FDA Statistical Review and Evaluation

Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

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Gardasil™: Human Papillomavirus [Types 6, 11, 16 and 18] Recombinant Vaccine

Indication: Prevention of Cervical Cancer, Vulvar and Vaginal Pre-cancer and Cancers, Precancerous Lesions, and Genital Warts Caused by Human Papillomavirus Types 6, 11, 16, and 18.

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A major goal of the quadrivalent human papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particles (VLP) vaccine clinical program was to determine whether the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduced the incidence of cervical and genital disease caused by vaccine HPV types in adolescent and young adult women. This statistical briefing document includes two protocols (Protocol 013 and Protocol 015) to address this efficacy goal and relevant information on immunogenicity, manufacturing lot consistency, and safety profile.

Efficacy Trials
Reference P013V1

Protocol Title:
"A Study to Evaluate the Efficacy of Quadrivalent human papillomavirus (HPV) (Types 6, 11, 16, and 18) L1 Virus-Like Particles (VLP) Vaccine in Reducing the Incidence of HPV 6-, 11-, 16-, and 18-Related CIN, AIS, and Cervical Cancer, and HPV 6-, 11-, 16-, and 18-Related External Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer in 16- to 23-Year-Old Women – the F.U.T.U.R.E. I Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)"

STUDY OBJECTIVES

Primary Efficacy Objectives:
(1) To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18-related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer, or vaginal cancer, compared with placebo.
(2) To demonstrate that the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18-related cervical dysplasia (any grade Cervical Intraepithelial Neoplasia [CIN]), Adenocarcinoma In Situ (AIS), or cervical cancer, compared with placebo.

To meet each of the co-primary objectives, the criterion states that the quadrivalent HPV vaccine will reduce each aforementioned combined incidence by 80% compared with placebo. The statistical hypothesis testing is to reject the null hypothesis that the vaccine efficacy against each of aforementioned composite endpoint is less than 20%. Thus, a statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 20% or less.

Secondary Efficacy Objectives:
(1) To demonstrate that the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 16/18-related cervical dysplasia (any grade CIN), AIS, or cervical cancer, compared with placebo.
(2) To demonstrate that the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer, compared with placebo.

Primary Safety Objective:
To demonstrate that a 3-dose regimen of quadrivalent HPV vaccine is generally well tolerated.

STUDY DESIGN

This is a randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multi-center efficacy study in 5455 subjects. Each subject was also enrolled in 1 of 2 immunogenicity sub-studies (Protocol 011, Protocol 012). Subjects were randomized in a 1:1 ratio to receive either quadrivalent HPV vaccine or placebo. To assess efficacy, Papanicolaou (Pap) testing was to be done at scheduled visits and Pap test abnormalities were followed up according to a pre-defined mandatory triage algorithm. External genital lesion inspection was to be performed at scheduled visits and when a subject presented with symptoms. To evaluate immunogenicity, sera were to be obtained at scheduled visits. To evaluate safety, subjects completed a vaccination report card (VRC) after each vaccination.

SUBJECTS DISPOSITION

	Quadrivalent HPV Vaccine	Placebo	Total
SCREENING FAILURES			1008
RANDOMIZED:	2723	2732	5455
Female (age range - years)	16 to 24	16 to 24	16 to 24
(Vaccination Period Day 1 through Month 7):			
ENTERED	2717	2725	5442
COMPLETED	2582	2586	5168
DISCONTINUED	135	139	274
Clinical adverse experience	2	7	9
Lost to follow-up	48	44	92
Moved	14	18	32
Pregnancy	5	8	13
Withdrew consent	54	60	114
Other reasons	12	2	14
(Follow-up Period After Month 7):			
ENTERED	2592	2595	5187
CONTINUING	2536	2537	5073
DISCONTINUED	56	58	114
Clinical adverse experience	1	1	2
Lost to follow-up	30	30	60
Moved	9	6	15
Withdrew consent	16	21	37

STATISTICAL ANALYSIS AND EVALUATION CRITERIA

The study had two co-primary efficacy endpoints, namely, (1) HPV 6/11/16/18-related external genital lesions and (2) HPV 6/11/16/18-related CIN. The protocol specified that

the primary analyses of efficacy were to be conducted in the per-protocol efficacy (PPE) population. This cohort consisted of subjects who received all 3 vaccinations, did not deviate from the study protocol in ways that could potentially interfere with the efficacy of the vaccine, and were seronegative to the relevant HPV type(s) at baseline and during the 6-month vaccination regimen as well as for 1 month thereafter (to allow for induction of immune responses to Dose 3 of the vaccine). Cases of the primary endpoint were counted starting after Month 7.

This study employed a fixed-event design, whereby the analyses of the primary efficacy hypotheses were scheduled to be conducted at the time that specific target numbers of cases of the primary endpoints had been observed. Although the study was to continue for 4 years, the study conclusions regarding vaccine efficacy with respect to the primary endpoints were to be based on the analyses conducted when at least 38 cases of HPV 6/11/16/18-related external genital/vaginal lesions and at least 38 cases of HPV 6/11/16/18-related CIN were observed in the PPE population. [Details are explained in the section on sample size and power analysis.]

Point estimates of vaccine efficacy and corresponding multiplicity-adjusted confidence intervals (CIs) were provided for each of the primary endpoints. Each of the two primary hypotheses was tested by constructing a two-sided exact 97.5% CI for vaccine efficacy. A lower bound of the 97.5% CI >20% led to rejection of the null hypothesis. Success in the study was achieved if either of the primary hypothesis tests were successful. Therefore, each primary efficacy hypothesis was tested at the 0.025 (two-sided) level to control the overall type I error rate at the 0.05 (two-sided) level.

Vaccine Efficacy (VE) is defined as

$$100\% \times \left(1 - \frac{\text{risk of becoming a case in the vaccine group}}{\text{risk of becoming a case in the placebo group}}\right).$$

An exact conditional procedure proposed by Martin and Austin[1] was used to test this set of hypotheses. Under the assumption that the number of cases in each of the two vaccination groups are independent Poisson random variables, then conditional on the total number of cases (in the two vaccination groups combined) being fixed, the number of cases in the vaccine group follows a binomial distribution. This conditional binomial distribution accounting for any differential follow-up was used as the basis for calculating the point and exact 2-sided confidence interval estimates of vaccine efficacy.

For the primary PPE analysis, follow-up for both primary endpoints began following the Month 7 visit. Therefore, each subject's follow-up time was computed by calculating the number of days between her Month 7 visit date and her final visit date. This value was converted to person-years by dividing by 365.25. For subjects who became cases, the final visit date was the visit date at which the defined symptoms were detected. If a subject developed more than one case of a given endpoint, it was the date at which the first case of the endpoint was detected.

[1] Martin and Austin "Exact Estimate for a Rate ratio" Epidemiology 1996; 7(1): 29-33

Immunogenicity: Serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses were measured using a multiplex competitive Luminex immunoassay (cLIA). For HPV 6, 11, 16, and 18, the cutoff for seropositivity was defined as an anti-HPV cLIA antibody level ≥ 20, 16, 20 and 24 milli Merck units (mMU)/mL, respectively. The exploratory immunogenicity objective was addressed by summarizing anti-HPV 6, 11, 16, and 18 geometric mean titers (GMTs) and corresponding 95% CIs at Month 7, Month 12, and Month 24. Seropositivity percentages for HPV 6, 11, 16, and 18 and the corresponding 95% CIs were also computed.

SAMPLE SIZE AND POWER ANALYSIS

The sample size for the study was calculated to allow observation of 38 HPV 6/11/16/18-related CIN cases by Month 36. The required sample size was determined under the following assumptions:

(1) 27% attrition rate through Month 36 (including subjects who dropped out and subjects who violated inclusion/exclusion criteria);
(2) positivity rates of 15%, 18%, and 18%, respectively, for HPV 6/11, 16, and 18 (by serology at Day 1 or PCR Day 1 through Month 7);
(3) HPV 6/11-related cumulative CIN incidence rate of 1.25%, HPV 16-related cumulative CIN incidence rate of 1%, and HPV 18-related cumulative CIN incidence rate of 0.25% in the placebo group over the first 2.5 years of Postdose 3 follow-up; and
(4) Cases might occur only in the placebo group (if the true vaccine efficacy is very high) before the efficacy analysis may be performed.

Under these assumptions, approximately 5400 subjects (2700 per vaccination group) were required in the study. Under all of the same assumptions above and assuming a HPV 6/11-related cumulative wart incidence rate of 3.75% in the placebo group over the first 2.5 years of Postdose 3 follow-up, 62 cases of HPV 6/11/16/18-related external genital warts were expected to be observed with a sample size of 5400 subjects by Month 36, although only 38 cases were required to have adequate power.

Assuming true vaccine efficacy of at least 80%, conducting the test of the primary efficacy hypotheses at the time when at least 38 cases of HPV 6/11/16/18-related external genital warts and at least 38 cases of HPV 6/11/16/18-related CIN were observed provided the study 91% power to declare the vaccine efficacious against each endpoint with a 2-sided $\alpha = 0.025$ (incorporates multiplicity adjustment).

At the time of the primary analysis, 18 cases of the secondary endpoint of HPV 16/18-related CIN were expected. Assuming true vaccine efficacy of at least 80%, conducting the test of the secondary efficacy hypothesis regarding HPV 16/18-related CIN at the time of the primary analysis would provide the study 83.2% power to declare the vaccine efficacious against HPV 16/18-related CIN with a 2-sided $\alpha=0.05$. At the time of the primary analysis, 67 cases of the secondary endpoint of external genital warts/VIN/VaIN

due to any HPV type were expected. Assuming true vaccine efficacy of at least 70%, conducting the test of the secondary efficacy hypothesis regarding external genital warts/VIN/VaIN at the time of the primary analysis would provide the study 99.7% power to declare the vaccine efficacious against external genital warts/VIN/VaIN with a 2-sided $\alpha = 0.05$.

EFFICACY ANALYSIS POPULATIONS

Five populations were considered for HPV type-specific efficacy analyses: one per-protocol population (PPE) and four modified intention-to-treat (MITT) populations. The per-protocol population was the primary analysis population. The MITT populations were used to supplement the results of analyses in the per-protocol population. As defined in the Data Analysis Plan, the populations are:

- Per-Protocol Efficacy (PPE): Included subjects who (1) received all 3 vaccinations, (2) were seronegative to the appropriate HPV type(s) at Day 1 and PCR-negative to the appropriate HPV type(s) Day 1 through Month 7, and (3) generally did not deviate from protocol.

- MITT-1: Included subjects who: (1) received all 3 vaccinations, (2) were seronegative to the appropriate HPV type(s) at Day 1 and PCR-negative to the appropriate HPV type(s) Day 1 through Month 7, and (3) included general protocol violators;

- MITT-4: Included subjects who (1) received at least 2 vaccinations, and (2) were seronegative to the appropriate HPV type(s) at Day 1 and PCR negative to the appropriate HPV type(s) Day 1 through Month 3;

- MITT-2: Included subjects who (1) received at least 1 vaccination, and (2) were seronegative and PCR negative to the appropriate HPV type(s) at Day 1;

- MITT-3: Included all subjects who received at least 1 vaccination, regardless of initial serology and PCR status;

- Restricted MITT-2: Included all subjects who were seronegative and PCR negative at Day 1 to all vaccine HPV types AND had a normal Pap test result at Day 1. The analyses performed in the restricted MITT-2 population were intended to provide a "real world" estimate of the impact of the vaccine with regard to clinical disease caused by HPV among baseline HPV-naïve women. The subset of baseline HPV-naïve women cannot be completely identified without assay data for the non-vaccine HPV types. However, in the absence of such data, requiring that subjects have a normal Pap test result at baseline serves as a proxy for assessing baseline negativity for those HPV types.

