For the use only of registered medical practitioners or a hospital or a laboratory

HUMAN PAPILLOMAVIRUS 9-VALENT VACCINE, RECOMBINANT [Serotypes: Type 6 L1, 11 L1, 16 L1, 18 L1, 31 L1, 33 L1, 45 L1, 52 L1 & 58 L1]

GARDASIL®9
(Suspension for intramuscular injection)

GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on pre-formed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant formulation and the final purification buffer.

COMPOSITION

Active Ingredients
GARDASIL®9 is a sterile preparation for intramuscular administration.

Each 0.5-mL single dose contains:

HPV Type 6 L1 Protein*:	30 mcg
HPV Type 11 L1 Protein*:	40 mcg
HPV Type 16 L1 Protein*:	60 mcg
HPV Type 18 L1 Protein*:	40 mcg
HPV Type 31 L1 Protein*:	20 mcg
HPV Type 33 L1 Protein*:	20 mcg
HPV Type 45 L1 Protein*:	20 mcg
HPV Type 52 L1 Protein*:	20 mcg
HPV Type 58 L1 Protein*:	20 mcg

*L1 protein in the form of virus like particles produced in Yeast cell *Saccharomyces cerevisiae* CANADAE 3C-5 (Strain 1895) by recombinant DNA technology.

Inactive Ingredients (List of excipients)

Amorphous Aluminum Hydroxyphosphate Sulfate (as adjuvant):	500 mcg
Sodium chloride:	9.56 mg
L-histidine:	0.78 mg
Polysorbate 80:	50 mcg
Sodium borate:	35 mcg
Water for injection:	q.s.

The product does not contain a preservative or antibiotics.

Prior to agitation, GARDASIL®9 may appear as a clear liquid with a white precipitate. After thorough agitation, GARDASIL®9 a white, cloudy liquid.

DOSAGE FORM/S

GARDASIL®9 is a suspension for intramuscular administration available in 0.5-mL single-dose glass vial and prefilled syringe.

INDICATIONS

Girls and Women (9-26 years):
GARDASIL®9 is a vaccine indicated in girls and women from 9 - 26 years of age at 3 dose regimen (schedule: 0. 2 & 6 months) for the prevention of cervical, vulvar, vaginal, and anal cancer; precancerous or dysplastic lesions; genital warts; and persistent infections caused by Human Papillomavirus (HPV).

Boys (9-15 years):
GARDASIL®9 is indicated in boys from 9 – 15 years of age at 3 dose regimen (schedule: 0. 2 & 6 months) for the prevention of external genital lesions and persistent infections and the following diseases caused by HPV types included in the vaccine:

- Anal Cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

DOSE, METHOD OF ADMINISTRATION AND USAGE

Dosage
GARDASIL®9 should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. The second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Alternatively, in individuals 9 through 15 years of age, GARDASIL®9 can be administered according to a 2-dose schedule; the second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

The use of GARDASIL®9 should be in accordance with official recommendations.

Method of Administration

GARDASIL®9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL®9 must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

Administration of GARDASIL®9 In Individuals Who Have Been Previously Vaccinated with GARDASIL®.

It is recommended that individuals who receive a first dose of GARDASIL®9 complete the vaccination course with GARDASIL®9.

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for GARDASIL®9.

If the decision is made to administer GARDASIL®9 after receiving 3 doses of GARDASIL®, there should be an interval of at least 12 months between completion of vaccination with GARDASIL® and the start of vaccination with GARDASIL®9.

Instructions for Use:

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL®9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discolored.

Single-dose Vial Use
For single-use vials a separate sterile syringe and needle must be used for each individual. Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use
The prefilled syringe is for single use only and should not be used for more than one individual. Inject the entire contents of the syringe.

USE IN SPECIAL POPULATIONS

Pregnancy
Studies in Female Rats
Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL®9.

An evaluation of the effect of GARDASIL®9 on embryo-fetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental

signs, behavior, reproductive performance, or fertility of the offspring. GARDASIL®9 induced a specific antibody response against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 9 HPV types were transferred to the offspring during the period of gestation and lactation.

Clinical Studies in Humans
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pregnancy should be avoided during the vaccination regimen for GARDASIL®9.

