferior in women aged 27–45 years relative to women aged 16–26 years (Table 3).

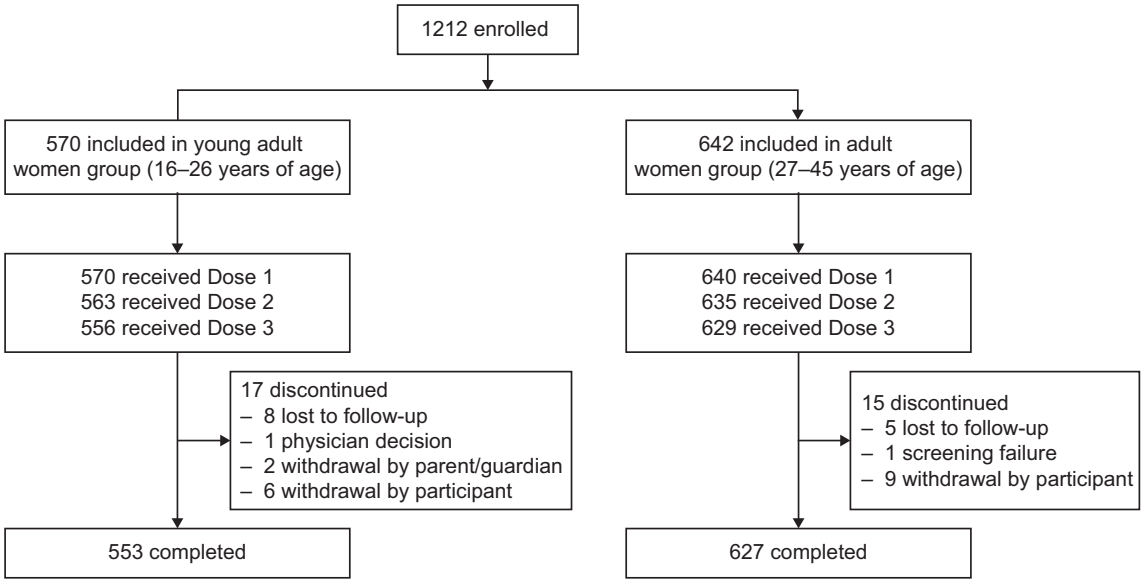

Fig. 1. Participant disposition.

The estimated fold differences for GMT ratios (women aged 27–45 years to women aged 16–26 years) ranged from 0.66 to 0.73, and the lower bound of the 95% CI of the GMT ratios ranged from 0.60 to 0.67, depending on the HPV types. Thus, the non-inferiority hypothesis was met ($p < 0.001$), as the lower bound of the 95% CI of the GMT ratio was >0.5 for each of HPV 16, 18, 31, 33, 45, 52, and 58. While HPV 6 and 11 were not included in the prespecified non-inferiority analysis, estimated fold differences in GMTs in the older versus younger groups of women were 0.81 and 0.76 (lower bound of the 95% CI: 0.73 and 0.69) for HPV 6 and 11, respectively, consistent with the results for the seven high-risk HPV types (Table 3).

More than 99% of participants seroconverted to all nine HPV types at month 7 in both age groups (Table 4). A secondary objective was to assess acceptability of the seroconversion rates for the seven high-risk HPV types in women aged 27–45 years. In this analysis, the lower bounds of the 95% CIs of the seroconversion percentages for HPV 16/18/31/33/45/52/58 ranged from 98.0–99.3%, exceeding the prespecified limit for acceptability (>90%).

In an exploratory analysis by age group and sub-groups defined by participant age (16–20, 21–26, 27–36, and 37–45 years of age), anti-HPV GMTs were highest in women aged 16–20 years with values generally declining with age for all HPV types (Table 5). Seroconversion percentages remained approximately 100% for all age strata.

Table 1
Participant baseline characteristics by age group (all participants).

