END OF STUDY SAFETY, IMMUNOGENICITY, AND EFFICACY OF QUADRIVALENT HPV (TYPES 6, 11, 16, 18) RECOMBINANT VACCINE IN ADULT WOMEN 24 TO 45 YEARS OF AGE

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Running head: Quadrivalent HPV vaccine in adult women

Abstract (247/250 words)

Objective: Previous analyses of data from a randomized placebo-controlled trial in women aged 24-45 has shown the quadrivalent HPV vaccine to be efficacious in the prevention of infection, cervical intraepithelial neoplasia (CIN) and external genital lesions (EGL) related to HPV 6, 11, 16 and 18. In this report we present end-of-study efficacy, safety and immunogenicity data with a mean follow-up time of 3.8 years.

Methods: This study enrolled 3,819 24-45 year old women with no history of cervical disease in the past 5 years, LEEP, hysterectomy, or genital warts. Women received quadrivalent vaccine or placebo at day 1, and months 2 and 6. Ascertainment of HPV-related CIN and EGL was accomplished via Pap testing, genital inspection and cervicovaginal sampling. The main analysis was conducted in a per-protocol efficacy population (received 3 doses of vaccine/placebo within 1 year of enrollment, were naïve to the relevant HPV types at day 1, and remained free of infection through month 7). Efficacy was also estimated in other naïve and non-naïve populations.

Results: Updated vaccine efficacy against the combined incidence of persistent infection, CIN or EGL related to HPV6/11/16/18 in the per-protocol population was 88.7% (95% CI: 78.1, 94.8). At month 48, 91.5%, 92.0%, 97.4% and 47.9% of vaccinated women were still considered seropositive to HPV 6, 11, 16 and 18, respectively. No serious vaccine-related adverse experiences were reported.

Conclusions: The data strengthen previous results on the efficacy, immunogenicity and safety of the qHPV vaccine in women up to age 45 years.

Funding: Merck & Co., Inc.

Keywords: HPV, vaccine, cervical, cancer, adult

Introduction

Persistent infection of the uterine cervix by 15 to 20 carcinogenic human papillomavirus (HPV) genotypes leads to the vast majority of cervical cancers[1, 2] and related precursor lesions.[3] While all sexually active women are at risk of HPV infection, the incidence of HPV infection peaks soon after the onset of sexual activity in most populations.[4-6] Incidence rates tend to decline thereafter, however women older than age 25 are likely to remain at significant risk for acquisition of new HPV infections.[7, 8]

Data from Colombia show that the 5-year cumulative risk of incident cervical HPV infection decreased from 42.5% in females 15-19 years old to 12.4% in women over 44 years of age (37% in those 20-24 years old, 30% in those 25-29 years old, 22% in those 30-44 years old).[9] However, a second peak in HPV DNA prevalence has been observed in women in the 4th and 5th decade of life.[10] Whether this second peak is due to new infections, viral reactivation, waning immunity, or another mechanism is unclear. The cohort study from Colombia supports the possibility of new infections, since the curve of incident high-risk HPV infections is also bimodal with a first peak in women under 25 years of age and a second peak after menopause.[9]

Previous literature has demonstrated that a prophylactic quadrivalent HPV (qHPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine with the adjuvant amorphous aluminum hydroxyphosphate sulfate (AAHS) was highly effective in preventing HPV 6, 11, 16, or 18-related high-grade cervical, vulvar, or vaginal intraepithelial neoplasia (CIN, VIN, or VaIN), as well as adenocarcinoma in situ (AIS) in women aged 16 to 26 who were naïve to the respective vaccine HPV types at enrollment.[11, 12] High efficacy against HPV 6 and 11-related genital warts was also seen.[11] Data from these trials indicated that women who are naïve to all 4 vaccine HPV types (negative by both serological and DNA testing) prior to vaccination derive full benefit (i.e.,

protection from disease caused by all 4 vaccine HPV types), while women who are infected with ≥1 vaccine HPV types before vaccination will derive partial benefit (i.e., protection from the types which the subjects were not infected with at time of vaccination).[13]

In addition, recently published data support the efficacy of the qHPV vaccine in susceptible women 24 to 45 years of age, building on the data in younger women. Among women 24 to 45 in vaccine HPV type-specific per-protocol populations (85.2% of all vaccinated subjects), vaccine efficacy against the combined incidence of infection of ≥6 months duration, cervical and external genital disease related to HPV 6, 11, 16, and 18 was 90.5% (95% CI: 73.7-97.5).[14] Vaccine efficacy against the co-primary endpoint (combined incidence of infection of ≥6 months duration, cervical and external genital disease related to HPV 16 and 18) was 83.1% (95% CI: 50.6, 95.8). While these data are encouraging, they were based on analyses of data with a mean follow-up time of 2.2 years. As this trial is now complete, a reanalysis of all data gathered during the trial is presented.

In this report we further evaluate the efficacy, safety and immunogenicity of the prophylactic qHPV vaccine in 24-45 year old women, using end of study data from an international randomized, placebo controlled phase III clinical trial with a mean follow-up time of 3.8 years. These data include an additional 1.6 years of follow-up from previously published analyses[14], and will help define the benefit women 24 to 45 years of age will experience from prophylactic HPV vaccination.

Methods

Study Design

Between June 18th, 2004 and April 30th, 2005, 3,819 women between the ages of 24 years, 0 days and 45 years, 364 days were enrolled from 38 international study sites into an ongoing randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study (protocol 019; NCT00090220). Subjects were enrolled from community health centers, academic health centers, and primary health care providers in Colombia, France, Germany, Philippines, Spain, Thailand, and the United States. The current report represents the end of study analysis, after a mean follow-up time of 3.8 years.

Women were eligible to participate in the study if they were not pregnant (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU β-hCG performed prior to each vaccination) and if they had not undergone hysterectomy. Subjects were asked to use effective contraception through month 7 of the study. Women with a history of genital warts, or current/past cervical disease were not eligible for enrollment. Those with prior cervical definitive therapy and those having undergone a cervical biopsy within the past 5 years were also excluded. Additionally, those subjects infected with human immunodeficiency virus (HIV) and those who were otherwise immunocompromised were not eligible for enrollment. Lifetime number of sexual partners was not an inclusion or exclusion criterion.