Summary of Key Efficacy Analysis Populations

	PPE	MITT-1	MITT-4	MITT-2	RMITT-2	MITT-3
Minimum number of doses required (Follow-up began 30 days following this dose)	3	3	2	1	1	1
Subjects excluded for:						
No follow-up data	x	x	x	X	X	x
General protocol violation	x					
Seropositivity at Day 1	x	x	x	X	X	
PCR positivity at or before follow-up	x	x	x	X	X	
Abnormal Pap diagnosis at Day 1					X	

PPE = Per-protocol efficacy; MITT = Modified intention-to-treat; RMITT = Restricted modified intention-to-treat.

CHANGES IN THE PLANNED STATISTICAL ANALYSIS

The data analysis plan stated that the primary efficacy analysis would occur when at least 62 cases of HPV 6/11/16/18-related external genital lesions and at least 38 cases of HPV 6/11/16/18-related CIN 1 or worse had been observed. In order to have ≥ 90% power to declare the vaccine efficacious against each of the primary endpoints, 38 cases of each of the endpoints were required. The sample size estimation was based on the assumed CIN event rate that was smaller than the assumed external genital lesion event rate. By the Month 36 visit, it was expected that 38 cases of HPV 6/11/16/18-related CIN 1 or worse would be observed and 62 cases of HPV 6/11/16/18-related external genital lesions would be observed, although only 38 cases of HPV 6/11/16/18-related external genital lesions were required for adequate power. Therefore, the required number of external genital lesion cases was changed from 62 to 38 in Protocol Amendment 013-02.

An exact test of homogeneity of relative risks across regions was performed based on the method of Martin and Austin, instead of a logistic regression analysis, to evaluate the presence of vaccination-group-by-region interaction. The exact method was used because the primary analysis of vaccine efficacy used an exact conditional procedure. Due to sample size limitations, vaccination-group-by-region interaction was assessed instead of vaccination-group-by-study-site interaction.

Tests of treatment-by-region interaction were not performed for the co-primary endpoints of HPV 6/11/16/18-related CIN and HPV 6/11/16/18-related EGL, as well as for the secondary endpoint of HPV 16/18-related CIN, because vaccine efficacy across all regions was 100% for these endpoints in the PPE population.

Poisson regression modeling to investigate a potential immunologic correlate of protection was not performed because insufficient numbers of cases were observed.

RESULTS

Efficacy:

Table 1 on page 9 shows the results of the Per-Protocol Efficacy (PPE) analysis. The observed vaccine efficacy against HPV external genital lesions (EGL) was 100%, which was statistically significantly greater than 20% with $p<0.001$. The lower bound of the 97.5% CI was 88.4%, which is greater than 20% and supports the conclusion that the quadrivalent HPV vaccine is efficacious against HPV 6/11/16/18-related external genital lesions. The observed efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related Cervical Intraepithelial Neoplasia (CIN) was 100%, which was statistically significantly greater than 20% with $p<0.001$. The lower bound of the 97.5% CI was 87.4%, which is greater than 20% and supports the conclusion that the quadrivalent HPV vaccine is efficacious against HPV 6/11/16/18-related CIN or worse.

In Table 2 on page 10, the vaccine efficacy against HPV 6/11/16/18-related CIN and corresponding confidence interval in the MITT-1, MITT-4, and MITT-2 populations were 100% (90.1% ~ 100%), 98.1% (89.1% ~ 100%), and 96.5% (86.7% ~ 99.6%), respectively. They are supportive of the primary PPE result. However, the corresponding results in MIT-3 were much lower: 42.9% (21.9%, 58.6%).

Table 3 on page 11 shows the results of the secondary analysis of CIN. The observed vaccine efficacy against the secondary endpoint of HPV 16/18-related CIN was 100%, which was statistically significantly greater than 0% with $p<0.001$. The lower bound of the 95% CI was greater than 0%, which supports the conclusion that the quadrivalent HPV vaccine is efficacious against HPV 16/18-related CIN or worse.

In Table 4 on page 12, the vaccine efficacy against HPV 6/11/16/18-related EGL and corresponding confidence interval in the MITT-1, MITT-4, and MITT-2 populations were 100% (91.1% ~ 100%), 100% (92.8% ~ 100%), and 94.9% (84.4% ~ 99.0%), respectively. They are supportive of the primary PPE result. However, the corresponding results in MIT-3 were much lower: 67.8% (49.3%, 80.1%).

Table 5 on page 13 shows the results of the secondary analysis of EGL The observed vaccine efficacy against the secondary endpoint of all external genital lesions was 62.3%, which was statistically significantly greater than 0% with $p<0.001$. The lower bound of the 95% CI was 39.4%, which supports the conclusion that the quadrivalent HPV vaccine is efficacious against all external genital lesions.

The results of the exploratory analysis of the impact of the quadrivalent HPV vaccine on the development of CIN regardless of causal HPV type in the restricted MITT-2 population are shown in Table 6 on page 14. The incidence of CIN lesions was lower in the quadrivalent HPV vaccine group than in the placebo group (24.9% observed efficacy; 95% CI: 2.2% ~ 42.5%). The observed reduction in incidence of CIN 2 and CIN 3/AIS was more pronounced than for CIN 1 lesions; however, the lower confidence bounds for the percent reduction in incidence for the lesion specific endpoints did not exceed 0.

The results of the exploratory analysis to evaluate the impact of the quadrivalent HPV vaccine with respect to the incidence of external genital lesions (caused by vaccine or non-vaccine HPV types) in the restricted MITT-2 population are shown in Table 7 on page 15. The incidence of EGLs overall and the incidence by lesion type were lower in quadrivalent HPV vaccine recipients compared with placebo recipients (overall observed efficacy of 48.5%; 95% CI: 22% ~ 67%). The observed reduction in incidence of EGLs increased with the severity of the lesion being evaluated, however, the lower confidence bound for the percent reduction in incidence for the endpoint of VIN 2/3 or VaIN 2/3 did not exceed 0.

Immunogenicity

In the Per-Protocol Immunogenicity (PPI) population, geometric mean titers in subjects vaccinated with quadrivalent HPV vaccine reached their highest measured levels at Month 7 and declined through Month 24 (Table 8 on page 16). Almost all subjects in the quadrivalent HPV vaccine group mounted an immune response to each vaccine HPV type by Month 7 and the percent of subjects who were seropositive to HPV 6, HPV 11, and HPV 16 remained high at Month 24 (Table 9 on page 17).

CONCLUSIONS

In the primary analysis based on the Per-Protocol Efficacy (PPE) population, the observed vaccine efficacy against HPV external genital lesions (EGL) was 100% with a 97.5% lower bound CI of 88.4%,, which was statistically significantly greater than 20% with $p<0.001$. The observed efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related Cervical Intraepithelial Neoplasia (CIN) was 100% with a 97.5% lower bound CI of 87.4%, which was statistically significantly greater than 20% with $p<0.001$. Both results support the conclusion that the quadrivalent HPV vaccine is efficacious against HPV 6/11/16/18-related EGL and CIN.

In the analyses based on various modified intention-to-treat populations, the results of vaccine efficacy against HPV 6/11/16/18-related CIN and EGL are supportive of the primary PPE result. However, the corresponding results in the MITT-3 population were lower and they were even lower in the RMITT-2 population.

Similar results were found in the secondary analysis. The results of vaccine efficacy against the secondary endpoints of HPV 16/18-related CIN and EGL were 100% in the PPE population. While supportive of the conclusion of an efficacious HPV vaccine, the results of vaccine efficacy were lower with respect to specific HPV type of EGL.

Table 1: Primary Analysis of Efficacy against HPV 6/11/16/18-Related Cervical Intraepithelial Neoplasia (CIN) and External Genital Lesions (EGL) (Per-Protocol Efficacy Population)

	Quadrivalent HPV Vaccine (N=2,717)				Placebo (N=2,725)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	97.5% Confidence interval	p-value
HPV 6/11/16/18-Related CIN	2,240	0	3,779.8	0.0	2,258	37	3,787.4	1.0	100.0	(87.4, 100.0)	< 0.001
HPV 6/11/16/18-Related EGL	2,261	0	3,865.2	0.0	2,279	40	3,868.4	1.0	100.0	(88.4, 100.0)	< 0.001

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population with at least one follow-up visit after Month 7.

Table 2: Primary Analysis of Efficacy against HPV 6/11/16/18-Related Cervical Intraepithelial Neoplasia (CIN)

	Quadrivalent HPV Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint HPV 6/11/16/18-Related CIN	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	Confidence* interval
PPE	2,240	0	3,779.8	0.0	2,258	37	3,787.4	1.0	100.0	(87.4, 100.0)*
MITT-1	2,416	0	4,031.7	0.0	2,422	39	4,030.7	1.0	100.0	(90.1, 100.0)
MITT-4	2,490	1	4,922.5	0.0	2,490	53	4,902.0	1.1	98.1	(89.1, 100.0)
MITT-2	2,557	2	5,490.1	0.0	2,573	57	5,489.0	1.0	96.5	(86.7, 99.6)
MITT-3	2,607	65	5,566.5	1.2	2,611	113	5,525.4	2.0	42.9	(21.9, 58.6)
By HPV Type (PPE)										
HPV 6-Related CIN	1,960	0	3,316.0	0.0	1,975	7	3,332.6	0.2	100.0	(30.3, 100.0)
HPV 11-Related CIN	1,960	0	3,316.0	0.0	1,975	3	3,334.9	0.1	100.0	(<0.0, 100.0)
HPV 16-Related CIN	1,887	0	3,201.0	0.0	1,847	22	3,130.6	0.7	100.0	(82.1, 100.0)
HPV 18-Related CIN	2,101	0	3,557.9	0.0	2,120	8	3,569.1	0.2	100.0	(41.2, 100.0)
By Lesion Type (PPE)										
CIN 1	2,240	0	3,779.8	0.0	2,258	25	3,789.7	0.7	100.0	(84.1, 100.0)
CIN 2 or Worse	2,240	0	3,779.8	0.0	2,258	20	3,794.4	0.5	100.0	(79.7, 100.0)
CIN 2	2,240	0	3,779.8	0.0	2,258	14	3,794.8	0.4	100.0	(69.7, 100.0)
CIN 3/AIS	2,240	0	3,779.8	0.0	2,258	10	3,796.2	0.3	100.0	(55.2, 100.0)
Cervical Cancer	2,240	0	3,779.8	0.0	2,258	0	3,796.6	0.0	NA	NA

PPE: Per-Protocol Efficacy Population; MITT: Modified Intention-to-Treat
* A 97.5% confidence interval is provided for the HPV 6/11/16/18-related CIN endpoint in PPE analysis population to correspond with the multiplicity adjusted primary hypothesis test. A 95% confidence interval is presented for all other efficacy analysis populations and the type-specific and lesion-specific endpoints in PPE analysis population for estimation purposes only.

Table 3: Secondary Analysis of Efficacy against HPV 16/18-Related Cervical Intraepithelial Neoplasia (CIN)
(Per-Protocol Efficacy Population)

	Quadrivalent HPV Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
HPV 16/18-Related CIN	2,200	0	3,716.7	0.0	2,222	28	3,732.0	0.8	100.0	(85.9, 100.0)
By HPV Type										
HPV 16-Related CIN	1,887	0	3,201.0	0.0	1,847	22	3,130.6	0.7	100.0	(82.1, 100.0)
HPV 18-Related CIN	2,101	0	3,557.9	0.0	2,120	8	3,569.1	0.2	100.0	(41.2, 100.0)
By Lesion Type										
CIN 1	2,200	0	3,716.7	0.0	2,222	17	3,734.2	0.5	100.0	(75.7, 100.0)
CIN 2 or Worse	2,200	0	3,716.7	0.0	2,222	19	3,736.0	0.5	100.0	(78.5, 100.0)
CIN 2	2,200	0	3,716.7	0.0	2,222	13	3,736.5	0.3	100.0	(67.0, 100.0)
CIN 3/AIS	2,200	0	3,716.7	0.0	2,222	10	3,737.8	0.3	100.0	(55.1, 100.0)
Cervical Cancer	2,200	0	3,716.7	0.0	2,222	0	3,738.2	0.0	NA	NA

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population with at least one follow-up visit after Month 7.