	Women aged 16–26 years (N = 570)	Women aged 27–45 years (N = 642)	Total (N = 1212)
Mean (SD) age, years	21.6 (2.8)	35.8 (5.5)	29.1 (8.3)
Age sub-group, n (%)			
16–20 years	256 (44.9)	0 (0.0)	256 (21.1)
21–26 years	314 (55.1)	0 (0.0)	314 (25.9)
27–36 years	0 (0.0)	322 (50.2)	322 (26.6)
37–45 years	0 (0.0)	320 (49.8)	320 (26.4)
Race, n (%)			
American Indian or Alaska Native	2 (0.4)	1 (0.2)	3 (0.2)
Asian	17 (3.0)	10 (1.6)	27 (2.2)
Black	5 (0.9)	3 (0.5)	8 (0.7)
Multi-racial	7 (1.2)	1 (0.2)	8 (0.7)
White	539 (94.6)	627 (97.7)	1166 (96.2)
Country, n (%)			
Austria	112 (19.6)	50 (7.8)	162 (13.4)
Belgium	64 (11.2)	128 (19.9)	192 (15.8)
Finland	136 (23.9)	127 (19.8)	263 (21.7)
Germany	89 (15.6)	76 (11.8)	165 (13.6)
Italy	81 (14.2)	73 (11.4)	154 (12.7)
Spain	88 (15.4)	188 (29.3)	276 (22.8)
Height (cm)			
Participants with data, n	570	640	1210
Mean (SD)	165.9 (6.4)	166.1 (6.8)	166.0 (6.6)
Weight (kg)			
Participants with data, n	570	640	1210
Mean (SD)	63.4 (12.9)	67.6 (14.0)	65.6 (13.7)

SD, standard deviation.

3.3. Safety

A summary of AEs is provided in Table 6. There was one discontinuation due to an AE: a woman from the 27–45 years of age group discontinued because of a non-vaccine-related A a non-vaccine-related AE of migraine with aura, which occurred 11 days after Dose 1. There were no vaccine-related SAEs. No participant died during the study.

The most common injection-site AEs (≥2% participants) were pain, swelling, and erythema, which occurred in 86.1%, 23.3%, and 19.5% of women aged 16–26 years, and 82.8%, 23.3%, and 16.9% of women aged 27–45 years, respectively. Most of these AEs were mild or moderate in intensity.

The most common vaccine-related systemic AEs (≥2% participants) were headache, pyrexia, and fatigue occurring in 12.6%, 3.0%, and 2.8% of women aged 16–26 years and 13.6%, 1.7%, and 3.4% of women aged 27–45 years.

Approximately 3.5% of women aged 16–26 years and 2.5% of women aged 27–45 years reported elevated temperatures within 5 days after any vaccination. Temperatures were self-reported, and most were low-grade fevers (37.8–38.9 °C).

A total of 15 SAEs were reported across 14 participants. Six participants in the younger (16–26 years of age) group experienced six SAEs (including abdominal pain, head injury, induced abortion

Table 2
PPI populations by age group and summary of exclusions from the PPI populations (all participants).

n (%) participants	Women aged 16–26 years (N = 570)	Women aged 27–45 years (N = 642)	Total (N = 1212)
Received at least one vaccine dose	570 (100)	640 (99.7)	1210 (99.8)
Included in the PPI population			
HPV 6	421 (73.9)	448 (69.8)	869 (71.7)
HPV 11	421 (73.9)	448 (69.8)	869 (71.7)
HPV 16	436 (76.5)	448 (69.8)	884 (72.9)
HPV 18	421 (73.9)	471 (73.4)	892 (73.6)
HPV 31	447 (78.4)	488 (76.0)	935 (77.1)
HPV 33	457 (80.2)	493 (76.8)	950 (78.4)
HPV 45	470 (82.5)	515 (80.2)	985 (81.3)
HPV 52	456 (80.0)	496 (77.3)	952 (78.5)
HPV 58	451 (79.1)	478 (74.5)	929 (76.7)
Excluded from the PPI population			
HPV 6	149 (26.1)	192 (29.9)	341 (28.1)
HPV 11	149 (26.1)	192 (29.9)	341 (28.1)
HPV 16	134 (23.5)	192 (29.9)	326 (26.9)
HPV 18	149 (26.1)	169 (26.3)	318 (26.2)
HPV 31	123 (21.6)	152 (23.7)	275 (22.7)
HPV 33	113 (19.8)	147 (22.9)	260 (21.5)
HPV 45	100 (17.5)	125 (19.5)	225 (18.6)
HPV 52	114 (20.0)	144 (22.4)	258 (21.3)
HPV 58	119 (20.9)	162 (25.2)	281 (23.2)
Reasons for exclusion			
Received immunosuppressives, IgG, or blood products	0 (0.0)	4 (0.6)	4 (0.3)
Concurrently enrolled in another clinical study of investigational agents	1 (0.2)	0 (0.0)	1 (0.1)
Received non-study vaccination[a]	8 (1.4)	12 (1.9)	20 (1.7)
Did not complete the three-dose regimen[b]	14 (2.5)	12 (1.9)	26 (2.1)
Missing serology samples/results at day 1 or month 7[c]	20 (3.5)	20 (3.1)	40 (3.3)
Vaccination 2 or 3 out of acceptable day range	15 (2.6)	20 (3.1)	35 (2.9)
Serum sample collection at day 1 or month 7 out of acceptable day range	46 (8.1)	60 (9.3)	106 (8.7)
Day 1 positive[d]			
HPV 6/11	77 (13.5)	104 (16.2)	181 (14.9)
HPV 16	58 (10.2)	98 (15.3)	156 (12.9)
HPV 18	73 (12.8)	78 (12.1)	151 (12.5)
HPV 31	47 (8.2)	60 (9.3)	107 (8.8)
HPV 33	34 (6.0)	47 (7.3)	81 (6.7)
HPV 45	17 (3.0)	24 (3.7)	41 (3.4)
HPV 52	33 (5.8)	46 (7.2)	79 (6.5)
HPV 58	39 (6.8)	69 (10.7)	108 (8.9)