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

Subjects were stratified into 2 age strata (≤34 and ≥35 years) and randomized in an approximate 1:1 ratio to receive either AAHS quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine (GARDASIL™/SILGARD™, Merck & Co., Inc., Whitehouse Station, NJ) or visually indistinguishable aluminum-containing placebo at day 1, and months 2 and 6. Details of the quadrivalent HPV vaccine have been published previously.[15]

A computer-generated allocation schedule was generated by the sponsor's Clinical Biostatistics department. Following informed consent and determination that all entry criteria were met, eligible subjects were randomized to a vaccination group, stratified in approximately equal proportions between the 2 age strata within each study center, using an Interactive Voice Response System (IVRS). All study site investigators and personnel, study participants, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the treatment allocation will be revealed to the study researchers after data collection and analyses are complete at end of study.

Efficacy Endpoints and Case Definition

The co-primary efficacy endpoints were (1) the combined incidence of HPV 6, 11, 16, or 18-related infection of ≥6 months duration, cervical and external genital disease (includes CIN, VIN, VaIN, AIS, cervical, vulvar, or vaginal cancer, and genital warts); and (2) the combined incidence of HPV 16 or 18-related infection of ≥6 months duration, cervical and external genital disease. The secondary efficacy endpoint was the combined incidence of HPV 6 or 11-related infection of ≥6 months duration, cervical and external genital disease. The first co-primary efficacy hypothesis was to be tested with ≥25 cases of the first co-primary efficacy endpoint and ≥14 cases of the second co-primary efficacy endpoint were observed (i.e., fixed event design).

The second primary hypothesis was to be tested only if the first co-primary hypothesis test was successful. The secondary hypothesis was to be tested when ≥19 cases of the secondary efficacy endpoint were observed, and only if both co-primary hypothesis tests were successful. Under an assumed incidence of 0.6, 0.2, and 0.6 per 100 person-years[16, 17] corresponding to HPV 16-, HPV 18-, and HPV 6/11-related persistent infection and disease, respectively, the study with 3,819 subjects has 87% and 80% power to achieve success on the co-primary and secondary hypothesis, respectively, if the vaccine is at least 80% efficacious.

Infection of ≥6 months duration was defined as detection of the same HPV type in cervicovaginal/anogenital swabs at ≥2 consecutive visits spaced ≥6 months apart (± 1 month visit window); or presence of cervical/genital disease associated with the relevant type with type-specific HPV DNA detected in cervicovaginal or anogenital swabs at the visit directly before or after biopsy. Disease was defined as a tissue sample diagnosed by a 4 member pathology panel as CIN, AIS, VIN, VaIN, genital warts, or cervical, vulvar, or vaginal cancer with type-specific HPV DNA detected in tissue from the same lesion, as described.[11]

Safety and Immunogenicity Objectives

The primary safety objective was to demonstrate that a 3-dose regimen of quadrivalent HPV vaccine is generally well tolerated in women 24 to 45 years of age. The primary immunogenicity objectives included (1) to evaluate the kinetics and age dependence of anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of quadrivalent HPV vaccine, and (2) to observationally compare anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of quadrivalent HPV vaccine among HPV-naïve women 24 to 45 years of age.

Clinical Follow-Up

For the ascertainment of disease, a complete gynecological exam was performed at day 1 and months 7, 12, 24, 36, and 48 which included a pelvic exam (both speculum and bimanual exams). External genital inspections were to be performed with a magnifying glass at day 1, and at months 7, 12, 18, 24, 30, 36, 42, and 48. Labial/vulvar/perineal and perianal swabs and endo/ecto cervical swabs for HPV Multiplex PCR testing were to be obtained at day 1 and months 7, 12, 18, 24, 30, 36, 42, and 48. ThinPrep™ (Cytyc, Boxborough, MA) Pap testing for cytology would take place during these visits. Once received, cytology specimens were evaluated using the Bethesda System—2001 [18]. Colposcopy referral was algorithm based. Biopsy material was first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN), and then read for endpoint determination by a blinded panel of 4 pathologists. If indicated, definitive therapy was performed.

Serum for immunogenicity testing was collected prior to vaccination on day 1, and at months 7, 12, 24, 36, and 48. Antibody responses and the proportion of subjects seroconverting for vaccine type epitope-specific neutralizing anti-HPV antibodies was analyzed with a competitive Luminex-based immunoassay (cLIA) developed by Merck Research Laboratories using technology from the Luminex corporation as described.[19]

Adverse experiences were solicited from subjects by general questioning at study visits and by use of a vaccine report card (VRC). The VRC was provided to the subject at each vaccination visit in order to record temperatures as well as local and systemic adverse experiences.

Statistical Analysis

No tests of hypothesis were conducted in the current analyses. The final tests relating to the study co-primary and secondary efficacy hypotheses were conducted previously, the results of which were published in Munoz et al.[14] The results presented in this report are the updated estimates of efficacy of the qHPV vaccine against the co-primary and secondary efficacy endpoints and against selected exploratory efficacy endpoints.

Populations studied

Efficacy analysis was conducted in the per-protocol efficacy (PPE) population, i.e., subjects who were seronegative at day 1 and PCR-negative (swab and biopsy specimens) from day 1 through month 7 to the relevant vaccine HPV type(s) and did not violate the protocol. PPE-eligible participants received all 3 vaccinations within 1 year, and had 1 or more follow-up visits following month 7. Case counting commenced at month 7.

Analyses were also conducted in an intention-to-treat (ITT) population consisting of subjects who received ≥1 dose of vaccine or placebo and returned for follow-up. These subjects could have been seropositive and/or PCR positive to vaccine HPV types at enrollment, and represent a general non-vaccinated population. Case counting in the ITT population commenced after day 1.

Additional analyses were conducted in a population of subjects deemed 'naïve to the relevant HPV type' (NRT). This population was DNA negative to HPV 6/11/16/18/31/33/35/39/45/52/55/56/58/59 at enrollment and seronegative for HPV 6/11/16/18 at enrollment and received at least one dose of vaccine or placebo. NRT case counting began after day 1.

