Supplementary Information

Table S1. Phase I Quadrivalent HPV Vaccine Trials.

Name	Subject Characteristics	Follow up Duration	Results
Study 001 [15]	N = 140 (Monovalent HPV-11 Vaccine and Placebo) Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6	Safety: No limiting toxicities or safety concerns Immunogenicity: Greater immune response with higher monovalent HPV vaccine doses of 20 μg, 40 μg, or 50 μg compared to 10 μg dose No increase in immune response with 80 μg dose compared to 50 μg dose
Study 002 [15]	N = 109 (Monovalent HPV-16 Vaccine and Placebo) Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6	Safety: No limiting toxicities or safety concerns Immunogenicity: Greater immune response with higher monovalent HPV vaccine doses of 20 μg, 40 μg, or 50 μg compared to 10 μg dose No increase in immune response with 80 μg dose compared to 50 μg dose
Study 004 [15]	N = 480 (Monovalent HPV-16 Vaccine and Placebo) Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6	Safety: No limiting toxicities or safety concerns Immunogenicity: Greater immune response with higher monovalent HPV vaccine doses of 20 μg, 40 μg, or 50 μg compared to 10 μg dose No increase in immune response with 80 μg dose compared to 50 μg dose
Study 006 [15]	N = 40 (Monovalent HPV-18 Vaccine and Placebo) Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6	Safety: No limiting toxicities or safety concerns Immunogenicity: Greater immune response with higher monovalent HPV vaccine doses of 20 μg, 40 μg, or 50 μg compared to 10 μg dose No increase in immune response with 80 μg dose compared to 50 μg dose

HPV: human papillomavirus; *N*: number of subjects.

Table S2. Phase II Quadrivalent HPV Vaccine Trials.

Name	Subject Characteristics	Follow up Duration	Results
Study 005 [15]	*N* = 2409 (1:1 Ratio of subjects to Monovalent HPV-16 to Placebo Groups) Age range: 18–25 years Sex: Female Other Inclusion Criteria: 4 or fewer sexual partners	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 7 months	Safety: No vaccine-related serious adverse events Increased injection-site reactions compared to placebo Efficacy: Of subjects with no evidence of HPV infection at baseline, 0/753 subjects in the monovalent vaccine group developed HPV-16-associated CIN compared to 16/750 subjects in the placebo group
Study 007 [22,23]	*N* = 2409 (1:1:1:1 Ratio of subjects to Low-dose, Medium-dose, High-dose, and Placebo Groups) Age range: 16–23 years Sex: Female Other Inclusion Criteria: No previous abnormal pap smears, 4 or fewer male sex partners	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Follow up: 3 years 241 subjects were followed an additional 2 years for 5-year total follow up	Safety: No vaccine-related serious adverse events Increased injection-site reactions compared to placebo Increase in rate of adverse events in higher dose groups compared to lower doses Acceptable safety profile at all doses Quadrivalent vaccine found safe at both 3-year and 5-year follow up Immunogenicity: at five-year follow up titers remained at or above the level following natural infection at 5 years Efficacy: Against the incidence of persistent HPV-6/11/16/18 infection at 3 years: 90% (95% CI = 70.7–97.3) with low-dose quadrivalent vaccine Against the incidence of HPV-6/11/16/18-associated precancerous cervical dysplasia and genital warts at 5 years: 100% (95% CI = 12%–100%) with low-dose quadrivalent vaccine

HPV: human papillomavirus; *N*: number of subjects; CI: confidence interval; CIN: cervical intraepithelial neoplasia.

Table S3. Phase III Quadrivalent HPV Vaccine Trials.