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of GARDASIL®9. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL®9 were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

The overall proportion of pregnancies occurring at any time during the studies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 14.1% (145/1,028) in women who received GARDASIL®9 and 17.0% (168/991) in women who received GARDASIL®. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL®9 or GARDASIL®. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL®9 or GARDASIL®. In pregnancies with onset more than 30 days following vaccination, 20 and 21 cases of congenital anomaly were observed in women who have received GARDASIL®9 and GARDASIL®, respectively. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in the general population.

Thus, there is no evidence to suggest that administration of GARDASIL®9 adversely affects fertility, pregnancy, or infant outcomes.

Nursing Mothers
GARDASIL®9 may be administered to lactating women.

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

A total of 86 women were breast feeding during the vaccination period of the clinical studies for GARDASIL®9. In these studies, vaccine immunogenicity was comparable between nursing women and women who did not nurse. In addition, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period.

Pediatric Use
The safety and efficacy of GARDASIL®9 have not been evaluated in children younger than 9 years.

Immunocompromised Individuals

The immunologic response to GARDASIL®9 may be diminished in immunocompromised individuals *[see DRUG INTERACTIONS, Use with Steroids]*.

CONTRA-INDICATIONS

GARDASIL®9 is contraindicated in patients with hypersensitivity to either GARDASIL®9 or GARDASIL® or any of the inactive ingredients in either vaccine.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL®9 or GARDASIL® should not receive further doses of GARDASIL®9.

WARNINGS AND PRECAUTIONS

As for any vaccine, vaccination with GARDASIL®9 may not result in protection in all vaccine recipients.

This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, or anal cancers; CIN, VIN, VaIN, or AIN.

This vaccine will not protect against diseases that are not caused by HPV.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL®9.

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization. *[See DRUG INTERACTIONS, Use with Steroids and USE IN SPECIAL POPULATIONS, Immunocompromised Individuals.]*

This vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

DRUG INTERACTIONS

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL®9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (dTap-IPV).

Use with Hormonal Contraceptives
In 7,269 women (16 through 26 years of age, from Protocols 001 and 002), 60.2% used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL®9.

Use with Steroids
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines. *[See USE IN SPECIAL POPULATIONS, Immunocompromised Individuals.]*

UNDESIRABLE EFFECTS

Clinical Trials Experience
Clinical Trials Experience with GARDASIL®9 and GARDASIL®
The safety of GARDASIL®9 was evaluated in 6 clinical studies (Protocols 001, 002, 005, 006, 007, 009) that included 13,307 individuals who received at least one dose of GARDASIL®9 and had safety follow-up. Protocol 001 and Protocol 009 included 7,378 individuals who received at least one dose of GARDASIL® and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL®9 or GARDASIL®.

The individuals who were monitored using VRC-aided surveillance included 8,027 women 16 through 26 years of age and 5,280 girls and boys 9 through 15 years of age (3,481 girls and 1,799 boys) at enrollment who received GARDASIL®9 and 7,078 women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL®.

Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL®9
The vaccine-related adverse experiences that were observed among recipients of either GARDASIL®9 or GARDASIL® at a frequency of at least 1% are shown in Tables 1 and 2. Few individuals (GARDASIL®9 = 0.1% vs. GARDASIL® <0.1%) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL®9 and GARDASIL® in women, girls and boys.

Table 1: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% in Individuals Who Received GARDASIL®9 from All Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age	Girls and Boys 9 Through 15 Years of Age
	GARDASIL®9 (N=8027) %	GARDASIL®9 (N=5280) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain†	89.6	78.8
Swelling†	40.2	33.8
Erythema†	34.3	28.0
Pruritus	5.6	2.6
Bruising	1.7	0.0
Hematoma	1.3	2.0
Mass	1.2	0.2

Hemorrhage	0.9	1.0
Induration	0.7	1.1
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	14.7	12.7
Pyrexia	5.1	8.9
Nausea	4.2	2.2
Dizziness	2.9	1.6
Fatigue	2.3	1.3
Diarrhea	1.2	0.5
Oropharyngeal pain	1.0	0.8
Abdominal pain upper	0.7	1.3