Table 4: Primary Analysis of Efficacy against HPV 6/11/16/18-Related External Genital Lesions (EGL)

	Quadrivalent HPV Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint HPV 6/11/16/18-Related EGL	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	Confidence* interval
PPE	2,261	0	3,865.2	0.0	2,279	40	3,868.4	1.0	100.0	(88.4, 100.0)*
MIT-1	2,439	0	4,128.6	0.0	2,444	43	4,120.2	1.0	100.0	(91.1, 100.0)
MIT-4	2,516	0	5,033.9	0.0	2,511	53	5,002.0	1.1	100.0	(92.8, 100.0)
MIT-2	2,620	3	5,617.4	0.1	2,628	59	5,601.5	1.1	94.9	(84.4, 99.0)
MIT-3	2,671	26	5,697.6	0.5	2,668	80	5,648.4	1.4	67.8	(49.3, 80.1)
By HPV Type (PPE)										
HPV 6-Related EGL	1,978	0	3,378.7	0.0	1,991	23	3,391.1	0.7	100.0	(82.5, 100.0)
HPV 11-Related EGL	1,978	0	3,378.7	0.0	1,991	10	3,399.0	0.3	100.0	(55.1, 100.0)
HPV 16-Related EGL	1,890	0	3,232.7	0.0	1,855	10	3,166.6	0.3	100.0	(56.3, 100.0)
HPV 18-Related EGL	2,120	0	3,627.5	0.0	2,136	3	3,647.8	0.1	100.0	(<0.0, 100.0)
By Lesion Type (PPE)										
Condyloma, VIN, VaIN 1	2,261	0	3,865.2	0.0	2,279	34	3,870.7	0.9	100.0	(88.5, 100.0)
VIN, VaIN 2/3	2,261	0	3,865.2	0.0	2,279	7	3,887.5	0.2	100.0	(30.2, 100.0)
Vulvar, Vaginal Cancer	2,261	0	3,865.2	0.0	2,279	0	3,890.7	0.0	NA	NA

* A 97.5% confidence interval is provided for the HPV 6/11/16/18-related EGL endpoint in PPE analysis population to correspond with the multiplicity adjusted primary hypothesis test. A 95% confidence interval is presented for all other efficacy analysis populations and the type-specific and lesion-specific endpoints in PPE analysis population for estimation purposes only.
VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia;

Table 5
Secondary Analysis of Efficacy against External Genital Lesions (EGL) Due to Any HPV Type† (Per-Protocol Approach‡)

	Quadrivalent HPV Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
EGL Any HPV Type	2,380	25	4,041.2	0.6	2,390	66	4,023.4	1.6	62.3	(39.4, 77.2)
Condyloma, VIN, VaIN 1	2,380	23	4,042.2	0.6	2,390	60	4,025.3	1.5	61.8	(37.3, 77.5)
VIN, VaIN 2/3	2,380	2	4,051.9	0.0	2,390	11	4,057.6	0.3	81.8	(16.6, 98.0)
Vulvar, Vaginal Cancer	2,380	1	4,053.2	0.0	2,390	0	4,061.9	0.0	NA	NA

†An external genital lesion due to any HPV type is defined as a tissue sample diagnosed by the Pathology Panel as VIN, VaIN, an external genital wart, or vulvar or vaginal cancer.
‡Includes subjects who were not general protocol violators and received all 3 vaccinations. Subjects were required to be seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s) when assessing disease due to vaccine HPV types and were required to have a Pap test diagnosis of "Negative for SIL" Day 1 through Month 7 when assessing all other disease. Cases were counted starting after Month 7.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population with at least one follow-up visit after Month 7.
SIL = Squamous intraepithelial lesion; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Table 6: Analysis of Efficacy against CIN Due to Any HPV Type† (Restricted MITT-2 Population‡)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint	n	Number of Cases	Person-Years at Risk	Rate Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Rate Per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
CIN Due to Any HPV Type	1,683	102	3,635.8	2.8	1,697	135	3,613.1	3.7	24.9	(2.2, 42.5)
CIN 1	1,683	90	3,639.4	2.5	1,697	117	3,624.4	3.2	23.4	(<0.0, 42.5)
CIN 2 or Worse	1,683	26	3,681.7	0.7	1,697	43	3,690.3	1.2	39.4	(<0.0, 64.2)
CIN 2	1,683	19	3,682.5	0.5	1,697	31	3,692.1	0.8	38.5	(<0.0, 67.2)
CIN 3/AIS	1,683	10	3,684.9	0.3	1,697	22	3,702.7	0.6	54.3	(<0.0, 80.7)
Cervical Cancer	1,683	0	3,685.7	0.0	1,697	0	3,704.8	0.0	NA	NA

†A CIN due to any HPV type is defined as a tissue sample diagnosed by the Pathology Panel as CIN or cervical cancer. Cervical biopsies that were performed in the absence of an abnormal Pap test result at the antecedent visit were excluded.
‡Includes all subjects who received ≥1 vaccination. Subjects were required to be seronegative and PCR negative for all vaccine HPV types and have a Pap test diagnosis of "Negative for SIL" at Day 1. Cases were counted starting 30 days after Day 1. 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 in the given population with at least one follow-up visit following 30 days after Day 1.
AIS = Adenocarcinoma in situ; CIN = Cervical intraepithelial neoplasia.
PCR = Polymerase chain reaction; SIL = Squamous intraepithelial lesion.

Table 7: Analysis of Efficacy against External Genital Lesions Due to Any HPV Type†(Restricted MITT-2 Population‡)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=2,717)				Placebo (N=2,725)					
Endpoint	n	Number of Cases	Person-Years at Risk	Rate Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Rate Per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
EGL Due to Any HPV Type	1,726	35	3,683.3	1.0	1,733	68	3,685.1	1.8	48.5	(21.5, 66.8)
Condyloma, VIN 1, or VaIN 1	1,726	31	3,684.8	0.8	1,733	64	3,686.5	1.7	51.5	(24.5, 69.5)
VIN 2/3 or VaIN 2/3	1,726	3	3,708.0	0.1	1,733	10	3,728.3	0.3	69.8	(<0.0, 94.7)
Vulvar or Vaginal Cancer	1,726	1	3,709.5	0.0	1,733	0	3,732.1	0.0	NA	NA

†An external genital lesion due to any HPV type is defined as a tissue sample diagnosed by the Pathology Panel as VIN, VaIN, an external genital wart, or vulvar or vaginal cancer.
‡Includes all subjects who received ≥1 vaccination. Subjects were required to be seronegative and PCR negative for all vaccine HPV types and have a Pap test diagnosis of "Negative for SIL" at Day 1. Cases were counted starting 30 days after Day 1. 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 in the given population with at least one follow-up visit following 30 days after Day 1.
EGL = External genital lesions; PCR = Polymerase chain reaction.
SIL = Squamous intraepithelial lesion; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Table 8: Summary of Anti-HPV cLIA Seropositivity Rates by Vaccination Group
(Per-Protocol Immunogenicity Population)

Assay (cLIA)	Time Point	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=2,717)				Placebo (N=2,725)			
			Seropositivity				Seropositivity		
		n	m	Percent	95% CI	n	m	Percent	95% CI
Anti-HPV 6	Month 7	1,773	1,770	99.8	(99.5%, 100%)	1,802	24	1.3	(0.9%, 2.0%)
	Month 12	1,739	1,727	99.3	(98.8%, 99.6%)	1,774	21	1.2	(0.7%, 1.8%)
	Month 24	1,655	1,581	95.5	(94.4%, 96.5%)	1,697	72	4.2	(3.3%, 5.3%)
Anti-HPV 11	Month 7	1,773	1,769	99.8	(99.4%, 99.9%)	1,802	14	0.8	(0.4%, 1.3%)
	Month 12	1,739	1,727	99.3	(98.8%, 99.6%)	1,774	9	0.5	(0.2%, 1.0%)
	Month 24	1,655	1,622	98.0	(97.2%, 98.6%)	1,697	17	1.0	(0.6%, 1.6%)
Anti-HPV 16	Month 7	1,694	1,692	99.9	(99.6%, 100%)	1,687	29	1.7	(1.2%, 2.5%)
	Month 12	1,662	1,655	99.6	(99.1%, 99.8%)	1,663	23	1.4	(0.9%, 2.1%)
	Month 24	1,591	1,583	99.5	(99.0%, 99.8%)	1,585	59	3.7	(2.8%, 4.8%)
Anti-HPV 18	Month 7	1,903	1,894	99.5	(99.1%, 99.8%)	1,931	10	0.5	(0.2%, 1.0%)
	Month 12	1,874	1,673	89.3	(87.8%, 90.6%)	1,897	13	0.7	(0.4%, 1.2%)
	Month 24	1,781	1,310	73.6	(71.4%, 75.6%)	1,812	30	1.7	(1.1%, 2.4%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m = Number of seropositive subjects.
cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.

Table 9
Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group
(Per-Protocol Immunogenicity Population)

		Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=2,717)			Placebo (N=2,725)	
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)
Anti-HPV 6	Month 7	1,773	551.3	(530.8, 572.5)	1,802	<8
	Month 12	1,739	206.4	(197.9, 215.3)	1,774	<8
	Month 24	1,655	118.1	(112.7, 123.8)	1,697	<8
Anti-HPV 11	Month 7	1,773	786.7	(753.0, 822.0)	1,802	<8
	Month 12	1,739	261.5	(250.0, 273.6)	1,774	<8
	Month 24	1,655	152.2	(145.1, 159.6)	1,697	<8
Anti-HPV 16	Month 7	1,694	2,270.4	(2,135.3, 2,414.1)	1,687	<12
	Month 12	1,662	909.9	(863.2, 959.0)	1,663	<12
	Month 24	1,591	493.3	(468.0, 520.0)	1,585	<12
Anti-HPV 18	Month 7	1,903	466.1	(444.4, 489.0)	1,931	<8
	Month 12	1,874	112.7	(106.3, 119.5)	1,897	<8
	Month 24	1,781	55.5	(51.9, 59.3)	1,812	<8

Efficacy Trials
Reference P015V2

Protocol Title:
"A Randomized, Worldwide, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16-/18-Related CIN 2/3 or Worse of the Quadrivalent human papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in 16- to 23-Year Old Women - The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)"

STUDY OBJECTIVE

Primary Safety Objective:
To demonstrate that a 3-dose regimen of quadrivalent HPV vaccine is generally well tolerated.

Primary Efficacy Objective:
To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 16- and 18-related high-grade Cervical Intraepithelial Neoplasia (CIN 2/3) or HPV 16- and 18-related invasive cervical carcinoma in seronegative subjects.
Note: Seronegative subjects are those study subjects who are polymerase chain reaction (PCR) negative and seronegative at baseline as well as PCR negative through Month 7 (one month after completion of the vaccination series) for the relevant HPV type.

Secondary Immunogenicity Objective:
To evaluate the persistence of vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in seronegative subjects.

Exploratory Efficacy Objectives:
(1) To estimate the impact of the administration of the quadrivalent HPV vaccine on the incidence of the composite endpoint of ALL CIN 2/3 or invasive cervical carcinoma (caused by any vaccine or nonvaccine HPV type) in seronegative subjects for high-risk HPV types.
(2) To estimate the impact of the administration of the quadrivalent HPV vaccine on the incidence of the composite endpoint of HPV 6-/11-/16-/18-related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), or Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer or vaginal cancer in seronegative subjects for the relevant HPV type(s).