cLIA, competitive Luminex immunoassay; HPV, human papillomavirus; IgG, immunoglobulin G; PPI, per-protocol immunogenicity.
[a] Received an inactivated vaccine within ±14 days of study vaccination or received a live virus vaccine within −21 to +14 days of study vaccination.
[b] Two randomized subjects did not receive any dose.
[c] Includes subjects with a missing serum sample or missing cLIA results for at least one HPV type.
[d] Seropositivity at Day 1. Applies only to the analysis populations for the respective HPV type(s).

Table 3
Anti-HPV GMTs for HPV types 6/11/16/18/31/33/45/52/58 at month 7 in women aged 16–26 years and women aged 27–45 years (PPI population).

Assay (cLIA)	Women aged 16–26 years (N = 570)			Women aged 27–45 years (N = 640)			Estimated fold difference[a] Women aged 27–45 years/women aged 16–26 years (95% CI)
		GMT (mMU/mL)			GMT (mMU/mL)		
	n	GMT	95% CI	n	GMT	95% CI	
Anti-HPV 6	421	787.8	732.5–847.2	448	638.4	594.9–685.0	0.81 (0.73–0.90)
Anti-HPV 11	421	598.7	558.7–641.6	448	453.5	424.1–485.0	0.76 (0.69–0.83)
Anti-HPV 16	436	3075.8	2863.4–3303.9	448	2147.5	2001.1–2304.5	0.70 (0.63–0.77)[b]
Anti-HPV 18	421	744.5	685.0–809.1	471	532.1	491.8–575.7	0.71 (0.64–0.80)[b]
Anti-HPV 31	447	596.1	551.1–644.9	488	395.7	367.0–426.6	0.66 (0.60–0.74)[b]
Anti-HPV 33	457	354.5	331.7–378.9	493	259.0	242.9–276.1	0.73 (0.67–0.80)[b]
Anti-HPV 45	470	214.9	197.7–233.7	515	145.6	134.4–157.7	0.68 (0.60–0.76)[b]
Anti-HPV 52	456	346.5	324.0–370.5	496	244.7	229.4–261.0	0.71 (0.64–0.78)[b]
Anti-HPV 58	451	428.0	399.4–458.6	478	296.4	277.1–317.0	0.69 (0.63–0.76)[b]

CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HPV, human papillomavirus; mMU, Milli Merck units; PPI, per-protocol immunogenicity.
N = number of participants randomized to the respective age group who received at least one injection.
n = number of subjects contributing to the analysis.
[a] Fold difference calculated from an analysis of variance model with response of log individual titers and a fixed effect for age groups.
[b] Non-inferiority of GMTs in women aged 27–45 years relative to women aged 16–26 years was achieved ($p < 0.001$), as the lower limit of the 95% CI for the fold difference for the GMT ratio was>0.5 for the given HPV type (for HPV types 16/18/31/33/45/52/58).