*Data from Protocols 001,002, 005, 006, 007, 009
†Designates a solicited adverse reaction
N=number of subjects vaccinated

Table 2: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL®9 Compared with GARDASIL® from Two Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL®9 (N=7071) %	GARDASIL® (N=7078) %	GARDASIL®9 (N=299) %	GARDASIL® (N=300) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)				
Pain†	89.9	83.5	89.3	88.3
Swelling†	40.0	28.8	47.8	36.0
Erythema†	34.0	25.6	34.1	29.3
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	‡	‡
Mass	1.3	0.6	‡	‡
Hemorrhage	1.0	0.7	1.0	2.0
Hematoma	0.9	0.6	3.7	4.7
Warmth	0.8	0.5	0.7	1.7
Induration	0.8	0.2	2.0	1.0
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Postvaccination)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0.0	2.7
Diarrhea	1.2	1.0	0.3	0.0
Myalgia	1.0	0.7	0.7	0.7
Oropharyngeal pain	1.0	0.6	2.7	0.7
Abdominal pain upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

*The data for women are from Protocol 001 and data for girls are from Protocol 009.
†Designates a solicited adverse reaction
‡There are no reports of injection-site bruising or mass for girls.

N=number of subjects vaccinated

Solicited Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL®9

Temperature and injection-site pain, swelling, and erythema were solicited using VRC-aided surveillance for 5 days after each injection of GARDASIL®9 during the clinical studies. The incidence and severity of solicited adverse reactions that occurred within 5 days following each dose of GARDASIL®9 are shown in Table 3.

Table 3: Postdose Evaluation of Solicited Systemic and Injection-Site Adverse Reactions by Incidence and Severity from All Clinical Studies* (1 to 5 Days Postvaccination)

Solicited Systemic Adverse Reaction	Severity	Dose 1 N=13,174 %	Dose 2 N=12,913 %	Dose 3 N=12,741 %	Any Dose N=13,224 %
Temperature	< 37.8 °C (100.0 °F)	96.9	97.3	96.7	92.0
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.7	2.3	2.7	6.6
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.4	0.3	0.5	1.2
	≥ 39.9 °C (103.8 °F) < 40.9 °C (105.6 °F)	0.1	0.1	0.1	0.2
	≥ 40.9 °C (105.6 °F)	0.0	0.0	0.0	0.0
Solicited Injection-site Adverse Reaction	**Severity**	**Dose 1 N=13,304**	**Dose 2 N=13,142**	**Dose 3 N=13,005**	**Any Dose N=13,307**
Pain	Mild	53.5	47.6	45.3	51.1
	Moderate	11.5	16.3	17.8	30.3
	Severe	0.7	1.6	2.3	3.9
Swelling†	Mild	9.6	15.3	18.5	25.4
	Moderate	1.8	3.9	4.9	7.8
	Severe	0.8	1.7	2.7	4.3
Erythema†	Mild	8.6	14.0	16.6	25.3
	Moderate	0.9	2.0	2.7	4.6
	Severe	0.2	0.5	1.2	1.7

*Data from Protocols 001, 002, 005, 006, 007, 009

†Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

N=Number of individuals with follow-up

Clinical Trials Experience for GARDASIL®9 in Individuals Who Have Been Previously Vaccinated with GARDASIL®

A clinical study (Protocol 006) evaluated the safety of GARDASIL®9 in 12- through 26-year-old girls and women who had previously been vaccinated with 3 doses of GARDASIL®. The time interval between the last injection of GARDASIL® and the first injection of GARDASIL®9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL®9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL®9 or saline placebo in these individuals. The individuals who

were monitored included 608 individuals who received GARDASIL®9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL®9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL®9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall, the safety profile was similar between individuals vaccinated with GARDASIL®9 who were previously vaccinated with GARDASIL® and those who were naïve to HPV vaccination.