STUDY DESIGN

This is a phase III, randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multicenter, multinational efficacy study in 11,500 16- to 23-year-old female subjects. Within this study, subjects may have also been enrolled in any of 3 separate sub-studies:

(1) Non-Serious Adverse Experience Sub-study (NSAE) prospectively assessed the tolerability of the quadrivalent HPV vaccine,
(2) Consistency Lot Sub-study demonstrated the consistency of manufacture of the quadrivalent HPV vaccine, (the study evaluation is reported in P015v1) and
(3) Registry Sub-study confirmed complete ascertainment of cytology and pathology specimens. This part of the study will be evaluated at the end of the 4-year study.

Subjects were randomized in a 1:1 ratio to receive either quadrivalent HPV vaccine or placebo. To assess efficacy, Papanicolaou (Pap) testing was to be done at scheduled visits and Pap test abnormalities were followed up according to a pre-defined mandatory triage algorithm. External genital lesion (EGL) inspection was to be performed at scheduled visits or when a subject presented with symptoms. To evaluate immunogenicity in the Consistency Lot sub-study, sera were to be obtained at scheduled visits. To evaluate safety, subjects in the NSAE sub-study completed a vaccination report card (VRC) after each vaccination.

SUBJECTS DISPOSITION:

	HPV Vaccine	Placebo	Total
SCREENING FAILURES:			539
RANDOMIZED:	6087	6080	12167
Female (age range – 15 to 26 years old)			
ENTERED: (Vaccination Period Day 1 through Month 7)	6082	6075	12157
COMPLETED: (Day 1 through Month 7)	5916	5953	11869
DISCONTINUED: (Day 1 through Month 7)	166	122	288
WITH LONG-TERM FOLLOW-UP	24	14	38
Clinical adverse experience	2	3	5
Other reasons	15	4	19
Pregnancy	7	6	13
WITHOUT LONG-TERM FOLLOW-UP	142	108	250
Clinical adverse experience	6	2	8
Lost to follow-up	42	36	78
Moved	13	13	26
Other reasons	9	4	13
Protocol deviations	2	1	3
Withdrew consent	70	52	122
ENTERED: (Follow-up Period After Month 7)	5935	5953	11888
CONTINUING: (Follow-up Period After Month 7)	5895	5919	11814
DISCONTINUED: (Follow-up Period After Month 7)	40	34	74
Clinical adverse experience	2	4	6
Lost to follow-up	18	15	33
Moved	1	4	5
Other reasons	2	3	5
Withdrew consent	17	8	25

STATISTICAL ANALYSIS AND EVALUATION CRITERIA

The protocol specified that the primary analysis of efficacy was to be conducted in the per-protocol efficacy (PPE) population. This cohort consisted of subjects who received

all 3 vaccinations, did not deviate from the study protocol in ways that could potentially interfere with the efficacy of the vaccine, and were seronegative at baseline and PCR negative at baseline and during the 6-month vaccination regimen and for 1 month thereafter (to allow for induction of immune responses to Dose 3 of the vaccine), to the relevant HPV type(s). Cases of the primary endpoint were counted starting after Month 7.

Same as Study 013 described previously, an exact conditional procedure proposed by Martin and Austin (1996) was used to test the statistical hypotheses.

This study employed a fixed event design, whereby the interim and final primary efficacy analyses were scheduled to be conducted at the time that specific target numbers of cases of the primary endpoint had been observed. Specifically, this interim analysis was conducted when at least 19 cases of HPV 16/18-related CIN 2/3 or worse were observed among subjects in the per-protocol efficacy population (PPE). A one-sided test of the null hypothesis that the vaccine efficacy (VE) was ≤0% was used to address the primary hypothesis. The alternative hypothesis was that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine was efficacious relative to placebo (i.e., VE >0%). A point estimate of the VE and the corresponding multiplicity-adjusted two-sided exact 97.96% confidence interval (CI) was provided to control the overall Type I error rate for the interim analyses and the end of study analyses at the 0.025 (1-sided) level. A lower bound of the 97.96% CI for VE >0% led to rejection of the null hypothesis. (A 95% confidence interval is presented for the type-specific and lesion-specific endpoints for estimation purposes only.) A p-value <0.0102 (1-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 0% and supports the conclusion that the vaccine is efficacious against the given endpoint.

Protocol 015 was a multicenter study. Prior to conducting the formal statistical analyses described above, the DAP specified that tests for study-site-by-treatment-group interaction were to be performed. As detailed in Section of Result, this test, based on the efficacy results, was not necessary because the vaccine efficacy in the PPE population was 100% across all regions.

SAMPLE SIZE AND POWER ANALYSIS

The efficacy study was powered based on a fixed event design with an interim analysis. To ensure adequate power for the interim analysis (80 to 90% power) and the final analysis (90%) for varying true vaccine efficacies after the multiplicity adjustment, at least 19 cases of HPV 16-related or HPV 18-related CIN 2/3 or worse were required for the interim analysis, and 29 cases are required for the final analysis. To observe 29 cases of the primary endpoint by Month 48, an overall sample size of approximately 11,500 subjects (5,750 in each vaccination group) was required for the study. The sample size was estimated using the following assumptions:

— ~18% of the subjects enrolled would be HPV 16 seropositive at Day 1 or PCR positive between Day 1 and Month 7;
— ~18% of the subjects enrolled would be HPV 18 seropositive at Day 1 or PCR positive between Day 1 and Month 7;

— the attrition rate would be no more than 15% through Month 7 of the study and no more than 5% per year thereafter;
— all subjects followed beyond Month 7 would be eligible to be endpoints and any subject who discontinued the study would be at risk for HPV 16- or HPV 18-related CIN 2/3 or worse for half of the study;
— the incidence of CIN 2/3 or worse related to HPV Type 16 would be ~0.19% per year in the placebo group, while the incidence of CIN 2/3 or worse related to HPV Type 18 would be ~0.038% per year in the placebo group; and
— if the vaccine efficacy was extremely high, all cases would have to accrue in the placebo group before the efficacy analysis would be performed.
— assuming a true vaccine efficacy of at least 80%, conducting a test of the primary efficacy hypotheses at the time when 19 cases were observed would provide at least 80% power at the interim time point to declare the vaccine efficacious with a multiplicity-adjusted 2-sided α=0.0204. A multiplicity adjustment was made to account for the 2 separate efficacy analyses (the interim and the final) of the data. The overall 2-sided α level for the study was controlled at the 0.05 level.

INTERIM ANALYSIS AND DATA MONITORING EFFICACY

Efficacy

This interim analysis of Protocol 015 was performed in conjunction with an interim analysis of the combined data from Protocols 005, 007, 013, and 015, and, therefore, was conducted when at least 19 cases of CIN 2/3 or cervical cancer related to HPV 16 or 18 were observed in Protocol 015 *and* at least 33 cases were observed across all 4 studies.

The interim analysis of Protocol 015 was performed by a designated unblinded statistician otherwise unrelated to the study. The unblinded statistician provided the results of the analysis to a DSMB along with the results of the interim analysis of the combined data (Protocols 005, 007, 013, and 015). The DSMB communicated to the HPV vaccine project team at the Sponsor that the interim analyses of Protocol 015 and the combined data set met the primary statistical criteria for success. Following this communication, a copy of the frozen database was unblinded for reporting on this interim analysis.

Safety

In order to ensure that no alarming, unusual, or unexpected safety problems were occurring with the vaccine, safety was monitored during the study by the DSMB, which was to determine whether any actions should be taken based on the data. Periodically during the study (approximately every 6 months during the vaccination period and approximately every year thereafter), all available safety data from the study were summarized by vaccination group by the designated unblinded Sponsor statistician and sent to the DSMB.

MULTIPLE COMPARISONS / MULTIPLICITY

A multiplicity adjustment was necessary for this analysis because it includes an interim analysis of the primary efficacy hypothesis. In order to control the overall type I error rate for

the efficacy study at α = 0.05 for a 2-sided test, the α-levels used at the interim and final analyses were adjusted to account for the multiple, correlated analyses. The effective α-levels at the interim and final analyses were computed using the power boundaries of Wang and Tsiatis[2]. Using an alpha boundary shape of 0.2 (where 0.0 represents the O'Brien-Fleming boundary and 0.5 represents the Pocock boundary), a two-sided alpha of 0.0204 would be spent at the interim analysis, and a two-sided alpha of 0.0411 would be spent at the final analysis.
No multiplicity adjustments were made for other efficacy analyses due to their secondary nature. No multiplicity adjustments were made for vaccination group comparisons of multiple safety endpoints.

EFFICACY ANALYSIS POPULATIONS

Same as Study 013 described previously, four subject populations, 1 per-protocol efficacy (PPE) and 3 modified intention-to-treat (MITT), were considered for the primary evaluation of vaccine efficacy. Primary study conclusions were drawn from the analysis in the per-protocol population. The MITT populations were used to confirm/support the results of the analysis in the per-protocol population.

CHANGES IN THE PLANNED STATISTICAL ANALYSIS

An additional criterion for defining the per-protocol efficacy population was added to those outlined in the DAP. To ensure the Day 1 prevaccination serum and swab samples were appropriate for assessing baseline HPV status, day ranges were applied to the samples. The Day 1 prevaccination serum sample was required to be obtained within 14 days prior to the first vaccination or on the day of the first vaccination. The Day 1 prevaccination swab samples were required to be obtained within 14 days prior to and within 10 days after the first vaccination.

The planned test of treatment-by-study-site interaction was replaced with a treatment-by-region-interaction test. This analysis was changed because the 19 (or more) cases of HPV 16/18-related CIN 2/3 or worse required for the fixed-case analysis was sparse relative to the number of study sites that enrolled subjects (90). Thus, study sites were grouped by region for tests of interaction.

Due to the similarity between the per-protocol efficacy population and the MITT-1 population, the analysis of HPV 16/18-related CIN 2/3 or worse using the central laboratory diagnosis and including biopsies outside the context of the study was not performed in the MITT-1 population.

The Kaplan-Meier time-to-event analyses for HPV 16/18-related CIN 2/3 or worse were not performed in the PPE, MITT-1, and MITT-2 populations because there were too few subjects who developed a case of the endpoint in the quadrivalent HPV vaccine group.

[2] Wang SK and Tsiatis AA. Approximately optimal one-parameter boundaries for group sequential trials. Biometrics 1987; 43: 193-199.

RESULTS

Table 10 on page 27 shows the results of the primary analysis of the efficacy of the quadrivalent HPV vaccine with respect to the combined incidence of HPV 16- or HPV 18-related CIN 2/3, AIS, or invasive cervical cancer in the PPE population at the protocol's interim analysis time point. Inference regarding the efficacy of the quadrivalent HPV vaccine is drawn from the results of this analysis. The observed vaccine efficacy is 100%, a statistically significant result with $p<0.001$ compared with the multiplicity-adjusted critical α of 0.0102 (one-sided). [Note: the corresponding 97.96% lower confidence limit is 75.8%. A 97.96% confidence interval is used to adjust for multiplicity and to control the overall Type I error rate for the interim analyses and the end of study analyses at the 0.025 (1-sided) level.] This result supports the conclusion that administration of a 3-dose regimen of quadrivalent HPV vaccine is efficacious in preventing the development of HPV 16- or HPV 18-related CIN 2/3, AIS, or invasive cervical cancer lesions among subjects who are defined as in PPE population.

No multiplicity adjustment was made for HPV type-specific or lesion-specific analyses presented. Thus, a 95% confidence interval is used for the type-specific and lesion-specific endpoints for estimation purposes only. Also, the MITT analyses and sensitivity analyses are provided as support for the primary efficacy analysis.

The lower bound of the 95% confidence intervals for HPV 16-related CIN 2/3 or AIS and HPV 18-related CIN 2/3 or AIS are 74.8% and 42.3%, respectively. Both demonstrate the efficacy with respect to the 2 high-risk HPV types contained in the vaccine.