Role of the Funding Source

The studies were designed by the sponsor (Merck & Co, Inc.) in collaboration with external investigators and an external data and safety monitoring board. The sponsor collated the data, monitored the conduct of the study, performed the statistical analysis and coordinated the writing of the manuscript with all authors. The authors were actively involved in the collection, analysis or interpretation of the data, the revising of the manuscript for intellectual content, and approved the final manuscript**.** All authors had access to data and took part in the decision on where to submit the paper for publication.

Results

3,819 women were enrolled into the study and randomized to receive either quadrivalent HPV vaccine or placebo. A total of 3,692 women (96.7%) received all three vaccinations and entered the follow-up period. Key baseline demographic characteristics were generally similar between subjects in the vaccine and placebo groups. Almost all women were non-virgins at enrollment (99.9%); and the mean age of sexual debut was 19 (±3.7) years. Detailed information on enrollment, baseline characteristics and sexual history of the study population can be seen in Muñoz et al.[14]

One third of women (33.2%) were positive to HPV 6, 11, 16 or 18 at baseline by serology or DNA testing, but most of these women (91%) were positive to none or only 1 of the 4 vaccine types. Geometric mean antibody titers in response to qHPV vaccine peaked at month 7 and declined to relative stability between months 24 and 48 (Figure 1). A vast majority of previously

HPV naïve vaccinated women seroconverted for HPV 6 (98.4%), 11 (98.1%), 16 (98.8%) and 18 (97.3%) by month 7. At month 48, 91.5%, 92.0%, 97.4% and 47.9% of vaccinated women were still considered seropositive to HPV 6, 11, 16 and 18, respectively (as defined by the cLIA assay). In general, women seropositive to a particular vaccine HPV type at enrollment had higher antibody titers for that type at throughout follow-up, when compared to women who were naïve to that type at enrollment, likely due to immune memory caused by previous HPV exposure (Supplemental Figure 1). Month 48 geometric mean titer levels were greater in women seropositive and DNA negative for HPV 6, 11, 16 and 18 at enrollment by 7.8 fold, 13.2 fold, 4.2 fold and 15.9 fold, respectively.

In the per-protocol efficacy population (PPE) an additional 53 cases related to vaccine HPV types were observed (7 vaccine and 46 placebo) subsequent to the original analyses of data previously published (Table 1).[14] All 7 additional cases observed in the vaccine group were cases of persistent infection. The one case of CIN 2/3 in the vaccine group at end of study was observed in the original study follow-up. In the naïve-to the relevant type (NRT) and intention-to-treat populations (ITT), 60 and 68 additional cases of infection and/or disease related to vaccine HPV types were observed.

Updated vaccine efficacy against the combined incidence of persistent infection, CIN or EGL related to vaccine HPV types in the PPE and NRT and ITT populations was 88.7% (95% CI: 78.1, 94.8), 79.9% (95% CI: 69.4, 87.3) and 47.2% (95% CI: 33.5, 58.2) respectively (Table 1). These data were comparable to the original efficacy estimates published in Muñoz et al.[14] of 90.5% (95% CI: 73.7, 97.5), 74.6% (95% CI: 58.1, 85.3) and 30.9% (95% CI: 11.1, 46.5). Similar to earlier results, efficacy against the combined incidence of persistent infection, CIN or EGL in the PPE population related to vaccine HPV types was 91.3% (95% CI: 78.4, 97.3) in

women aged 24-34 and 83.8% (95% CI: 57.9, 95.1) in women aged 35-45 (data not shown). Efficacy against any grade CIN related to vaccine HPV types was statistically significant for all three analysis populations; however, efficacy estimates for CIN 2/3 or worse in the PPE, NRT and ITT analysis populations are not statistically significant (1 in the vaccine group and 6 in the placebo group in the PPE, 3 vs 8 in the NRT, and 21 vs 27 in the ITT) due to the study's lack of power to demonstrate statistically significant efficacy for this endpoint. Vaccine efficacy against the combined incidence of persistent infection, CIN or EGL in the PPE and ITT populations related to HPV 16/18 was 84.7% (95% CI: 67.5, 93.7) and 41.6% (95% CI: 24.3- 55.2), respectively (Table 1). Vaccine efficacy against the combined incidence of persistent infection, CIN or EGL in the PPE and ITT populations related to HPV6/11 was 100% (95% CI: 79.0, 100) and 47.1% (95% CI: 11.4, 69.2), respectively. Prevalent infection, which is present at baseline, was largely responsible for the lower estimate of efficacy against the composite endpoint. Supplemental Figure 2 illustrates the marked differences in incidence by baseline infection status. Overall efficacy estimates were somewhat lower in the older age group (35-45 years) but differences were not statistically significant. In addition, efficacy estimates for HPV infection of at least 6- and 12-months duration were comparable.

In the ITT analysis of high grade CIN due to any HPV type, there was an imbalance of baseline infection and disease at randomization that resulted in a higher number of cases of CIN 2/3 or worse in the vaccine group as compared to the placebo group. As shown in Table 2, this excess number of CIN2/3 cases were mainly due to non-vaccine HPV types. Supplemental Table 1 shows that HPV types 33, 39, 51 and 58 accounted for a substantial proportion of the cases of infection at baseline. The high level of background HPV infection due to these 4 HPV types accounted for 20 cases of CIN 2/3 or worse in the vaccine group versus 5 cases in the

placebo group. Of the 20 cases of CIN 2/3 or worse, 11 were diagnosed within the first 4 months of the study (Supplemental Table 2).

Vaccine efficacy in reducing the incidence of any abnormal Pap smear related to any vaccine HPV types during follow-up was 97.4% (95% CI: 84.5, 99.9) in the PPE population and 50.1% (95% CI: 24.2, 67.8) in the ITT population (Table 3). Efficacy point estimates did not differ substantially by age group, HPV type, or severity of Pap abnormality. Efficacy against the incidence of abnormal Pap smears related to HPV 16 or 18 was 96.3% (95% CI: 77.7, 99.9) in the PPE population and 47.5% (95% CI: 16.9, 67.4) the ITT population (data not shown).