Name	Subject Characteristics	Follow up Duration	Results
Future I [15,16, 22,27]	*N* = 5455 (Quadrivalent HPV Vaccine = 2721, Placebo = 2744) Age range: 16–23 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Mean follow up: 3 years	Safety: Similar rates of systemic and serious adverse events between vaccine and placebo groups Higher rate of injection-site reactions with vaccine *versus* placebo Increased rate of adverse events with vaccine *versus* placebo included injection-site pain with a 10% risk difference (95% CI =7.8–12.1) and fever in the range of 100°F and 102°F with risk difference of 3.0% (95% CI = 1.3–4.8) Efficacy: 100% efficacy for prevention of HPV-6/11/16/18-associated precancerous and cancerous lesions of the cervix, vagina and vulva and genital warts 34% rate of reduction of any vulvar, vaginal, or perianal lesions regardless of causal HPV type (95% CI = 15–49) 20% rate of reduction of cervical lesions regardless of the cervical HPV type (95% CI = 8–31)
Future II [15,16]	*N* = 12,167 (1:1 Ratio of subjects in Quadrivalent HPV Vaccine and Placebo groups) Age range: 16–23 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Mean follow up: 1.4 years	Safety: Similar rates of systemic and serious adverse events between vaccine and placebo groups Higher rate of injection-site reactions with vaccine *versus* placebo Increased rate of adverse events with vaccine *versus* placebo included headache (11.1% *versus* 10.7%), pyrexia (5.5% *versus* 4.6%), nasopharyngitis (2.6% *versus* 2.3%), and nausea (2.9% *versus* 2.5%) Efficacy: In women HPV-negative at baseline, 100% efficacy for prevention of incident HPV-16/18-associated CIN 2/3 and cervical adenocarcinoma in situ (95% CI = 79–100) In women HPV-negative at baseline, 94% efficacy for prevention of vulvar or vaginal HPV-related lesions (95% CI = 81%–99%)

Table S3. *Cont.*

Olsson *et al*. [26]	*N* = 552 (Quadrivalent HPV Vaccine = 276, Placebo = 276) Age range: 16–23 years	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Mean follow up: 3 years 114 subjects in quadrivalent vaccine group and 127 in placebo group were followed for 5 years and were challenged at month 60 with a 4th dose of quadrivalent HPV vaccine	Safety: Similar rates of systemic and serious adverse events between vaccine and placebo groups Immunogenicity: Anti-HPV levels decline post-vaccination and plateau at month 24 with a stable level at month 60 Dramatic rise of anti-HPV levels following the administration of a challenge dose at month 60 1-week post-challenge levels comparable to levels at 1 month following completion of the 3-dose vaccination series 1-month post-challenge levels higher than levels at 1 month following completion of 3-dose vaccination series

HPV: human papillomavirus; *N*: number of subjects; CI: confidence interval; CIN: cervical intraepithelial neoplasia.

Table S4. Post-Licensure Quadrivalent HPV Vaccine Studies.

Name	Subject Characteristics	Follow up Duration	Results
Brotherton *et al*. [30]	Data from Victoria Cervical Cytology Registry between 2003–2009 used to compare the incidence of CIN2+ and adenocarcinoma in situ before and after implementation of free quadrivalent HPV vaccination in women aged 12–26 years Age range: 12–26 years Sex: Female	Time point 1:3 years prior program implementation, Program implementation: 2007, Time point 2:2 years following program implementation	Efficacy: 0.38% decrease in the incidence of CIN2+ and adenocarcinoma in situ in girls aged 12–18 years when comparing 2 years after to 3 years prior to program implementation No significant difference in girls aged 13–26 years
Crowe *et al*. [31]	Case-control of 108,353 Australians based on their first Pap smear (CIN2+ or adenocarcinoma *in situ* = 1062, another cervical abnormality on cytology or histology = 10,877, controls with no evidence of cervical lesions = 96,404) Age range: 12–26 years Sex: Female		Efficacy: Decreased risk of CIN2+ or adenocarcinoma in situ when compared to no vaccine (adjusted OR= 0.54, 95% CI = 0.43–0.67) with vaccine efficacy of 46% and number needed to vaccinate of 125 Decreased risk of other cervical abnormalities when compared to no vaccine (adjusted OR= 0.66, 95% CI = 0.62–0.7) with vaccine efficacy of 34% and number needed to vaccinate of 22
Kahn *et al*. [32]	Surveillance study (Pre-vaccination group = 368, post-vaccination group = 409) Age range: 13–26 years Sex: Female		Prevalence: HPV-6/11/16/18 prevalence in the pre-vaccination group was 31.7% *versus* 13.4% in the post-vaccination group ($p < 0.0001$)