All cases in the primary PPE analysis were either CIN 2 or CIN 3/AIS. Ten subjects developed a case of HPV 16- or HPV 18-related CIN 2 and a case of HPV 16- or HPV 18-related CIN3/AIS. For CIN 2, the lower bound of the 95% confidence interval for vaccine efficacy was 72.3%, and the lower bound of the 95% confidence interval for vaccine efficacy against CIN 3/AIS was 74.2%.

Vaccine efficacy was also evaluated in various MITT populations designed to reflect specific populations of women likely to receive the HPV vaccine following licensure. Table 11 on page 28 and Table 12 on page 29 summarize the results of the efficacy analyses with respect to the combined incidence of HPV 16- or HPV 18-related CIN 2/3, AIS, or invasive cervical cancer in the MITT-2, and MITT-3 populations, respectively. (The corresponding results of the MITT-1 population are not shown due to the similarity to those of the per-protocol efficacy population.)

In the MITT-2 population, the additional 16 subjects who were identified as cases of HPV 16- or HPV 18-related CIN 2/3 or AIS in this analysis were subjects who became infected with the relevant HPV type(s) during the vaccination period and were PCR positive to the relevant HPV type(s) by Month 7. One subject was in the quadrivalent HPV vaccine group and 15 were in the placebo group. The vaccine efficacy estimate is 97.2% with a 95% lower confidence limit at 83.4%.

Compared with the MITT-2 population, 141 additional subjects in the MITT-3 population (66 subjects in the quadrivalent HPV vaccine group and 75 subjects in the placebo group) were observed to have a case of HPV 16- and/or HPV 18-related CIN 2/3 or AIS. These cases occurred among subjects who were HPV 16 seropositive and/or PCR positive or HPV 18 seropositive and/or PCR positive at enrollment. The vaccine efficacy estimate is 39.2% with a 95% lower confidence limit at 16.9%.

Table 13 on page 30 shows the exploratory assessment of efficacy of the quadrivalent HPV vaccine with respect to the combined incidence of HPV 6/11/16/18-related CIN or AIS. No multiplicity adjustment was made for the exploratory analyses. The vaccine efficacy in the PPE population with respect to the combined incidence of HPV 6/11/16/18-related CIN was 90.7% with CI: 74% ~ 98%. The efficacy results of the MITT-1 and MITT-2 analyses were comparable to the efficacy observed in the PPE population. However, in the MITT-3 population, which reflects the presence of HPV 6/11/16/18 infection or CIN among subjects at enrollment, the observed efficacy was 46.6% with CI: 31.8% ~ 58.4%, which was much lower than other populations.

Table 14 on page 31 shows the exploratory assessment of efficacy of the quadrivalent HPV vaccine with respect to the combined incidence of HPV 6/11/16/18-related external genital lesions (including genital warts, VIN, VaIN, vulvar cancer, and vaginal cancer). No multiplicity adjustment was made for the exploratory analyses. Vaccine efficacy in the PPE population with respect to the combined incidence of HPV 6/11/16/18-related EGL was 98.6% with a 95% lower bound at 91.8%. The efficacy results of the MITT-2 analyses, VE: 94.6%, CI: 87.8% ~ 98.1%, were consistent with those observed in the PPE population. However, in the MITT-3 population, which reflects the presence of HPV 6/11/16/18 infection or CIN among subjects at enrollment, the observed efficacy was 71.0% with CI: 58.8% ~ 79.9%, which was lower than for other populations.

Table 15 on page 32 shows the exploratory assessment of efficacy of the quadrivalent HPV vaccine on the combined incidence of HPV 6/11/16/18-related cervicovaginal and external genital lesions. No multiplicity adjustment was made for the exploratory analyses. Vaccine efficacy in the PPE population with respect to the combined incidence of HPV 6/11/16/18-related disease was 95.3% with a 95% lower bound at 88.6%. The efficacy results of the MITT-2 analyses, VE: 92.5%, CI: 86.9% ~ 96.1%, were lower than those observed in the PPE population. However, in the MITT-3 population, the observed efficacy was 55.4% with CI: 45.3% ~ 63.7%, which was much lower than for other populations.

Immunogenicity

Serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses were measured using a multiplex competitive Luminex immunoassay (cLIA). In the per-protocol immunogenicity (PPI) population, subjects vaccinated with the quadrivalent HPV vaccine mounted an immune response at Month 7 that declined by Month 24 (Table 16 on page 33).

For HPV 6, 11, 16, and 18, the cutoff for seropositivity was defined as an anti-HPV cLIA antibody level >20, 16, 20, and 24 milli Merck Units (mMU)/mL, respectively. Almost all subjects in the quadrivalent HPV vaccine group mounted an immune response to each vaccine HPV type by Month 7 and the percents of subjects who were seropositive to HPV 6, HPV 11, and HPV 16 remained high at Month 24 (Table 17 on page 34).

Safety

Table 18 on page 35 shows clinical adverse experience within 15 days following any vaccination visit for all vaccinated subjects. Two subjects in the quadrivalent HPV vaccine group died, although neither death was considered by the investigator to be vaccine related. The proportion of subjects who reported vaccine-related serious adverse experiences was comparable between the two vaccination groups. The proportion of subjects who discontinued due to a serious adverse experience was also comparable between the two vaccination groups.

Furthermore, Table 19 on page 36 shows the clinical adverse experience summary of the Detailed Safety Cohort in the United States within 15 days of any vaccination visit for study subjects. Very high proportions of subjects who reported at least one clinical adverse experience within 15 days of any vaccination visit were observed in this study and it was somewhat higher in the quadrivalent HPV vaccine group (91.3%) than in the placebo group (88.4%). The proportions of subjects who reported (1) at least 1 injection-site adverse experience, (2) at least one systemic adverse experience, and (3) moderate- or severe-intensity injection-site adverse experiences were all somewhat higher in the quadrivalent HPV L1 VLP vaccine group than in the placebo group.

CONCLUSION

In the primary analysis based on the Per-Protocol Efficacy (PPE) population, the observed vaccine efficacy against HPV 16/18 related cervical intraepithelial neoplasia (CIN) 2/3 or worse was 100% with a lower bound CI of 73.8%, which was statistically significantly greater than 0% with $p<0.001$. In the exploratory analyses of efficacy against HPV 6/11/16/18-related disease, the observed efficacy of the quadrivalent HPV vaccine against CIN was 90.7% with a lower bound CI of 74.4%; the observed efficacy against external genital lesions was 98.6% with a lower bound CI of 91.8%; and the observed efficacy against cervicovaginal and external genital lesions was 95.3% with a lower bound CI of 88.6%. All results support the conclusion that the quadrivalent HPV vaccine is efficacious against HPV 6/11/16/18-related EGL and CIN.

In the analyses based on various modified intention-to-treat populations, the results of vaccine efficacy against HPV 6/11-related CIN 2/3 or worse in the MITT-2 population are supportive of the primary PPE result. However, the corresponding results in the MITT-3 population were lower.

A similar pattern of results was also found in the secondary analysis. The results of vaccine efficacy against the secondary endpoints of HPV 6/11/16/18-related CIN and EGL were high in the PPE population. While supportive of the conclusion of an efficacious HPV vaccine, the results of vaccine efficacy were lower with respect to specific HPV type of EGL.

Table 10: Primary Analysis of Efficacy against HPV 16/18-Related Cervical Intraepithelial Neoplasia (CIN) 2/3 or Worse (Per-Protocol Efficacy Population)

	Quadrivalent HPV Vaccine				Placebo					
Endpoint	N 6,082 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	N 6,075 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	Confidence interval
HPV 16/18-Related CIN 2/3 or worse	5,301	0	7,435.1	0.0	5,258	21	7,385.5	0.3	100.0	(73.8, 100.0)
By HPV Type										
HPV 16-Related CIN	4,552	0	6,407.9	0.0	4,405	16	3,130.6	0.3	100.0	(74.8, 100.0)
HPV 18-Related CIN	5,051	0	7,083.2	0.0	4,968	8	3,569.1	0.1	100.0	(42.3, 100.0)
By Lesion Type										
CIN 2	5,301	0	7,435.1	0.0	5,258	15	3,736.5	0.2	100.0	(72.3, 100.0)
CIN 3/AIS	5,301	0	7,435.1	0.0	5,258	16	3,737.8	0.2	100.0	(74.2, 100.0)
Cervical Cancer	5,301	0	7,435.1	0.0	5,258	0	3,738.2	0.0	NA	NA

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population with at least one follow-up visit after Month 7.

A 97.96% confidence interval is provided for the primary analysis of HPV 16/18-Related CIN 2/3 or worse to adjust for multiplicity and to control the overall Type I error rate for the interim analyses and the end of study analyses at the 0.025 (1-sided) level.
A 95% confidence interval is presented for the type-specific and lesion-specific endpoints for estimation purposes only.
A p-value <0.0102 (1-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 0% and supports the conclusion that the vaccine is efficacious against the given endpoint.

Table 11: Analysis of Efficacy against HPV 16/18-Related CIN 2/3 or Worse (Modified Intention-to-Treat Population 2)

	Quadrivalent HPV Vaccine				Placebo					
Endpoint	N 6,082 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	N 6,075 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
HPV 16/18-Related CIN 2/3 or worse	5,736	1	10,797.2	0.0	5,766	36	10,881.5	0.3	97.2	(83.4, 99.9)
By HPV Type										
HPV 16-Related CIN	4,944	1	9,350.3	0.0	4,957	28	9,392.6	0.3	96.4	(78.3, 99.9)
HPV 18-Related CIN	5,477	0	10,313.6	0.0	5,508	11	10,408.0	0.1	100.0	(59.8, 100.0)
By Lesion Type										
CIN 2	5,736	1	10,797.2	0.0	5,766	27	10,883.1	0.2	96.3	(77.4, 99.9)
CIN 3/AIS	5,736	0	10,797.2	0.0	5,766	27	10,885.2	0.2	100.0	(85.2, 100.0)
Cervical Cancer	5,736	0	7,435.1	0.0	5,766	0	10,887.1	0.0	NA	NA

A p-value <0.025 (1-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 0% and supports the conclusion that the vaccine is efficacious against the given endpoint.
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 in the given population with at least one follow-up visit following 30 days after Day 1.
AIS = Adenocarcinoma in situ; CIN = Cervical intraepithelial neoplasia; DNA = Deoxyribonucleic acid;

Table 12: Analysis of Efficacy against HPV 16/18-Related CIN 2/3 or Worse (Modified Intention-to-Treat Population 3)

	Quadrivalent HPV Vaccine				Placebo					
Endpoint	N 6,082 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	N 6,075 n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
HPV 16/18-Related CIN 2/3 or worse	5,947	67	11,159.5	0.6	5,973	111	11,243.9	1.0	39.2	(16.9, 55.8)
By HPV Type										
HPV 16-Related CIN	5,947	62	11,161.1	0.6	5,973	99	11,247.4	0.9	36.9	(12.4, 54.8)
HPV 18-Related CIN	5,947	5	11,176.5	0.0	5,973	22	11,264.1	0.2	77.1	(38.0, 93.2)
By Lesion Type										
CIN 2	5,947	36	11,169.5	0.3	5,973	74	11,254.8	0.7	51.0	(26.0, 68.0)
CIN 3/AIS	5,947	47	11,167.5	0.4	5,973	85	11,256.5	0.8	44.3	(19.5, 61.8)
Cervical Cancer	5,947	0	11,178.0	0.0	5,973	0	11,267.9	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 in the given population with at least one follow-up visit following 30 days after Day 1.
AIS = Adenocarcinoma in situ; CIN = Cervical intraepithelial neoplasia; DNA = Deoxyribonucleic acid;