Among vaccinated women in the PPE population there was a 12.6%, 16.3% and 30.9% reduction seen in the occurrence of colposcopy, biopsy and any definitive therapy, respectively (Table 4). None of these reductions were statistically significant.

Table 5 presents vaccine efficacy estimates against HPV6/11/16/18-related persistent infection (there were no cases of CIN) in women with serological evidence of previous HPV infection, but without evidence of current infection (seropositive/DNA negative). Overall efficacy in these women was 66.9% (95% CI: 4.3, 90.6). Women aged 35 to 45 showed higher efficacy than women aged 24 to 34; however the differences seen were not statistically significant (81.3% versus 27.4%, respectively).

Vaccine safety and tolerability data can be seen in Table 6. There was a slightly higher occurrence of overall adverse experiences and vaccine-related adverse experiences in the vaccinated group. This is largely due to the higher incidence of overall and vaccine-related injection-site adverse experiences which were reported. There were no serious vaccine-related adverse experiences reported in either the vaccine or placebo cohorts. Reasons for discontinuation due to a vaccine-related adverse experience in the vaccine group included

hypersensitivity, urticaria, mouth ulceration, injection-site swelling, and facial edema. Reasons for discontinuation due to a vaccine-related adverse experience in the placebo group included fatigue and overdose. Reasons for death in the vaccine group (n = 7) included two cardiac arrests (one secondary to breast cancer metastasis, and one secondary to cerebrovascular accident), acute liver disease secondary to nasopharyngeal cancer, breast cancer, tuberculosis, pulmonary embolism, and pericarditis. The death in the placebo group resulted from pulmonary embolism.

Discussion

In this report we demonstrate that vaccine efficacy against the combined incidence of persistent infection, CIN or EGL related to vaccine HPV types in the PPE and NRT populations was 88.7% (95% CI: 78.1, 94.8) and 79.9% (95% CI: 69.4, 87.3), respectively. While the observed efficacy of most endpoints was largely comparable to previous evaluations in this population[14], there were exceptions, particularly for the HPV 16 and 18-related endpoints in the ITT population (Table 1). These newly significant efficacy results are likely the result of additional follow-up and endpoint accrual and possible resolution of prevalent infections present at enrollment. Additionally, the extra endpoints accrued during the 1.6 additional years of follow-up between the previously published data[14] and the data in the current report result in increased precision of the efficacy estimates given, when compared to those previously reported.[14] These data reaffirm previous conclusions that prophylactic administration of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing HPV 6, 11, 16, and 18-related infection and disease (genital warts, AIS, any grade CIN, VIN2/3, VaIN2/3).

In the PPE population, there were 10 cases of infection and/or disease related to vaccine HPV types in the vaccine group as shown in Table 1. Three cases were observed during the 2007 endpoint driven analysis and 7 in the additional follow-up period. Only one of the 10 cases had HPV 16 persistent infection alone. HPV 6, 11, 16, and 18 antibody titers at month 7 for this potential breakthrough case were 2,513, 3,775, 7,850 and 1,532 (uMU/mL), respectively. Six other cases had infections with both HPV 16 and other high-risk non-vaccine types, 1 case had HPV 16 and 18 persistent infection with other high-risk non-vaccine types, and 2 cases had HPV 6 persistent infection with other high-risk non-vaccine types.

Consistent with trial data from younger women, this end of study analysis among women aged 24 to 45 years confirms that the qHPV vaccine is also highly efficacious in women with evidence of previous exposure to HPV 6/11/16/18 infection but with no evidence of current infection (seropositive and DNA negative). Efficacy against combined endpoint was 66.9% overall and reached 81.3% in the older age group (35 to 45 years). These data suggest that women who had had previous infections or previous exposure to HPV may benefit from vaccination with the qHPV vaccine.

Vaccination with qHPV vaccine produced robust antibody responses in women 24 to 45 years of age. Seropositivity to each of the 4 vaccine HPV types exceeded 97% at 4 weeks post-dose 3.[14] At month 48, 91.5%, 92.0%, 97.4%, and 47.9% of women were still seropositive for HPV 6, HPV 11, HPV 16 and HPV 18, respectively. While these data indicate that HPV 18 seropositivity declined more quickly than other vaccine HPV types, no cases of infection or disease related to HPV 18 were seen among vaccinees in the PPE population, similar to previous results seen in younger women.[20]

Administration of the qHPV vaccine was generally well tolerated. The proportions of subjects who reported serious adverse experiences were comparable among the qHPV vaccine group and the placebo group. Few subjects discontinued study participation due to an adverse experience. While there was a slightly higher incidence of adverse experiences in the vaccine group, these results are largely due to increases in injection-site reactions, as seen in other studies of the qHPV vaccine in women.[11, 12, 14] While there were no serious vaccine-related adverse experiences, there was an imbalance in the number of women discontinuing due to adverse experiences, likely due to increased injection-site adverse experiences. Moreover, considering the entire study follow-up there were more women who died in the vaccine group (n = 7) when

compared to the placebo group (n = 1). Reasons for death in these subjects included cardiac arrest secondary to breast cancer metastasis, cardiac arrest secondary to cerebrovascular accident, and acute liver disease secondary to nasopharyngeal cancer. No study deaths were deemed by investigators as related to vaccination.

The current study has several limitations. First, certain restrictions to study entry may indicate that women in our study were at somewhat lower risk of acquiring HPV than women in the general population (disease history, etc). However, the baseline prevalence and incidence of HPV 16/18 infection in our placebo group were similar of those reported in the literatureamong women of similar age (data not shown). Second, the amount of disease that will be prevented by vaccinating women between the ages of 25 and 45 outside of a clinical trial is unknown. HPV infections that occur in women of this age may lead to high-grade lesions and cancer at different rates than infections that occur shortly after sexual debut. However, in a cohort study of Colombian women the incidence of CIN 2+ in women with normal cytology at baseline and with incident HPV 16 infection was similar in women under 30 years of age and in women older than 30 years.[21] Third, because only 50-70% of HPV infections result in detectable anti-HPV responses, the baseline serology test may have underestimated prior exposure to HPV-6/11/16/18 in the study population. Lastly, this study was not powered to demonstrate statistically significant efficacy for high-grade disease endpoints and the randomization was not designed to achieve treatment group balance with respect to baseline prevalent infections on a by-HPV type basis. Thus, the study was not able to demonstrate statistically significant efficacy against CIN 2/3 in women aged 24-45. The treatment group imbalance with respect to baseline prevalent infections further negatively impacted the study's ability to demonstrate positive vaccine

efficacy on high grade CIN due to any HPV type as well as on cervical and external genital procedures.