Table 4
Seropositivity rates at month 7 for HPV types 6/11/16/18/31/33/45/52/58 in women aged 16–26 years and women aged 27–45 years (PPI population).

Assay (cLIA)	Women aged 16–26 years (N = 570)			Women aged 27–45 years (N = 640)		
		Seropositivity			Seropositivity	
	n	m (%)	95% CI	n	m (%)	95% CI
Anti-HPV 6	421	420 (99.8)	98.7–100.0	448	448 (100.0)	99.2–100.0
Anti-HPV 11	421	421 (100.0)	99.1–100.0	448	447 (99.8)	98.8–100.0
Anti-HPV 16	436	436 (100.0)	99.2–100.0	448	448 (100.0)	99.2–100.0 [a]
Anti-HPV 18	421	421 (100.0)	99.1–100.0	471	469 (99.6)	98.5–99.9 [a]
Anti-HPV 31	447	447 (100.0)	99.2–100.0	488	487 (99.8)	98.9–100.0 [a]
Anti-HPV 33	457	457 (100.0)	99.2–100.0	493	492 (99.8)	98.9–100.0 [a]
Anti-HPV 45	470	468 (99.6)	98.5–99.9	515	511 (99.2)	98.0–99.8 [a]
Anti-HPV 52	456	456 (100.0)	99.2–100.0	496	496 (100.0)	99.3–100.0 [a]
Anti-HPV 58	451	451 (100.0)	99.2–100.0	478	477 (99.8)	98.8–100.0 [a]

CI, confidence interval; cLIA, competitive Luminex immunoassay; HPV, human papillomavirus; PPI, per-protocol immunogenicity.
N = number of participants randomized to the respective age group who received at least one injection.
n = number of subjects contributing to the analysis.
m = number of subjects seropositive to the relevant HPV type.
[a] Acceptability of seroconversion percentages in women aged 27–45 years was achieved ($p < 0.001$), as a p-value <0.025 corresponds to a lower bound of the 2-sided 95% CI >90%, which supports the conclusion that the given anti-HPV seroconversion percentage is acceptable.

[two participants], rectal abscess, tonsillitis); eight participants in the older (27–45 years of age) group experienced nine SAEs (including basilar migraine, cervical vertebral fracture, fetal death, induced abortion, ligament injury and meniscus injury, pneumonia, rotator cuff syndrome, and tonsillitis). None of these SAEs were considered related to the study vaccine by the reporting investigator.

A total of eight participants became pregnant (all single pregnancies) during the course of the study. The outcomes of seven pregnancies were known: three resulted in a live birth, and four resulted in fetal loss (one spontaneous abortion at 9 weeks of gestation, and three induced abortions). No congenital anomalies were reported.

4. Discussion

Previous analyses conducted in the placebo arm of a large clinical trial showed that adult women are at risk of acquiring new HPV infections: in these analyses, most (86%) women were not infected with any of the 9 HPV types targeted by the 9vHPV vaccine, and for those who were infected, only one HPV type was found in most infections [24]. Therefore, the 9vHPV vaccine could provide broad protection against HPV infection in adult women. We report here the first immunogenicity and safety assessment of the 9vHPV vaccine in adult women. This study showed that the 9vHPV vaccine was highly immunogenic in women 16–45 years of age. Anti-HPV 16/18/31/33/45/52/58 antibody responses in women 27–45 years of age were non-inferior to those observed in women 16–26 years of age (i.e., the population used to establish 9vHPV vaccine efficacy [21,22]). The 9vHPV vaccine was generally well tolerated, and the safety profile was similar between women 16–26 years of age and women 27–45 years of age. This supports bridging of efficacy findings from young women 16–26 years of age to women 27–45 years of age.