Table 13: Analysis of Efficacy against HPV 6/11/16/18-Related Cervical Intraepithelial Neoplasia (CIN)

	Quadrivalent HPV Vaccine (N=6,082)				Placebo (N=6,075)					
Endpoint HPV 6/11/16/18-Related CIN	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	Confidence interval
PPE	5,383	4	7,542.1	0.1	5,370	43	7,534.0	0.6	90.7	(74.4, 97.6)
MITT-1	5,636	4	7,851.4	0.1	5,659	46	7,878.7	0.6	91.3	(76.1, 97.7)
MITT-2	5,810	7	10,926.3	0.1	5,844	79	11,004.1	0.7	91.1	(80.7, 96.5)
MITT-3	5,947	102	11,129.9	0.9	5,973	192	11,186.3	1.7	46.6	(31.8, 58.4)
By HPV Type (PPE)										
HPV 6-Related CIN	4,723	0	6,622.1	0.0	4,643	11	6,514.2	0.2	100.0	(60.8, 100.0)
HPV 11-Related CIN	4,723	0	6,622.1	0.0	4,643	2	6,515.4	0.0	100.0	(<0.0, 100.0)
HPV 16/18-Related CIN	5,301	4	7,431.5	0.1	5,258	33	7,381.7	0.4	88.0	(66.1, 96.9)
HPV 16-Related CIN	4,552	4	6,404.2	0.1	4,405	25	6,212.5	0.4	84.5	(55.1, 96.1)
HPV 18-Related CIN	5,051	0	7,083.2	0.0	4,968	11	6,979.5	0.2	100.0	(60.7, 100.0)
By Lesion Type (PPE)										
CIN 1	5,383	4	7,542.1	0.1	5,370	31	7,535.7	0.4	87.1	(63.5, 96.7)
CIN 2 or Worse	5,383	0	7,545.7	0.0	5,370	22	7,541.5	0.3	100.0	(81.8, 100.0)
CIN 2	5,383	0	7,545.7	0.0	5,370	16	7,542.3	0.2	100.0	(74.1, 100.0)
CIN 3/AIS	5,383	0	7,545.7	0.0	5,370	16	7,542.7	0.2	100.0	(74.1, 100.0)
Cervical Cancer	5,383	0	7,545.7	0.0	5,370	0	7,543.6	0.0	NA	NA

Table 14: Analysis of Efficacy against HPV 6/11/16/18-Related External Genital Lesions (EGL)

	Quadrivalent HPV Vaccine (N=6,082)				Placebo (N=6,075)					
Endpoint HPV 6/11/16/18-Related EGL	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
PPE	5,401	1	7,545.8	0.0	5,387	70	7,513.7	0.9	98.6	(91.8, 100.0)
MIT-2	5,875	6	10,957.0	0.1	5,897	111	10,983.6	1.0	94.6	(87.8, 98.1)
MIT-3	6,016	42	11,165.8	0.4	6,027	145	11,183.8	1.3	71.0	(58.8, 79.9)
By HPV Type (PPE)										
HPV 6-Related EGL	4,738	1	6,617.7	0.0	4,656	56	6,495.0	0.9	98.2	(89.8, 100.0)
HPV 11-Related EGL	4,738	0	6,619.0	0.0	4,656	9	6,512.8	0.1	100.0	(50.1, 100.0)
HPV 16-Related EGL	4,558	0	6,374.5	0.0	4,410	15	6,161.4	0.2	100.0	(73.1, 100.0)
HPV 18-Related EGL	5,067	0	7,073.7	0.0	4,980	6	6,965.3	0.1	100.0	(16.4, 100.0)
By Lesion Type (PPE)										
Condyloma, VIN, VaIN 1	5,401	1	7,545.8	0.0	5,387	65	7,514.6	0.9	98.5	(91.2, 100.0)
VIN, VaIN 2/3	5,401	0	7,547.1	0.0	5,387	6	7,535.4	0.1	100.0	(15.2, 100.0)
Vulvar, Vaginal Cancer	5,401	0	7,547.1	0.0	5,387	0	7,536.7	0.0	NA	NA

VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia;

Table 15: Analysis of Efficacy against HPV 6/11/16/18-Related Cervicovaginal and External Genital Lesions (EGL)

	Quadrivalent HPV Vaccine (N=6,082)				Placebo (N=6,075)					
Endpoint HPV 6/11/16/18-Related Disease	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Per 100 Person-Years at Risk	Observed Efficacy (%)	95% Confidence interval
PPE	5,403	5	7,694.9	0.1	5,387	105	7,664.6	1.4	95.3	(88.6, 98.5)
MIT-2	5,880	13	11,118.4	0.1	5,899	174	11,128.4	1.6	92.5	(86.9, 96.1)
MIT-3	6,021	140	11,230.0	1.2	6,029	313	11,210.2	2.8	55.4	(45.3, 63.7)
By HPV Type (PPE)										
HPV 6-Related Disease	4,739	1	6,743.1	0.0	4,656	63	6,621.8	1.0	98.4	(91.0, 100.0)
HPV 11-Related Disease	4,739	0	6,744.4	0.0	4,656	10	6,646.1	0.2	100.0	(56.0, 100.0)
HPV 16-Related Disease	4,559	4	6,490.5	0.1	4,410	39	6,282.5	0.6	90.1	(72.5, 97.4)
HPV 18-Related Disease	5,068	0	7,216.8	0.0	4,980	17	7,112.2	0.2	100.0	(76.1, 100.0)

Table 16: Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group in Consistency Lot Substudy (Per-Protocol Immunogenicity Population)

Assay (cLIA)	Time Point	Quadrivalent HPV Vaccine (N=1,512)			Placebo (N=1,511)		
		n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Month 7	1,057	527.6	(503.2, 553.2)	1,058	<8	(<8, <8)
	Month 24	988	107.4	(101.1, 114.1)	980	<8	(<8, <8)
Anti-HPV 11	Month 7	1,057	732.9	(694.7, 773.2)	1,058	<8	(<8, <8)
	Month 24	988	136.6	(128.3, 145.5)	980	<8	(<8, <8)
Anti-HPV 16	Month 7	1,016	2,388.2	(2,215.2, 2,574.7)	995	<12	(<12, <12)
	Month 24	953	435.1	(406.9, 465.3)	927	<12	(<12, <12)
Anti-HPV 18	Month 7	1,140	451.6	(425.4, 479.4)	1,119	<8	(<8, <8)
	Month 24	1,060	46.9	(43.0, 51.2)	1,043	<8	(<8, <8)

N: # of subjects in the Consistency Lot substudy randomized to the respective vaccination group who received at least 1 injection.
n: # Number of subjects contributing to the analysis.
cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Table 17: Summary of Anti-HPV cLIA Seropositivity Rates by Vaccination Group in Consistency Lot Substudy
(Per-Protocol Immunogenicity Population)

Assay (cLIA)	Time Point	Quadrivalent HPV Vaccine (N=1,512)				Placebo (N=1,511)			
		n	Seropositivity			n	Seropositivity		
			m	Percent	95% CI		m	Percent	95% CI
Anti-HPV 6	Month 7	1,057	1,055	99.8	(99.3%, 100%)	1,058	13	1.2	(0.7%, 2.1%)
	Month 24	988	944	95.5	(94.1%, 96.7%)	980	39	4.0	(2.8%, 5.4%)
Anti-HPV 11	Month 7	1,057	1,054	99.7	(99.2%, 99.9%)	1,058	5	0.5	(0.2%, 1.1%)
	Month 24	988	962	97.4	(96.2%, 98.3%)	980	10	1.0	(0.5%, 1.9%)
Anti-HPV 16	Month 7	1,016	1,013	99.7	(99.1%, 99.9%)	995	15	1.5	(0.8%, 2.5%)
	Month 24	953	946	99.3	(98.5%, 99.7%)	927	33	3.6	(2.5%, 5.0%)
Anti-HPV 18	Month 7	1,140	1,133	99.4	(98.7%, 99.8%)	1,119	12	1.1	(0.6%, 1.9%)
	Month 24	1,060	723	68.2	(65.3%, 71.0%)	1,043	17	1.6	(1.0%, 2.6%)

Table 18: Clinical Adverse Experience Summary (Days 1 to 15 Following Any Vaccination Visit)
(All Vaccinated Subjects)

	Quadrivalent HPV Vaccine (N=6,075)		Placebo (N=6,076)	
	n	(%)	n	(%)
Subjects in analysis population	6075		6076	
Subjects without follow-up	56		45	
Subjects with follow-up	6019		6031	
Number (%) of subjects:				
with serious adverse experiences	17	(0.3)	16	(0.3)
with serious vaccine-related† adverse experiences	3	(0.0)	2	(0.0)
who died	2	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	6	(0.1)	4	(0.1)
discontinued due to a vaccine-related adverse experience	4	(0.1)	1	(0.0)
discontinued due to a serious adverse experience	2	(0.0)	1	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	1	(0.0)

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

Table 19: Clinical Adverse Experience Summary (Days 1 to 15 Following Any Vaccination Visit)
Detailed Safety Cohort (United States)

	Quadrivalent HPV Vaccine (N=457)		Placebo (N=454)	
	n	(%)	n	(%)
Subjects in analysis population	457		454	
Subjects without follow-up	9		7	
Subjects with follow-up	448		447	
Number (%) of subjects:				
with no adverse experience	39	(8.7)	52	(11.6)
with one or more adverse experiences	409	(91.3)	395	(88.4)
injection-site adverse experiences	379	(84.6)	349	(78.1)
systemic adverse experiences	271	(60.5)	266	(59.5)
with vaccine-related† adverse experiences	394	(87.9)	369	(82.6)
injection-site adverse experiences	379	(84.6)	349	(78.1)
systemic adverse experiences	147	(32.8)	142	(31.8)
with serious adverse experiences	1	(0.2)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	1	(0.2)	0	(0.0)
discontinued‡ due to an adverse experience	3	(0.7)	0	(0.0)
discontinued due to a vaccine-related adverse experience	2	(0.4)	0	(0.0)
discontinued due to a serious adverse experience	1	(0.2)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

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

Efficacy Trials
Reference P015V1

Protocol Title:
"A Randomized, Worldwide, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16-/18-Related CIN 2/3 or Worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in 16- to 23-Year Old Women - The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)"

STUDY OBJECTIVE

Primary Objective:
To demonstrate that the Final Manufacturing Process (FMP) results in quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine that, when given in a 3-dose regimen, induces consistent serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3.

Secondary Objective:
To evaluate the persistence of vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in subjects who are PCR negative and seronegative at baseline and PCR negative 1 month after completion of the vaccination series for the relevant HPV type.

To meet the objective that the three separate lots of the quadrivalent HPV vaccine will induce similar immune response, the criterion for the primary endpoint sets the ratio for each pair of GMTs to be less than 2.0. The statistical hypothesis testing is to reject two one-sided null hypotheses that the ratio of GMTs is (1) less than 0.5 and (2) greater than 2.0. Thus, the statistical criterion for success requires that the entire confidence interval for the ratio of GMTs falls within the pre-defined lot consistency limits [0.5 ~ 2.0]. The criterion for the secondary endpoint sets the difference in seroconversion rate between each pair of lots is less then five percentage points. The statistical hypothesis testing is to reject two one-sided null hypotheses that the seroconversion rate difference between the pairwise lots is (1) less than –0.05 and (2) greater than +0.05. Thus, a statistical criterion for success requires that the entire confidence interval for the difference in seroconversion rate between the pairwise lots falls within the pre-defined lot consistency limits [–0.05 ~ +0.05].