Table 4: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥ 1% and Greater Than Saline Placebo for GARDASIL®9 in 12- through 26-year-old Girls and Women Who Have Been Previously Vaccinated with GARDASIL®*

Adverse Reaction	GARDASIL®9 (N=608) %	SALINE PLACEBO (N=305) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain†	90.3	38.0
Swelling†	49.0	5.9
Erythema†	42.3	8.5
Pruritus	7.7	1.3
Hematoma	4.8	2.3
Reaction	1.3	0.3
Mass	1.2	0.7
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain upper	1.5	0.7
Influenza	1.2	1.0

*The data for GARDASIL®9 and Placebo are from Protocol 006.
†Designates a solicited adverse reaction
N=number of subjects vaccinated

Clinical Trials Experience for Concomitant Administration of GARDASIL®9 with Other Vaccines

The safety of GARDASIL®9 when administered concomitantly with other vaccines was evaluated in clinical studies.

There was an increase in injection-site swelling reported at the injection site for GARDASIL®9 when GARDASIL®9 was administered concomitantly with Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV) or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) and Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine as compared to non-concomitant vaccination. The majority of injection-site swelling seen with concomitant administration with other vaccines was reported as being mild to moderate in intensity.

Post-marketing Experience

The post-marketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

The safety profile of GARDASIL®9 and GARDASIL® are similar. The post-marketing adverse experience with GARDASIL® is relevant to GARDASIL®9 since the vaccines are similar in composition and contain L1 HPV proteins of 4 of the same HPV types.

GARDASIL®9

In addition to the adverse reactions reported in the clinical studies, the following adverse experiences have been spontaneously reported during post-approval use of GARDASIL®9:

Nervous system disorders: syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: vomiting.

GARDASIL®

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL®:

Infections and infestations: cellulitis.

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy.

Immune system disorders: hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Nervous system disorders: acute disseminated encephalomyelitis, Guillain-Barré syndrome.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

General disorders and administration site conditions: asthenia, chills, malaise.

OVERDOSE

There have been no reports of administration of higher than recommended doses of GARDASIL®9.

CLINICAL PHARMACOLOGY

Therapeutic Class
GARDASIL®9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV).

Mechanism of Action
HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

DISEASE BURDEN
HPV infection is very common; in the absence of vaccination, the majority of sexually active individuals will become infected with HPV during their lifetime.

Most HPV infections clear without sequelae but some progress to HPV-related diseases including cervical cancers and their precursors (Cervical Intraepithelial Neoplasia or CIN

grades 1, 2, and 3), anal, vulvar, vaginal, and penile cancers and their precursors (Anal Intraepithelial Neoplasia or AIN, Vulvar Intraepithelial Neoplasia or VIN, Vaginal Intraepithelial Neoplasia or VaIN and Penile Intraepithelial Neoplasia or PIN), genital warts, and lesions in the aerodigestive tract including oropharyngeal cancers and recurrent respiratory papillomatosis.

Worldwide, over 530,000 cases of cervical cancer are diagnosed annually. Cervical cancer prevention focuses on repeat screening (e.g., Papanicolaou's [Pap] testing and/or Human Papillomavirus [HPV] testing) and early intervention. This strategy has reduced cancer rates by approximately 75% in the developed world but has shifted the burden from managing cervical cancer to monitoring and treating a large number of premalignant lesions.

GARDASIL®9 is a recombinant vaccine with L1 proteins resembling 9 HPV types. Because the L1 proteins contain no viral DNA, they cannot infect cells or reproduce. GARDASIL®9 contains the 4 HPV types (6, 11, 16, and 18) that are in GARDASIL® plus an additional 5 HPV types (31, 33, 45, 52, and 58) adsorbed on amorphous aluminum hydroxyphosphate adjuvant (AAHS). The attribution of the 9 HPV types in GARDASIL®9 to HPV-related disease worldwide is presented in Table 5.