While the three-dose regimen of 9vHPV induced robust anti-HPV 6/11/16/18/31/33/45/52/58 responses in both women aged 27–45 years and women aged 16–26 years, a trend towards lower GMTs for all HPV types was observed in the older versus younger group. Combined immunogenicity analyses of five 9vHPV vaccine studies also showed a decrease in GMT with increasing age among girls and women 9–26 years of age [32]. Based on the data presented in this study, this observation can be extended to girls and women 9–45 years of age. Immunogenicity analyses of 4vHPV vaccine clinical studies also showed a decrease in GMT with increasing age among girls and women 9–45 years of age [17,33]. Nevertheless, the efficacy of the 4vHPV vaccine in clinical trials was high in women across the 16–45 years age range [14–17]. No difference in 4vHPV vaccine efficacy was observed between women 24–34 years of age and women 35–45 years of age [16,17]. The durable effectiveness of the 4vHPV vaccine, defined as no breakthrough disease related to vaccine HPV types for $\geq$10 years after the first vaccine dose, has been demonstrated for girls and women vaccinated at 9–45 years of age [34–36]. The consistent high efficacy and long-term effectiveness of the 4vHPV vaccine across the 9–45 years age range suggest that the decrease in HPV vaccine immunogenicity with age does not have clinical relevance.

The 9vHPV vaccine was generally well tolerated, and there were no vaccine-related SAEs, no discontinuations due to a vaccine-related AE, and no deaths during the study. Moreover, the safety profile of the vaccine was similar between women 16–26 years of age and women 27–45 years of age. A previously reported combined analysis of the safety of the 9vHPV vaccine across seven phase 3 studies also demonstrated that the vaccine is generally well tolerated in individuals 9–26 years of age [37]. Overall, this study supports a favorable safety profile of the vaccine in individuals up to age 45 years.

The main strength of this study is that the design was informed by a large body of existing evidence, including established methods and extensive efficacy, immunogenicity, and safety assessment of the 4vHPV and 9vHPV vaccines; nevertheless, this study has several limitations. First, this study was limited to European countries; however, the evidence generated by this study can reasonably be extrapolated to other regions of the world. Accrued clinical evidence for the 9vHPV vaccine indicates that its efficacy, immunogenicity, and safety is consistent and reproducible across age range, ethnicities, and geographical regions [21,32,37–39]. Another potential limitation of this study is that there was no assessment of clinical efficacy in terms of disease prevention. The efficacy of 4vHPV and 9vHPV vaccines has been extensively demonstrated in women 16–45 years of age and women 16–26 years of age, respectively [14–17,21,22]. Clinical trial results with the 4vHPV vaccine are considered relevant to the 9vHPV vaccine since the two vaccines are manufactured similarly, share virus-like particles for four HPV types (HPV 6/11/16/18), and have comparable immunogenicity and efficacy [3,21,22]. Considering the results of this study, it is reasonable to infer efficacy of the 9vHPV vaccine in women 27–45 years of age and conclude that

Table 5
Summary of month 7 anti-HPV GMTs and seroconversion percentages for HPV types 6/11/16/18/31/33/45/52/58 by age sub-stratification (PPI population).