STUDY DESIGN

This sub-study was part of a large, randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multi-center, multinational study about 11,500 subjects. The 3-dose vaccination regimen was administered at Day 1, Month 2, and Month 6. This report addresses visits conducted between Day 1 and Month 7, inclusive. The efficacy of the quadrivalent HPV vaccine and the persistence of anti-HPV 6, anti-

HPV 11, anti-HPV 16, and anti-HPV 18 responses to the vaccine are previously summarized in the Main CIN 2/3 Efficacy Study (Protocol 015V2).

A total of 2054 subjects were screened in the Consistency Lot sub-study. About 74% were enrolled into this study. Of the 1514 randomized subjects, most (96.8%) completed the 3-dose vaccination regimen and the entire vaccination period (through Month 7). The detailed subject dispositions are listed in the following table. The number of subjects who discontinued during the vaccination period were generally comparable among the three consistency lot groups. The most common reason for discontinuation in the vaccination period was consent withdrawal. The proportions of subjects who discontinued the study and the distributions of reasons for discontinuation were generally comparable among the three consistency lot groups.

SUBJECTS DISPOSITIONS

	Quadrivalent HPV Vaccine			
	Lot 1	Lot 2	Lot 3	Total
	n (%)	n (%)	n (%)	n (%)
Screening Failures				540
Randomized	500	510	504	1514
Vaccination:				
Dose 1	499 (99.8)	509 (99.8)	504 (100.)	1512 (99.9)
Dose 2	489 (97.8)	503 (98.6)	494 (98.0)	1486 (98.2)
Dose 3	481 (96.2)	498 (97.6)	486 (96.4)	1465 (96.8)
Entered	499	509	504	1512
Completed†	478 (95.8)	494 (97.1)	480 (95.2)	1452 (96.0)
Continuing	5 (1.0)	3 (0.6)	6 (1.2)	14 (0.9)
Discontinued	16 (3.2)	12 (2.4)	18 (3.6)	46 (3.0)
With long-term follow-up‡	3 (0.6)	0 (0.0)	1 (0.2)	4 (0.3)
Other reasons	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.1)
Pregnancy	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)
Without long-term follow-up §	13 (2.6)	12 (2.4)	17 (3.4)	42 (2.8)
Clinical AE	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Lost to follow-up*	4 (0.8)	3 (0.6)	5 (1.0)	12 (0.8)
Moved	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Withdrew consent	8 (1.6)	8 (1.6)	10 (2.0)	26 (1.7)

† Subjects who completed the 3-dose regimen and entered the long-term follow-up period.
‡ Subjects who received fewer than 3 doses of vaccine and entered the long-term follow-up period.
§ Subjects who discontinued on or before Month 7 and did not enter the long-term follow-up period.
* One subject continued with long-term follow-up due to a clinical adverse experience.

STATISTICAL ANALYSIS AND EVALUATION CRITERIA

Immunogenicity

The primary immunogenicity objective of the Consistency Lot substudy was to demonstrate that the FMP results in the quadrivalent HPV vaccine that, when given in a 3-dose regimen, induces consistent serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3. This objective was addressed through the

primary immunogenicity hypothesis for the Consistency Lot sub-study that three separate lots of the quadrivalent HPV vaccine would induce similar immune responses, as measured by the serum GMTs to HPV 6, 11, 16, 18, at Week 4 Postdose 3.

Using the methodology of Wiens, Heyse and Matthews[3] [1.1.45], the evaluation of similarity in GMTs among lots was based on 3 pairwise comparisons for each vaccine HPV type for the primary immunogenicity endpoints. For each HPV type, an analysis of variance (ANOVA) model was constructed with natural log Month 7 titer as the dependent variable with vaccination group and geographic region as fixed effects. Using the mean squared error (MSE) from the final ANOVA model as an estimate of variance, GMTs at Week 4 Postdose 3 from each pair of lots was compared using 2 one-sided tests (within an equivalence margin of 2-fold) at the $\alpha = 0.05$ level, for an overall type I error rate of 0.05. Because there were 3 consistency lots, there were 6 one-sided comparisons for each vaccine HPV type.

Two lots were considered equivalent for a given HPV type if both one-sided p-values associated with the 2 comparisons within the pair were <0.05 (corresponding to the rejection of the associated null hypothesis of a 2-fold or more difference). This criterion for similarity between a pair of consistency lots with respect to GMTs was equivalent to requiring the two-sided 90% confidence interval (CI) for the GMT ratio between the pair of lots to be entirely within (0.5, 2). All 3 lots would be considered consistent with respect to GMTs for a given vaccine HPV type if all 3 pairwise 90% two-sided CIs of the GMT ratio for the vaccine HPV type were entirely within (0.5, 2).

[Note that, to be consistent with current evaluation criteria, CBER requested the sponsor to compute a two-sided 95% confidence interval (CI) for the GMT ratio and difference in response rates between each pair of lots in this study.]

The secondary analysis of seroconversion rates by Week 4 Postdose 3 was based on 3 pairwise comparisons for each vaccine HPV type. For each HPV type, each pairwise comparison was intended to demonstrate the equivalence of 2 of the 3 lots within 5 percentage points using 2 one-sided tests at the $\alpha = 0.05$ level. The tests were stratified by geographic region. The success criterion for similarity between a pair of consistency lots with respect to seroconversion rates was equivalent to requiring that the two-sided 90% CI for the difference in response rates between the pair of lots to be entirely within (-0.05, 0.05). All 3 lots would be considered consistent with respect to seroconversion rates for a given vaccine HPV type if all 3 pairwise 90% two-sided CIs for the vaccine HPV type were entirely within (-0.05, 0.05). The method for testing equivalence of seroconversion rates was based on a test for a non-zero difference in binomial proportions by Miettinen and Nurminen[4] after stratification by study center.

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[3] Wiens, Heyse and Matthews. Similarity of three treatments, with application to vaccine development. Proceedings of the Biopharmaceutical Section of the American Statistical Association. 1996: 203-206

[4] Miettinen and Nurminen, Comparative Analysis of Two Rates. Statistics in medicine, Vol 4, 213-226 (1985)

Only subjects enrolled in the Consistency Lot substudy were evaluated for the primary immunogenicity objective.

Safety

The primary safety objective of this study was to demonstrate that a 3-dose regimen of the quadrivalent HPV vaccine is generally well tolerated in 16- to 23-year-old female subjects. All subjects who participated in both the Consistency Lot substudy and the NSAE substudy and received at least one injection and had follow-up data were included in the safety summary.

The expected attrition rate through Month 7 of this study was ~15%. Missing data (due to attrition or other causes) were not included in any analyses of immunogenicity, as reflected in the various study population definitions given above.

No interim analysis was performed for the Consistency Lot substudy of Protocol 015.

All immunogenicity hypothesis testing was to be stratified by study center, after an assessment of treatment by study center interaction was performed. All interaction tests were conducted at the $\alpha = 0.10$ level.

There was only one primary immunogenicity hypothesis for the Consistency Lot substudy. However, the success of the substudy required that consistency be established for all 4 vaccine HPV types with respect to GMTs, so no multiplicity adjustment was necessary for the substudy.

SAMPLE SIZE AND POWER ANALYSIS

The primary time point for the immunogenicity analysis was Month 7. It was expected that the attrition rate through Month 7 of the study would be no more than 15%. In addition, it was assumed that 15%, 18%, and 18% of the subjects enrolled in the Consistency Lot substudy would be seropositive at Day 1 or PCR positive Day 1 through Month 7 for HPV Types 6/11, 16, and 18, respectively. Therefore, it was expected that 361 (500 x 0.85 x 0.85) of the 500 subjects randomized to receive each of the consistency lots would be evaluable for the HPV 6 and 11 endpoints and 348 (500 x 0.82 x 0.85) of the 500 subjects would be evaluable for the HPV 16 and 18 endpoints.

For the primary immunogenicity hypothesis involving the consistency of the 3 lots of quadrivalent HPV vaccine with respect to anti-HPV 6/11/16/18 GMTs, the standard deviations (in natural logarithm) of the Month 7 titers were assumed to be no more than 1.2 for each HPV type. The assumed standard deviation was based on competitive radioimmunoassay (cRIA) data from previous Protocols 001, 002, and 004. With 361 evaluable subjects for the HPV 6 and 11 endpoints and 348 evaluable subjects for the HPV 16 and 18 endpoints, this study had 99.9% power to rule out a ≥2-fold difference in the ratio of GMTs among the 3 lots ($\alpha = 0.05$) for each HPV type. Assuming

independence of the 4 HPV types, the overall power for the primary immunogenicity hypothesis was 99.6%.

For the secondary immunogenicity hypothesis involving the consistency of the 3 lots with respect to the percentage of subjects who seroconverted by Week 4 Postdose 3, the expected response rate for each HPV type was 99% (based on competitive Luminex immunoassay (cLIA) data from Protocol 007). With 361 and 348 evaluable subjects for HPV 6 and 11 and HPV 16 and 18, respectively, this study had >99% power to rule out a ≥5-percentage point difference in rates among the 3 lots ($\alpha = 0.05$) for each HPV type. Assuming independence of the 4 HPV types, the overall power for the seroconversion hypothesis was >99%.

ANALYSIS POPULATIONS

Two populations were considered for the immunogenicity summaries: the "per-protocol" population and the "all type-specific HPV-naïve subjects with serology data" population. The primary approach to the analysis of immunogenicity was per-protocol.

The per-protocol population for immunogenicity analysis included all subjects without protocol violations who received all 3 vaccinations within acceptable day ranges, who were seronegative at Day 12 and PCR negative from Day 1 through Month 7 to the relevant vaccine HPV type(s), and who had a valid serology result within an acceptable day range following the third injection. Baseline seropositivity was determined based on the cLIA serostatus cutoff for each HPV type: 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, for HPV Types 6, 11, 16, and 18, respectively.

The all type-specific HPV-naïve subjects with serology data population included all subjects who were seronegative by cLIA to the appropriate vaccine component(s) at Day 1, who were PCR-negative to the appropriate vaccine component(s) Day 1 through Month 7 (on swabs and biopsies), and who had a valid serology result after the third injection. This population included general protocol violators and considered incorrectly randomized subjects in the analysis according to the vaccination group to which they were randomized.

CHANGES IN STATISTICAL ANALYSIS

The statistical analyses performed for this study differed from those stated in the study protocol as follows:

1. The secondary immunogenicity objective regarding persistence of responses will be addressed in the final efficacy Clinical Study Report (CSR) because the complete post-Month 7 immunogenicity data were not available at the time data for the consistency lot substudy was unblinded.
2. Because the numbers of subjects enrolled in some of the study sites were very small, the study sites were pooled into four regions (North America, Latin America, Asia-Pacific, and Europe) in lieu of "study center" to compute the

overall GMT ratio and the difference of proportions of subjects seroconverted by Month 7.

3. The GMT ratio in the primary analysis was calculated using the average of those across geographic regions instead of the average weighted by sample size of the study center. The GMT ratios were fairly comparable across geographic regions and no interaction between consistency lot and geographic region was found to be significant (p>0.1) in modeling the natural log of anti-HPV cLIA responses.

RESULTS

Immunogenicity

The primary immunogenicity hypothesis for the Consistency Lot substudy stated that 3 separate lots of quadrivalent HPV vaccine would induce similar immune responses, as measured by the serum GMTs to HPV 6/11/16/18 at Week 4 Postdose 3.

Table 20 on page 44 lists the results of type-specific GMT comparisons among subjects randomized to the three quadrivalent HPV vaccine consistency lots in the PPI population. For each comparison, the lower bound of the 90% confidence interval of GMT ratio between the comparison lots was greater than 0.5 and the corresponding upper bound was less than 2.0. Therefore, equivalence can be established in all three pairwise comparisons for each vaccine HPV type.

A corresponding summary table for comparisons of type-specific 7 GMTs in the ANSS population is provided in Table 21 on page 45. The results were consistent with the findings in PPI population and support the consistency of the vaccine from three FMP lots.