The implications of these findings are relevant to elaborate accurate recommendations on cervical cancer preventative strategies in adult women. Based on the reported efficacy estimates of the qHPV vaccine and other trial data, mathematical modelers are now provided with new data to perform more precise cost-benefit and cost-effectiveness analyses assessing a variety of single and combined strategies for cervical cancer prevention in adult women. It is clear that HPV vaccination is likely to be beneficial to sexually active adult women as they are at a continuous risk of acquiring new HPV infections and of developing abnormal Pap smears, CIN, and cervical cancer.[22] However, public health recommendations for mass vaccination must take into consideration the cost-effectiveness of vaccination programs. Current vaccine and implementation costs modelling studies have shown that vaccination becomes less cost-effective with the increasing age of the target vaccination group. That's the main reason why the key priority of all public health recommendations concerning HPV vaccination is to target girls and young women for routine vaccination, with or without catch-up programs up to ages 25 or 26 years. Since the overall cost–benefit becomes progressively less favorable with increasing age, most health authorities have not widely recommended routine vaccination of older women. Nevertheless, as documented in this trial, sexually active women over the age of 26 also have the potential to benefit from vaccination and should be allowed the opportunity to choose to be vaccinated on an individual basis.

In summary, the data presented in this report strengthen previous results on the immunogenicity, safety and high efficacy of the qHPV vaccine in adult women up to 45 years of age regardless of previous exposure to HPV vaccine types.

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Authors Contributions: EB, RH, SH, and AS managed the sponsor's operations. JM, RM, PP, and DT set up study sites and enrolled participants into the study. KA, EM, JL, and NM helped draft the protocol. JB developed the PCR-based HPV 6/11/16/18 detection assays and tested the genital swab and biopsy samples using the assays. OMB developed and instituted the data analysis plan. XC and SV drafted the manuscript, to which all others contributed and approved before submission.

Conflict of Interest Statement:

XC has received travel and speaker honoraria and investigator grants from Merck & Co., Inc, GlaxoSmithKline, and Sanofi-Pasteur MSD. NM has received honoraria from Merck & Co., Inc and Sanofi-Pasteur MSD and is a member of the Merck global advisory board for HPV vaccine as well as a member of Sanofi-Pasteur MSD HPV steering committee. JL has received travel and speaker and investigator grants from Sanofi-Pasteur MSD. JM has conducted HPV vaccine studies for Merck & Co., Inc. and GlaxoSmithKline, and is on the medical advisory board for GlaxoSmithKline, Geneprobe, Sanofi-Pasteur MSD, Roche, and Abbott diagnostics. KA has conducted HPV vaccine studies for Merck & Co., Inc. and GlaxoSmithKline, and as acted as a consultant to Merck & Co., Inc. EM has served as a consultant to Merck & Co., Inc. NM, JL, KA, JM and EM are members of the Merck & Co., Inc. HPV steering committee. OB, SM, JB, SV, AS, and RH are employees of Merck & Co., Inc. and potentially own stock and/or stock options in the company.

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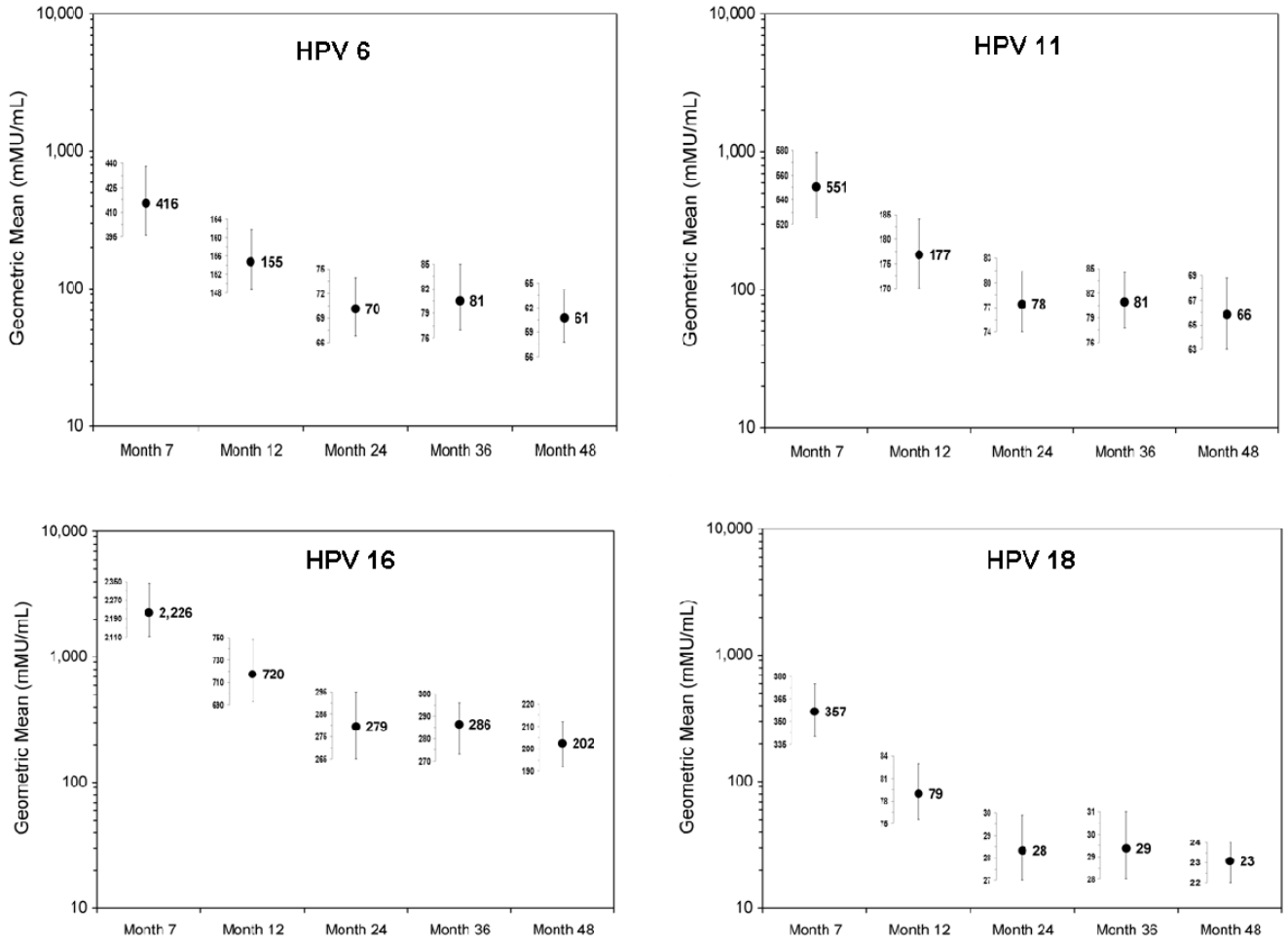
Tables and Figures