		9vHPV vaccine (N = 1210)			
		GMT (mMU/mL)		Seroconversion	
Assay (cLIA)	n	GMT	95% CI	m (%)	95% CI
Anti-HPV 6					
16–20 years of age	198	909.0	823.2–1003.8	198 (100.0)	98.2–100.0
21–26 years of age	223	693.8	629.1–765.1	222 (99.6)	97.5–100.0
27–36 years of age	215	667.6	605.4–765.1	215 (100.0)	98.3–100.0
37–45 years of age	233	612.6	550.4–681.7	233 (100.0)	98.4–100.0
Anti-HPV 11					
16–20 years of age	198	680.8	614.4–754.5	198 (100.0)	98.2–100.0
21–26 years of age	223	534.1	485.4–587.7	223 (100.0)	98.4–100.0
27–36 years of age	215	470.9	428.9–517.1	215 (100.0)	98.3–100.0
37–45 years of age	233	438.0	399.1–480.8	232 (99.6)	97.6–100.0
Anti-HPV 16					
16–20 years of age	204	3422.3	3100.1–3777.9	204 (100.0)	98.2–100.0
21–26 years of age	232	2800.2	2560.1–3062.8	232 (100.0)	98.4–100.0
27–36 years of age	206	2269.3	2034.3–2531.3	206 (100.0)	98.2–100.0
37–45 years of age	242	2048.9	1847.6–2272.2	242 (100.0)	98.5–100.0
Anti-HPV 18					
16–20 years of age	190	861.1	762.6–972.3	190 (100.0)	98.1–100.0
21–26 years of age	231	660.5	593.6–734.9	231 (100.0)	98.4–100.0
27–36 years of age	229	558.5	497.1–627.5	229 (100.0)	98.4–100.0
37–45 years of age	242	508.2	453.9–569.0	240 (99.2)	97.0–99.9
Anti-HPV 31					
16–20 years of age	207	685.2	614.7–763.8	207 (100.0)	98.2–100.0
21–26 years of age	240	528.7	476.4–586.7	240 (100.0)	98.5–100.0
27–36 years of age	232	410.2	366.8–458.7	232 (100.0)	98.4–100.0
37–45 years of age	256	383.0	343.7–426.9	255 (99.6)	97.8–100.0
Anti-HPV 33					
16–20 years of age	210	386.5	350.8–425.8	210 (100.0)	98.3–100.0
21–26 years of age	247	329.5	301.0–360.6	247 (100.0)	98.5–100.0
27–36 years of age	236	273.1	250.3–298.0	236 (100.0)	98.4–100.0
37–45 years of age	257	246.6	224.5–270.9	256 (99.6)	97.9–100.0
Anti-HPV 45					
16–20 years of age	219	242.1	212.9–275.3	217 (99.1)	96.7–99.9
21–26 years of age	251	193.7	174.4–215.3	251 (100.0)	98.5–100.0
27–36 years of age	251	152.3	135.9–170.8	251 (100.0)	98.5–100.0
37–45 years of age	264	139.5	124.3–156.5	260 (98.5)	96.2–99.6
Anti-HPV 52					
16–20 years of age	211	388.7	351.9–429.3	211 (100.0)	98.3–100.0
21–26 years of age	245	313.8	287.8–342.3	245 (100.0)	98.5–100.0
27–36 years of age	240	260.0	238.1–284.0	240 (100.0)	98.5–100.0
37–45 years of age	256	231.1	209.9–254.6	256 (100.0)	98.6–100.0
Anti-HPV 58					
16–20 years of age	207	469.4	425.0–518.4	207 (100.0)	98.2–100.0
21–26 years of age	244	395.7	360.3–434.7	244 (100.0)	98.5–100.0
27–36 years of age	232	307.1	278.8–338.3	232 (100.0)	98.4–100.0
37–45 years of age	246	286.6	260.4–315.4	245 (99.6)	97.8–100.0

CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HPV, human papillomavirus; mMU, Milli Merck units; PPI, per-protocol immunogenicity.
N = number of participants randomized to the respective age group who received at least one injection.
n = number of subjects contributing to the analysis.
m = number of subjects seropositive to the relevant HPV type.

conducting a complex and lengthy efficacy trial in that population is not justified. Of note, this has been accepted by regulatory agencies: the 9vHPV vaccine is licensed for use in individuals aged nine years and older in the European Union [40] and in individuals 9–45 years of age in the United States [41]. Also, the Advisory Committee on Immunization Practices has extended its recommendation regarding HPV vaccination for all adults 27–45 years of age based on shared decision making [42].

While national immunization programs are primarily focused on HPV vaccination of pre-adolescents and adolescents, optimal vaccine coverage has not yet been achieved in many countries. Moreover, catch-up vaccination of unvaccinated adults has not been consistently implemented. Therefore, most adults remain susceptible to acquiring one or more new, HPV-vaccine preventable infections. Vaccination may also be useful to prevent re-infection with HPV types encountered previously, as the 4vHPV vaccine prevented re-infection in women with serological evidence of previous HPV infection but no evidence of current infection (i.e., HPV seropositive and HPV DNA negative) [16]. While decline in prevalence of vaccine-type HPV infection, high-grade cervical dysplasia and genital warts was observed in vaccination programs that include catch-up cohorts [43], implementation of vaccination strategies targeting multiple age cohorts would need to consider factors such as cost effectiveness and impact of existing screening programs, which vary from country to country.

The burden of HPV-related disease is substantial in adult women. The burden encompasses not only cancers, but also pre-cancers and the associated treatment-related morbidity. While approximately 600,000 cases of cervical cancer are expected in 2020, this number is anticipated to rise to an annual 1.3 million

Table 6
Summary of AEs among all vaccinated participants.