Note that when the two-sided 95% CIs for the ratio of GMTs are used to evaluate the lot consistency, the results will reach the same conclusion, except that, in Anti-HPV 16 type, the upper confidence bound of the ratio of the lot 2 GMT over the lot 3 GMT in the PPI population is just over the pre-specified 2.0.

The analysis of lot consistency with respect to GMTs included an adjustment for region. For all HPV types and pairs of lots, the treatment-by-region interaction was not significant (p>0.1).

The secondary immunogenicity hypothesis for the Consistency Lot substudy stated that three separate lots of quadrivalent HPV vaccine would induce similar immune responses, as measured by the percentage of subjects who achieved seroconversion for HPV Types 6/11/16/18, by Week 4 Postdose 3.

Table 22 on page 46 displays the comparison results of type-specific seroconversion rates from the three quadrivalent HPV vaccine consistency lots in the PPI population. Corresponding comparison results for the ANSS population are provided in Table 23 on page 47. In both study populations, the lower bound of the 90% confidence interval for

the difference in seroconversion rate between the comparison lots was greater than -0.05 and the corresponding upper bound was less than 0.05. Therefore, these results demonstrate that for all vaccine components, the HPV type-specific seroconversion rates from the three quadrivalent HPV vaccine lots were consistent.

Note that when the two-sided 95% CIs for the difference in seroconversion rate are used to evaluate the lot consistency, the results lead to the same conclusion.

Figures of the reverse cumulative distribution function (RCDF) plots of anti-HPV 6, 11, 16, and 18 responses at Month 7 in the PPI population (not presented in this report) show that the distributions of Month 7 anti-HPV serum cLIA type-specific responses for 3 consistency lots were very comparable.

Safety

Table 24 on page 48 lists a summary of clinical adverse experiences reported from Day 1 through Day 15 following any vaccination visit among the subjects enrolled in the consistency lot substudy in the United States, including Puerto Rico. A very small sample size, between 67 and 71 subjects per consistency lot, is included in these summaries. The occurrences of clinical adverse experiences, though very high around 90%, were generally comparable among the three consistency lot groups. Only one subject discontinued the study due to vaccine-related adverse experiences, in consistency lot group 3. No serious clinical adverse experience was reported from Day 1 to Day 15 following any vaccination visit in these 3 study groups.

CONCLUSION

Overall, for all HPV vaccine types, the Month 7 anti-HPV GMT responses from the three quadrivalent HPV vaccine manufacturing lots were consistent. In addition, these results suggest that the quadrivalent HPV vaccine was highly immunogenic and the seroconversion rates at Month 7 generated from quadrivalent HPV vaccine from 3 FMP consistency lots were comparable in each HPV type. Similar clinical adverse experiences were also reported from Day 1 through Day 15 following any vaccination visit among a small sample of the subjects enrolled in the consistency lot substudy in the United States, including Puerto Rico.

Table 20: Summary of Statistical Analysis of Equivalence of Geometric Mean Titers (GMT) at Month 7
Comparing Quadrivalent HPV Vaccine Consistency Lots 1, 2, and 3
(Per-Protocol Immunogenicity [PPI] Population†)

Assay cLIA	Comparison Group A vs. Group B	Group A			Group B			Fold ratio A/B (90% CI)
		N	n	GMT	N	n	GMT	
Anti-HPV 6	Lot 1 vs. Lot 2	499	349	554.8	509	364	602.3	0.92 (0.79, 1.07)
	Lot 1 vs. Lot 3	499	349	554.8	504	343	496.3	1.12 (0.96, 1.31)
	Lot 2 vs. Lot 3	509	364	602.3	504	343	496.3	1.21 (1.04, 1.42)
Anti-HPV 11	Lot 1 vs. Lot 2	499	349	737.7	509	364	807.3	0.91 (0.77, 1.08)
	Lot 1 vs. Lot 3	499	349	737.7	504	343	744.1	0.99 (0.83, 1.18)
	Lot 2 vs. Lot 3	509	364	807.3	504	343	744.1	1.08 (0.91, 1.29)
Anti-HPV 16	Lot 1 vs. Lot 2	499	326	2,414.7	509	356	2,932.4	0.82 (0.64, 1.06)
	Lot 1 vs. Lot 3	499	326	2,414.7	504	333	1,932.2	1.25 (0.96, 1.62)
	Lot 2 vs. Lot 3	509	356	2,932.4	504	333	1,932.2	1.52 (1.18, 1.95)
Anti-HPV 18	Lot 1 vs. Lot 2	499	367	480.9	509	392	519.3	0.93 (0.76, 1.13)
	Lot 1 vs. Lot 3	499	367	480.9	504	380	452.4	1.06 (0.87, 1.30)
	Lot 2 vs. Lot 3	509	392	519.3	504	380	452.4	1.15 (0.94, 1.40)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay

Table 21: Summary of Statistical Analysis of Equivalence of Geometric Mean Titers at Month 7
Comparing Quadrivalent HPV Vaccine Consistency Lots 1, 2, and 3
(All Type-Specific HPV-Naive Subjects with Serology Data [ANSS] Population)

Assay cLIA	Comparison Group A vs. Group B	Group A			Group B			Fold ratio A/B (90% CI)
		N	n	GMT	N	n	GMT	
Anti-HPV 6	Lot 1 vs. Lot 2	499	385	566.9	509	413	585.6	0.97 (0.83, 1.12)
	Lot 1 vs. Lot 3	499	385	566.9	504	388	496.3	1.14 (0.98, 1.33)
	Lot 2 vs. Lot 3	509	413	585.6	504	388	496.3	1.18 (1.02, 1.37)
Anti-HPV 11	Lot 1 vs. Lot 2	499	385	762.6	509	413	778.2	0.98 (0.83, 1.16)
	Lot 1 vs. Lot 3	499	385	762.6	504	388	741.5	1.03 (0.87, 1.22)
	Lot 2 vs. Lot 3	509	413	778.2	504	388	741.5	1.05 (0.88, 1.25)
Anti-HPV 16	Lot 1 vs. Lot 2	499	370	2,559.4	509	402	2,853.8	0.90 (0.70, 1.15)
	Lot 1 vs. Lot 3	499	370	2,559.4	504	377	1,987.4	1.29 (1.00, 1.66)
	Lot 2 vs. Lot 3	509	402	2,853.8	504	377	1,987.4	1.44 (1.13, 1.83)
Anti-HPV 18	Lot 1 vs. Lot 2	499	413	474.3	509	447	507.5	0.93 (0.77, 1.13)
	Lot 1 vs. Lot 3	499	413	474.3	504	427	455.2	1.04 (0.86, 1.27)
	Lot 2 vs. Lot 3	509	447	507.5	504	427	455.2	1.11 (0.92, 1.35)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay

Table 22: Summary of Statistical Analysis of Equivalence of Seroconversion at Month 7
Comparing Quadrivalent HPV Vaccine Consistency Lots 1, 2, and 3
(Per-Protocol Immunogenicity [PPI] Population)

Assay cLIA	Comparison Group A vs. Group B	Group A			Group B			Difference Groups A - B (90% CI)
		N	n	Rate %	N	n	Rate %	
HPV 6 cLIA ≥20 mMU/mL	Lot 1 vs. Lot 2	499	349	99.7	509	364	100	-0.3 (-1.3, 0.5)
	Lot 1 vs. Lot 3	499	349	99.7	504	343	99.7	0.0 (-1.0, 1.1)
	Lot 2 vs. Lot 3	509	364	100	504	343	99.7	0.3 (-0.4, 1.3)
HPV 11 cLIA ≥16 mMU/mL	Lot 1 vs. Lot 2	499	349	99.7	509	364	100	-0.3 (-1.3, 0.5)
	Lot 1 vs. Lot 3	499	349	99.7	504	343	99.4	0.3 (-0.8, 1.5)
	Lot 2 vs. Lot 3	509	364	100	504	343	99.4	0.6 (-0.2, 1.8)
HPV 16 cLIA ≥20 mMU/mL	Lot 1 vs. Lot 2	499	326	99.7	509	356	100	-0.3 (-1.4, 0.4)
	Lot 1 vs. Lot 3	499	326	99.7	504	333	99.4	0.3 (-0.8, 1.5)
	Lot 2 vs. Lot 3	509	356	100	504	333	99.4	0.6 (-0.2, 1.8)
HPV 18 cLIA ≥24 mMU/mL	Lot 1 vs. Lot 2	499	367	99.2	509	392	99.7	-0.6 (-1.9, 0.4)
	Lot 1 vs. Lot 3	499	367	99.2	504	380	99.2	0.0 (-1.3, 1.3)
	Lot 2 vs. Lot 3	509	392	99.8	504	380	99.2	0.6 (-0.4, 1.8)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay

Table 23: Summary of Statistical Analysis of Equivalence of Seroconversion at Month 7
Comparing Quadrivalent HPV Vaccine Consistency Lots 1, 2, and 3
(All Type-Specific HPV-Naive Subjects with Serology Data [ANSS] Population)

Assay cLIA	Comparison Group A vs. Group B	Group A			Group B			Difference Groups A - B (90% CI)
		N	n	Rate %	N	n	Rate %	
HPV 6 cLIA ≥20 mMU/mL	Lot 1 vs. Lot 2	499	385	99.7	509	413	100.0	-0.3 (-1.2, 0.4)
	Lot 1 vs. Lot 3	499	385	99.7	504	388	99.7	-0.0 (-0.9, 0.9)
	Lot 2 vs. Lot 3	509	413	100.0	504	388	99.7	0.3 (-0.4, 1.2)
HPV 11 cLIA ≥16 mMU/mL	Lot 1 vs. Lot 2	499	385	99.7	509	413	100	-0.3 (-1.2, 0.4)
	Lot 1 vs. Lot 3	499	385	99.7	504	388	99.5	0.3 (-0.7, 1.3)
	Lot 2 vs. Lot 3	509	413	100.0	504	388	99.5	0.5 (-0.1, 1.6)
HPV 16 cLIA ≥20 mMU/mL	Lot 1 vs. Lot 2	499	370	99.7	509	402	100.0	-0.3 (-1.2, 0.4)
	Lot 1 vs. Lot 3	499	370	99.7	504	377	99.5	0.3 (-0.7, 1.4)
	Lot 2 vs. Lot 3	509	402	100.0	504	377	99.5	0.5 (-0.1, 1.6)
HPV 18 cLIA ≥24 mMU/mL	Lot 1 vs. Lot 2	499	413	99.3	509	447	99.8	-0.5 (-1.6, 0.4)
	Lot 1 vs. Lot 3	499	413	99.3	504	427	99.3	-0.0 (-1.2, 1.2)
	Lot 2 vs. Lot 3	509	447	99.8	504	427	99.3	0.5 (-0.4, 1.6)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay

Table 24: Clinical Adverse Experience Summary
Consistency Lot Substudy Population, United States, Including Puerto Rico

	Lot 1		Lot 2		Lot 3	
	n	%	n	%	n	%
Subjects in analysis population	67		69		71	
Subjects without follow-up	1		1		2	
Subjects with follow-up	66		68		69	
Number (%) of subjects:						
with no adverse experience	4	(6.1)	8	(11.8)	6	(8.7)
with one or more adverse experiences	62	(93.9)	60	(88.2)	63	(91.3)
injection-site adverse experiences	61	(92.4)	55	(80.9)	61	(88.4)
systemic adverse experiences	41	(62.1)	38	(55.9)	41	(59.4)
with vaccine-related adverse experiences	61	(92.4)	57	(83.8)	63	(91.3)
injection-site adverse experiences	61	(92.4)	55	(80.9)	61	(88.4)
systemic adverse experiences	18	(27.3)	22	(32.4)	21	(30.4)
with serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	1	(1.4)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)	1	(1.4)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related	0	(0.0)	0	(0.0)	0	(0.0)