Figure 1. Summary of the persistence of anti-HPV geometric mean titers in women receiving the qHPV vaccine* (see also Supplemental Figure 1 stratified by baseline vaccine-type serostatus)



[*] The dots shown the in plot correspond to estimates of geometric mean titers (GMT). The vertical bars superimposed to each dot represent the 95% confidence interval associated with the estimated GMT. The mini vertical axes immediately to the left of the vertical bars show the range of the 95% confidence interval specific to each GMT estimate. The length of each vertical bar is relative only to the mini scale immediately to the left of the vertical bar. The length of the vertical bars across time points are not comparable. Comparisons of statistically significant difference or absence of statistically significant difference between GMTs over time should not be made on the basis of comparisons of the length of the vertical bars.

Table 1. End of study efficacy against the combined incidence of vaccine type-related infection of 6 months duration, CIN or EGL

Analysis Population Endpoint	HPV 6/11/16/18 related outcomes				HPV 16/18 related outcomes			
	n(m)		Observed		n(m)		Observed	
	qHPV	Placebo	Efficacy	95% CI	qHPV	Placebo	Efficacy	95% CI
Per-protocol efficacy population (PPE)								
Persistent Infection, CIN, or EGL	**10 (3)**	**86 (40)**	**88.7**	**(78.1, 94.8)**	**8 (3)**	**51 (22)**	**84.7**	**(67.5, 93.7)**
Persistent Infection	9 (2)	85 (39)	89.6	(79.3, 95.4)	7 (2)	50 (21)	86.2	(69.4, 94.7)
CIN (any grade)	1 (1)	17 (9)	94.1	(62.5, 99.9)	1 (1)	13 (7)	92.4	(49.1, 99.8)
CIN 2/3 or worse	1 (1)	6 (4)	83.3	(-37.6, 99.6)	1 (1)	6 (4)	83.4	(-36.7, 99.6)
EGL	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
Condyloma	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	NA	NA
HPV-naive to the relevant type population (NRT)								
Persistent Infection, CIN, or EGL	**27 (20)**	**130 (77)**	**79.9**	**(69.4, 87.3)**	**19 (14)**	**85 (48)**	**78.3**	**(64.0, 87.5)**
Persistent Infection	26 (19)	129 (76)	80.4	(69.9, 87.7)	18 (13)	84 (47)	79.1	(64.9, 88.2)
CIN (any grade)	3 (3)	27 (16)	89.0	(64.1, 97.9)	3 (3)	21 (12)	85.9	(52.7, 97.3)
CIN 2/3 or worse	3 (3)	8 (4)	62.7	(-55.5, 93.6)	3 (3)	8 (4)	62.9	(-54.6, 93.7)
EGL	2 (1)	11 (8)	81.9	(17.2, 98.1)	1 (1)	0 (0)	NA	NA
Condyloma	1 (0)	11 (8)	91.0	(37.9, 99.8)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	NA	NA
Intention to treat population (ITT)								
Persistent Infection, CIN, or EGL	**116 (108)**	**214 (154)**	**47.2**	**(33.5, 58.2)**	**95 (90)**	**160 (115)**	**41.6**	**(24.3, 55.2)**
Persistent Infection	110 (102)	211 (151)	49.0	(35.5, 59.9)	91 (86)	157 (112)	42.8	(25.5, 56.3)
CIN (any grade)	29 (25)	55 (41)	47.5	(16.3, 67.7)	28 (24)	48 (36)	41.9	(5.6, 64.9)
CIN 2/3 or worse	21 (19)	27 (21)	22.4	(-42.5, 58.3)	21 (19)	27 (21)	22.4	(-42.5, 58.3)
EGL	11 (9)	12 (9)	8.5	(-126.6, 63.4)	3 (2)	0 (0)	NA	NA
Condyloma	7 (6)	12 (9)	41.8	(-60.3, 80.6)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	2 (1)	0 (0)	NA	NA	2 (1)	0 (0)	NA	NA

n = number of cases at the end of study (mean follow-up time per subject of 3.8 years); m = number of cases in original report (mean follow-up time per subject of 2.2 years).