Table S4. *Cont.*

Herweijer *et al*. [33]	Retrospective cohort *N* = 1,045,165 Age range: 10–24 years Sex: Female	Mean follow up: 3.8 years	Efficacy: Three-dose quadrivalent HPV vaccination with first dose between age 10–19 years associated with decreased risk of condyloma when compared to no vaccine (RR = 0.2, 95% CI = 0.17–0.23), one dose (RR = 0.37, 95% CI = 0.28–0.48), and 2 doses (RR = 0.63, 95% CI = 0.48–0.82)
Giuliano *et al*. [34]	Randomized control trial *N* = 4065 (1:1 Ratio of subjects to Quadrivalent HPV Vaccine and Placebo Groups) Age range: 16–26 years Sex: Male	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Mean follow up: 2.9 years	Immunogenicity: 97.5% seroconversion rate one month following vaccine series completion Efficacy: External genital lesion rates for vaccine group *versus* placebo group included 0.8 *versus* 2 for external genital lesions ($p < 0.05$), 0.45 *versus* 1.11 for HPV-6 associated external genital lesions ($p < 0.05$), 0.13 *versus* 0.52 for HPV-11 associated external genital lesions ($p < 0.05$), 0.52 *versus* 1.58 for HPV-6/11 associated condyloma acuminata ($p < 0.05$), and 3.61 *versus* 6.92 for HPV-6/11/16/18 persistent infection ($p < 0.05$) No statistically significant reduction in HPV-16/18 associated external genital lesions or perineal epithelial neoplasia lesions
Palefsky *et al*. [35]	Randomized control trial *N* = 602 (1:1 Ratio of subjects to Quadrivalent HPV Vaccine and Placebo Groups) Age range: 16–26 years Sex: Male Other Inclusion Criteria: Men who have sex with men	All Subjects: Dose 1: month 0, Dose 2: month 2, Dose 3: month 6, Follow up: 7 months	Efficacy: Against AIN associated with HPV infection of any type: 25.7% (95% CI = −1.1–45.6) Against AIN associated with vaccine-type HPV infection: 50.3% (95% CI = 25.7–67.2) Against grade 2+ AIN associated with vaccine-type HPV infection: 54.2% (95% CI = 18.0–75.3) Against persistent HPV-6/11/16/18 infection: 59.4% (95% CI = 43.0–71.4)

HPV: human papillomavirus; *N*: number of subjects; CIN: cervical intraepithelial neoplasia; CI: confidence interval; OR: odds ratio; AIN: anal intraepithelial neoplasia.

Table S5. Phase I and II Bivalent HPV Vaccine Trials.

Phase	Name	Subject Characteristics	Follow up Duration	Results
I	HPV-002 [37]	N = 49 (Monovalent HPV-16 = 12, Monovalent HPV-18 = 12, Bivalent HPV-16/18 = 25) Age range: 18–30 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 1, Follow up: 56 days 8 Subjects in Monovalent HPV-16 Group: Dose 3: 112 days, Follow up: 140 days	Safety: No limiting toxicities or safety concerns Immunogenicity: Antibody and cell-mediated immune response generated Bivalent vaccine generated immune response to both HPV-16 and HPV-18 comparable to the monovalent vaccines Third dose of monovalent HPV-18 vaccine administered to 8 study subjects increased antibody levels in all cases
I/II	HPV-003 [37]	N = 61 (Bivalent HPV-16/18 = 31, Placebo = 30) Age range: 18–30 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 1 year	Safety: Similar safety profiles found between bivalent vaccine and placebo group No reported vaccine-related serious events Immunogenicity: Immune response to both HPV-16 and HPV-18 generated following second dose of vaccine Increase in HPV-16/18 antibody levels after administration of third dose Efficacy: No increase in the clearance rate of HPV-16/18 viral DNA in women with prior HPV-16 and/or HPV-18 infection

Table S5. *Cont.*

I/II	HPV-004 [37]	*N* = 60 (Bivalent with AS04 = 20, Bivalent with Aluminum Hydroxide = 20, Bivalent without Adjuvant = 20) Age range: 18–30 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 2 years	Safety: No reported vaccine-related serious events No significant difference in proportions of study subjects in the three groups with serious or systemic adverse events Higher rate of local injection-site reactions with AS04 adjuvant Immunogenicity: Immune response to both HPV-16 and HPV-18 generated following second dose of vaccine Increase in HPV-16/18 antibody levels after administration of third dose Higher ELISA titers in the AS04 adjuvant group than the aluminum hydroxide or no adjuvant groups at day 210 Anti-HPV-16/18 antibodies following bivalent vaccine administration had kinetic profiles comparable to the neutralizing antibody profile
II	HPV-005 [37]	*N* = 209 (12 μg with AS04 = 59, 40 μg with AS04 = 64, 120 μg with AS04 = 59, 40 μg with Aluminum Hydroxide = 27) Age range: 18–30 years Sex: Female Other Inclusion Criteria: HPV-16/18 Negative at Baseline	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 360 days	Safety: No reported vaccine-related serious events All vaccine doses generally tolerated Local injection-site reaction frequency proportional to increasing vaccine dose Immunogenicity: Immune response to both HPV-16 and HPV-18 generated following second dose of vaccine Increase in HPV-16/18 antibody levels after administration of third dose No significant effect of VLP dose of the AS04 formulations on the cellular immune response ELISA titers of three VLP doses of the AS04 formulations suggested that the 12 μg dose may produce less of a humoral immune response