	9vHPV vaccine			
	Women 16–26 years (N = 570)		Women 27–45 years (N = 640)	
	Count	(%)	Count	(%)
Participants with one or more AEs[a]	529	(92.8)	592	(92.5)
Injection-site event[b]	499	(87.5)	545	(85.2)
Pain	491	(86.1)	530	(82.8)
Mild	267	(46.8)	352	(55.0)
Moderate	207	(36.3)	166	(25.9)
Severe	17	(3.0)	12	(1.9)
Swelling	133	(23.3)	149	(23.3)
Mild (0 to ≤2.5 cm)	79	(13.9)	83	(13.0)
Moderate (>2.5 cm to ≤5.0 cm)	38	(6.7)	43	(6.7)
Severe (>5.0 cm)	14	(2.5)	12	(1.9)
Unknown	2	(0.4)	11	(1.7)
Erythema	111	(19.5)	108	(16.9)
Mild (0 to ≤2.5 cm)	77	(13.5)	72	(11.3)
Moderate (>2.5 cm to ≤5.0 cm)	25	(4.4)	29	(4.5)
Severe (>5 cm)	4	(0.7)	3	(0.5)
Unknown	5	(0.9)	4	(0.6)
Systemic event[c]	378	(66.3)	412	(64.4)
Vaccine-related[d] systemic event	143	(25.1)	154	(24.1)
Headache	72	(12.6)	87	(13.6)
Pyrexia	17	(3.0)	11	(1.7)
Fatigue	16	(2.8)	22	(3.4)
Serious event[a]	6	(1.1)	8	(1.3)
Vaccine-related[d] event	0	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)
Discontinuation[e] because of an AE[a]	0	(0.0)	1	(0.2)
Because of a vaccine-related[d] event	0	(0.0)	0	(0.0)
Because of a serious event	0	(0.0)	0	(0.0)
Because of a serious vaccine-related[d] event	0	(0.0)	0	(0.0)
Participants with temperature data	569		640	
Participants with the following maximum temperatures[b]				
≥37.8 °C	20	(3.5)	16	(2.5)
≥38.9 °C	2	(0.4)	2	(0.3)

AE, adverse event.
Injection-site and systemic AEs shown are those with incidence ≥2% in any vaccination group during the study.
N = number of participants as-treated who received at least one dose of the indicated vaccine and had at least one follow-up visit for AEs.
[a] At any time during the study.
[b] Days 1–5 following any vaccination visit.
[c] Days 1–15 following any vaccination visit.
[d] As determined by the reporting investigator.
[e] Study vaccination withdrawn.

cases in 2069 in the absence of changes to vaccination and screening coverage [44]. Practically, this would mean 44 million cervical cancer cases would occur during the 50-year period from 2020 to 2069 [44]. The rise is due to population growth, aging, and the increased exposure to risk factors. These figures reveal that there is a significant medical need for HPV vaccination in women and men of all ages. HPV-negative cervical cancer is rare (<5%) [45]. As early as 2015, international experts have proposed that combining HPV vaccination of adult women together with cervical HPV screening would result in a more rapid achievement of cervical-cancer prevention, a concept referred to as 'HPV-FASTER' [46]. The idea of the HPV-FASTER protocol is to offer HPV vaccination to women in a broad age range of 9–45 years, or even up to 50 years in some settings, irrespective of HPV-infection status. Incorporation of the HPV-FASTER concept into cervical cancer modeling suggests that achieving 80–100% vaccine coverage with the 9vHPV vaccine for females and males 12–15 years of age and 70% vaccination coverage in those 16–49 years of age would lead to approximately 14 million cancer cases averted over 50 years, making cervical cancer a rare disease by 2069 [45]. Moreover, HPV vaccination reduces the risk of subsequent cervical disease, including high-grade disease in women who have had surgical treatment for HPV-related disease [47–50]. The 9vHPV vaccine with its broad HPV coverage is a powerful element in HPV disease prevention in men and women of all ages.

Declaration of competing interest

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Author contributions

Elmar Joura contributed to study conception, design or planning, data acquisition, data analysis, interpretation of the results, drafting the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

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Frederick Wittke contributed to study conception, design or planning, analysis of the data, interpretation of the results, and critically reviewed or revised the manuscript for important intellectual content.

All authors approved the final version of the manuscript and had access to the relevant study data and related analyses and vouch for the completeness and accuracy of the data presented.

Appendix A. Supplementary material

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