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; EGL = External genital lesions; qHPV = Quadrivalent Human Papillomavirus (types 6, 11, 16, 18) Recombinant Vaccine; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Table 2. Cases of CIN 2/3 or worse due to vaccine and non-vaccine HPV types by baseline infection status

Causal HPV Type in CIN2/3	Baseline HPV status	qHPV vaccine		Placebo	
		Cases	Rate	Cases	Rate
Any Type	**Any**	**62**	**0.9**	**51**	**0.7**
Vaccine type(s)*		**21**	**0.3**	**27**	**0.4**
	Day 1-negative for causal type	3	0.1	8	0.1
	Day 1-positive for causal type	18	3.9	19	4.7
Non-vaccine type(s)**		**40**	**0.6**	**25**	**0.4**
	Day 1-negative for causal type	13	0.2	4	0.1
	Day 1-positive for causal type	30	2.3	22	1.8
Unknown type	**Any**	**9**	**0.1**	**9**	**0.1**

*Vaccine type(s) = 6, 11, 16, or 18
**Non-Vaccine type(s) = 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59
The sum of the vaccine type-, non-vaccine type-, and unknown type-related cases is not equal to the any type-related cases since some subjects can have both vaccine type- and non-vaccine type-related CIN 2/3 or worse.

Table 3. Vaccine impact on the incidence of HPV 6/11/16/18-related Pap diagnoses

Endpoint	qHPV Vaccine (N=1,910)				Placebo (N=1,907)				Efficacy (%)	95% CI
	n	Cases	PYR	Rate	n	Cases	PYR	Rate		
Per-protocol population										
HPV 6/11/16/18-Related ASC-US HR-HPV positive, or worse	1,578	1	5,028.7	0.0	1,583	38	5,006.5	0.8	97.4	(84.5, 99.9)
24 to 34 year-olds	771	1	2,397.2	0.0	785	25	2,442.5	1.0	95.9	(75.1, 99.9)
35 to 45 year-olds	807	0	2,631.5	0.0	798	13	2,564.0	0.5	100	(68.0, 100)
By HPV Type										
HPV 6-Related	1,299	0	4,142.1	0.0	1,304	12	4,158.5	0.3	100	(63.9, 100)
HPV 11-Related	1,299	0	4,142.1	0.0	1,304	4	4,169.3	0.1	100	(-52.5, 100)
HPV 16-Related	1,322	1	4,273.9	0.0	1,312	21	4,211.8	0.5	95.3	(70.8, 99.9)
HPV 18-Related	1,487	0	4,740.9	0.0	1,490	6	4,750.7	0.1	100	(14.9, 100)
By Severity										
ASC-US HR-HPV positive	1,578	1	5,028.7	0.0	1,583	13	5,028.3	0.3	92.3	(48.8, 99.8)
LSIL or worse	1,578	0	5,030.6	0.0	1,583	27	5,021.7	0.5	100	(85.4, 100)
LSIL	1,578	0	5,030.6	0.0	1,583	25	5,023.4	0.5	100	(84.1, 100)
ASC-H	1,578	0	5,030.6	0.0	1,583	1	5,044.7	0.0	100	(-3810.9, 100)
HSIL	1,578	0	5,030.6	0.0	1,583	0	5,045.5	0.0	NA	NA
AGC	1,578	0	5,030.6	0.0	1,583	1	5,044.7	0.0	100	(-3811.0, 100)
Adenocarcinoma	1,578	0	5,030.6	0.0	1,583	0	5,045.5	0.0	NA	NA
Squamous cell carcinoma	1,578	0	5,030.6	0.0	1,583	0	5,045.5	0.0	NA	NA
Intention-to-treat population										
HPV 6/11/16/18-Related ASC-US HR-HPV positive, or worse	1,815	35	6,675.9	0.5	1,824	70	6,656.4	1.1	50.1	(24.2, 67.8)
24 to 34 year-olds	884	23	3,169.6	0.7	911	50	3,268.9	1.5	52.6	(20.8, 72.4)
35 to 45 year-olds	931	12	3,506.2	0.3	913	20	3,387.5	0.6	42.0	(-24.5, 74.2)
By HPV Type										
HPV 6-Related	1,833	6	6,765.2	0.1	1,835	14	6,750.6	0.2	57.2	(-18.5, 86.5)
HPV 11-Related	1,833	1	6,769.6	0.0	1,836	4	6,763.4	0.1	75.0	(-152.4, 99.5)
HPV 16-Related	1,822	25	6,712.8	0.4	1,825	46	6,687.8	0.7	45.9	(10.0, 68.1)
HPV 18-Related	1,829	7	6,747.6	0.1	1,836	13	6,746.5	0.2	46.2	(-45.2, 81.8)
By Severity										
ASC-US HR-HPV positive	1,829	17	6,738.9	0.3	1,835	33	6,717.2	0.5	48.7	(5.1, 73.2)
LSIL or worse	1,820	31	6,696.4	0.5	1,825	47	6,695.2	0.7	34.1	(-6.0, 59.5)
LSIL	1,823	23	6,708.7	0.3	1,827	40	6,702.2	0.6	42.6	(1.7, 67.2)
ASC-H	1,832	5	6,766.6	0.1	1,835	2	6,761.3	0.0	-149.8	(-2523.3, 59.1)
HSIL	1,834	7	6,770.4	0.1	1,835	4	6,764.6	0.1	-74.9	(-714.5, 55.5)
AGC	1,833	0	6,770.5	0.0	1,836	1	6,765.8	0.0	100	(-3797.3, 100)
Adenocarcinoma	1,834	0	6,774.5	0.0	1,836	1	6,766.2	0.0	100	(-3795.2, 100)
Squamous cell carcinoma	1,834	0	6,774.5	0.0	1,836	0	6,766.2	0.0	NA	NA

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Day 1.

AGC = Atypical glandular cells; AIS = Adenocarcinoma in situ; ASC-H = Atypical squamous cells, cannot exclude HSIL; ASCUS = Atypical squamous cells of undetermined significance; CI = Confidence interval; HPV = Human papillomavirus; HR = High-risk probe result; HSIL = High-grade squamous intraepithelial lesion; LSIL = Low-grade squamous intraepithelial lesion; Pap = Papanicolaou; SIL = Squamous intraepithelial lesion; PYR = person years at risk; rate = incidence rate per 100 person years at risk.

Table 4. Vaccine impact on cervical and external genital procedures.