Table S5. *Cont.*

II	HPV-007 [38]	*N* = 1113 (Bivalent HPV-16/18 = 560, Placebo = 553) Age range: 15–25 years Sex: Female Other Inclusion Criteria: HPV-16/18 Negative and Normal Cervical Cytology at Baseline	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 27 months 393 Subjects in Bivalent Vaccine Group and 383 Subjects in Placebo Group: Follow up: 4.5 years	Safety: Similar safety profiles found between bivalent vaccine and placebo group No reported vaccine-related serious events Immunogenicity: Anti-HPV-16/18 antibody concentrations following vaccination remained 12-fold times greater than that achieved after natural infection Efficacy: Against HPV-16/18 infection incidence: 93.3% (95% CI = 87.4–98.7) Against 12-month persistent infection: 100% (95% CI = 81.8–100) Against HPV-16/18 associated CIN2+: 100% (95% CI = 51.3–100) Against lesions independent of HPV DNA type: 71.9% (95% CI = 20.6–91.9) Follow up: Vaccine is safe, immunogenic, and provides protection for up to 4.5 years[20] and 6.4 years[21]

HPV: human papillomavirus; *N*: number of subjects; CI: confidence interval; CIN: cervical intraepithelial neoplasia; PL: post-licensure.

Table S6. Phase III and Post-Licensure Bivalent HPV Vaccine Trials.

Phase	Name	Subject Characteristics	Follow up Duration	Results
III	PATRICIA [18]	Total Vaccine Group *N* = 18,644 (Bivalent HPV-16/18 = 9319, Placebo = 9325) Age range: 15–25 years Sex: Female Total Vaccine-naïve Group *N* = 11,641 (Bivalent HPV-16/18 = 5822, Placebo = 5819) Age range: 15–25 years Sex: Female Other Inclusion Criteria: Before sexual debut with no baseline evidence of HPV infection	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Mean follow up: 40.9 months	Safety: Similar rates of serious adverse events, medical conditions, and new-onset chronic and autoimmune disease similar between bivalent vaccine and control groups Efficacy: Against HPV-16/18 associated CIN2+: 92.9% (96.1% CI = 79.9–98.3) in primary analysis and 98.1% (96.1% CI = 88.4–100) adjusted for probable causality in lesions with multiple oncogenic types Against CIN2+ irrespective of HPV DNA type: 30.4% (96.1 CI = 16.4–42.1) in Total Vaccine Group and 70.2% (96.1% CI = 54.7–80.9) in Total Vaccine Group-naïve Group Against CIN2+ associated with 12 non-vaccine oncogenic HPV types: 54.0% (96.1% CI = 34.0–68.4)
III	Hildesheim *et al*. [39]	*N* = 2189 (Bivalent HPV-16/18 = 1088, Placebo = 1101) Age range: 18–25 years Sex: Female Other Inclusion Criteria: HPV DNA-positive at enrollment	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 6 months	Efficacy: No evidence of accelerated viral clearance in HPV-positive women at 6 or 12 months Vaccine efficacy of viral clearance at 6 months compared to placebo of 2.5% (95% CI = −9.8–13.5) Vaccine efficacy of viral clearance at 12 months compared to placebo of −2.09% (95% CI = −24.3–16.3)

Table S6. *Cont.*

III	Pedersen *et al*. [40]	*N* = 773 (10–14 Years of Age = 158, 15–25 Years of Age = 458) Age range: 10–25 years Sex: Female	All Subjects: Dose 1: month 0, Dose 2: month 1, Dose 3: month 6, Follow up: 7 months	Safety: No difference in safety profile of vaccine between two age groups Immunogenicity: Seroconversion similar between two age groups Antibody titers approximately twice as high in females aged 10–14 years compared to females aged 15–25 years
PL	Angelo *et al*. [42]	Post-licensure passive surveillance safety data from global pharmacovigilance	Data from May 18, 2007–November 17, 2011	Safety: Safety profile and reported adverse events comparable to pre-licensure data No evidence to support post-vaccine immune-mediated disease

HPV: human papillomavirus; *N*: number of subjects; CI: confidence interval; CIN: cervical intraepithelial neoplasia; PL: post-licensure.