Endpoint	qHPV Vaccine (N=1,910)				Placebo (N=1,907)				Percent Reduction	95% CI
	n	Cases	PYR	Rate	n	Cases	PYR	Rate		
Per-protocol population										
Colposcopy	968	109	3,536.5	3.1	976	126	3,571.5	3.5	12.6	(-13.8, 33.0)
Any Biopsy	976	102	3,557.4	2.9	988	123	3,590.6	3.4	16.3	(-9.7, 36.3)
External Genital Biopsy	975	19	3,674.7	0.5	987	23	3,741.8	0.6	15.9	(-61.5, 56.7)
Cervical Biopsy	968	94	3,569.3	2.6	976	112	3,599.6	3.1	15.4	(-12.3, 36.4)
Any Definitive Therapy	976	30	3,659.5	0.8	988	44	3,708.7	1.2	30.9	(-12.4, 58.1)
External Genital Definitive Therapy	975	9	3,686.3	0.2	987	12	3,750.3	0.3	23.7	(-97.3, 71.6)
Cervical Definitive Therapy	968	21	3,672.5	0.6	976	33	3,722.9	0.9	35.5	(-14.9, 64.5)
Intention-to-treat population										
Colposcopy	1,862	403	6,175.0	6.5	1,863	422	6,163.6	6.8	4.7	(-9.5, 17.1)
Any Biopsy	1,886	387	6,240.4	6.2	1,883	402	6,243.5	6.4	3.7	(-11.0, 16.4)
External Genital Biopsy	1,884	56	6,999.5	0.8	1,882	57	6,995.8	0.8	1.8	(-44.6, 33.3)
Cervical Biopsy	1,862	365	6,283.4	5.8	1,863	381	6,268.4	6.1	4.4	(-10.6, 17.4)
Any Definitive Therapy	1,885	150	6,795.1	2.2	1,883	164	6,777.1	2.4	8.8	(-14.5, 27.4)
External Genital Definitive Therapy	1,884	26	7,059.6	0.4	1,882	30	7,032.1	0.4	13.7	(-51.0, 51.0)
Cervical Definitive Therapy	1,862	128	6,836.4	1.9	1,863	140	6,818.3	2.1	8.8	(-16.7, 28.8)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Day 1.

CI = Confidence interval; PYR = person years at risk; Rate = incidence rate per 100 person years at risk.

Table 5. Efficacy against HPV6/11/16/18-related persistent infection and disease in seropositive and PCR negative subjects

Endpoint	qHPV Vaccine (N=1,910)				Placebo (N=1,907)				Observed Efficacy (%)	95% CI
	n	Cases	PYR	Rate	n	Cases	PYR	Rate		
HPV 6/11/16/18-related Persistent Infection, CIN, or EGL	506	5	1,882.3	0.3	513	15	1,868.0	0.8	66.9	(4.3, 90.6)
Persistent Infection	496	5	1,793.9	0.3	505	15	1,788.7	0.8	66.8	(3.8, 90.5)
CIN (any grade) or EGL	506	0	1,895.4	0.0	513	0	1,901.2	0.0	NA	NA
By HPV Type and Age Group										
HPV 6/11/16/18-related Persistent Infection (All Ages)	496	5	1,793.9	0.3	505	15	1,788.7	0.8	66.8	(3.8, 90.5)
24 to 34 year-olds	258	3	909.9	0.3	248	4	880.6	0.5	27.4	(-329.0, 89.4)
35 to 45 year-olds	238	2	884.0	0.2	257	11	908.2	1.2	81.3	(14.4, 98.0)
HPV 6/11-related Persistent Infection (All Ages)	307	2	1,128.2	0.2	297	4	1,066.0	0.4	52.8	(-229.7, 95.7)
24 to 34 year-olds	154	1	550.6	0.2	143	1	520.9	0.2	5.4	(-7325.9, 98.8)
35 to 45 year-olds	153	1	577.6	0.2	154	3	545.2	0.6	68.5	(-291.8, 99.4)
HPV 16/18-related Persistent Infection (All Ages)	284	3	1,020.9	0.3	312	11	1,112.9	1.0	70.3	(-12.5, 94.7)
24 to 34 year-olds	145	2	509.8	0.4	154	3	550.2	0.5	28.1	(-528.1, 94.0)
35 to 45 year-olds	139	1	511.1	0.2	158	8	562.8	1.4	86.2	(-2.7, 99.7)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection and were seropositive and DNA negative for the relevant vaccine HPV type at enrollment..
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; PYR = person years at risk; Rate = incidence rate per 100 person years at risk.

Table 6. Clinical adverse experience summary (entire study duration)

	Vaccine (N = 1,908)		Placebo (N = 1,902)	
	n	**(%)**	**n**	**(%)**
Subjects in analysis population	1,908		1,902	
Subjects with follow-up	1,890		1,888	
Number (%) of subjects:				
with one or more adverse experiences	1645	(87.0)	1535	(81.3)
injection-site adverse experiences	1450	(76.7)	1213	(64.2)
systemic adverse experiences	1121	(59.3)	1135	(60.1)
with vaccine-related adverse experiences	1565	(82.8)	1391	(73.7)
injection-site adverse experiences	1449	(76.7)	1213	(64.2)
systemic adverse experiences	746	(39.5)	697	(36.9)
with serious adverse experiences	14	(0.7)	16	(0.8)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	7	(0.4)	2	(0.1)
discontinued due to a vaccine-related adverse experience*	5	(0.3)	2	(0.1)
discontinued due to a serious adverse experience	2	(0.1)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)
who died**	7	(0.4)	1	(0.1)

N = number of subjects receiving at least one dose of vaccine or placebo with non-missing safety data; n = number of subjects contributing to the analysis.
*Reasons for discontinuation due to a vaccine-related adverse experience in the vaccine group included hypersensitivity, urticaria, mouth ulceration, injection-site swelling and facial edema. Reasons for discontinuation due to a vaccine-related adverse experience in the placebo group included fatigue and overdose.
**Reasons for death in the vaccine group included cardiac arrest secondary to breast cancer metastasis, cardiac arrest secondary to cerebrovascular accident, acute liver disease secondary to nasopharyngeal cancer, breast cancer, tuberculosis, pulmonary embolism, and pericarditis. Reasons for death in the placebo group included pulmonary embolism.