Table 5: Attribution of GARDASIL®9 HPV Types to HPV-related Disease Worldwide

Lesion Type	HPV Type Attribution		
	GARDASIL® (6/11/16/18)	**31/33/45/52/58**	**GARDASIL®9 (6/11/16/18/31/33/45/52/58)**
Cervical Cancer	70%	20%	90%
AIS	95%	<5%	>95%
CIN 2/3*	50%	30%	75 – 85%
CIN 1†	30 – 35%	25%	50 – 60%
Vulvar Cancer‡	70 – 75%	10 – 15%	85 – 90%
VIN 2/3‡	80 – 85%	15%	90 – 95%
VIN 1‡	45 – 65%	5%	50 – 70%
Vaginal Cancer‡	65%	20%	80 – 85%
VaIN 2/3‡	60 – 65%	15 – 20%	75 – 85%
VaIN 1‡	20 – 35%	20 – 35%	40 – 70%
Anal Cancer‡	85 – 90%	5 – 10%	90 – 95%
AIN 2/3‡	80 – 85%	5%	85 – 90%
Penile Cancer‡	75 – 80%	5 – 10%	85%
PIN 2/3‡	80%	10%	90%
Oropharyngeal Cancer‡§	85%	7%	>90%
Genital Warts¶	90%	¶	90%
Recurrent Respiratory Papillomatosis (RRP)¶	90%	¶	90%

*CIN 2/3 and AIS have been accepted as precursors of invasive cervical cancer. VIN 2/3, VaIN 2/3, AIN 2/3 and PIN 2/3 have been accepted as precursors of vulvar, vaginal, anal and penile cancer, respectively.
†HPV 6/11 are attributed to approximately 5% of CIN 1 lesions.
‡Type attribution among HPV positive cancers and lesions only
§HPV type 16 causes the majority of oropharyngeal cancer.
¶Genital Warts and RRP are primarily caused by HPV Types 6 and 11.

CLINICAL STUDIES

GARDASIL®9 includes the same four HPV types contained in GARDASIL® (HPV 6, 11, 16, 18) and five additional HPV types (31, 33, 45, 52, and 58).

Efficacy Data for GARDASIL®

GARDASIL® was first licensed in 2006. Efficacy was assessed in 6 AAHS-controlled, double-blind, randomized Phase II and III clinical studies evaluating 28,413 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age,3,817 women 24 through 45 years of age). The efficacy and long-term effectiveness of GARDASIL® against HPV 6-, 11-, 16-, and 18-related disease endpoints have been demonstrated in clinical studies in the PPE (Per Protocol Efficacy) population. The PPE population consisted of individuals who received all 3 vaccinations with GARDASIL® in the base study within 1 year of enrollment without major deviations from the study protocol, were seronegative to the relevant HPV type(s) (types 6, 11, 16 and 18) prior to dose 1, and among subjects 16 years and older at enrollment in the base study, PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

GARDASIL® was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18 in girls and women in the PPE population (Table 6). In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types. Individuals who had prior infection that had been resolved before vaccination (PCR negative and seropositive at baseline) were protected from reinfection or recurrence of infection leading to clinical disease with the same HPV type. GARDASIL® was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men in the PPE population. Efficacy against penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance (Table 6). GARDASIL® was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men in the PPE population (Table 6).

Table 6: Analysis of Efficacy of GARDASIL® in the Per Protocol Efficacy (PPE)* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL®		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- Through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- Through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).
†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N=Number of individuals with at least 1 follow-up visit after Month 7
CI=Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 6 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals compared to younger individuals. Therefore, to confirm the utility of GARDASIL® to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study was conducted.

GARDASIL® was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL® was also highly efficacious in reducing the incidence of a HPV 16/18-related

Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit.

On the basis of these efficacy findings, the efficacy of GARDASIL® with respect to prevention of cervical, vulvar, and vaginal cancers and related diseases in individuals up to and including age 45 years can be inferred.

Table 7: Analysis of Efficacy of GARDASIL® in the PPE Population of 24- through 45-Year-Old Women

Endpoint	GARDASIL®		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 6-, 11-, 16-, or 18-related CIN (any grade), Persistent Infection, or EGL	1,601	10*	1,599	86	88.7 (78.1, 94.8)
HPV 16- or 18-related CIN (any grade), Persistent Infection, or EGL	1,587	8	1,571	51	84.7 (67.5, 93.7)
HPV 6- or 11-related CIN (any grade), Persistent Infection, or EGL	1,316	2	1,316	38	94.8 (79.9, 99.4)
HPV 16/18-related Pap Diagnosis of ASC-US Positive for High-risk HPV	1,565	1	1,557	27	96.3 (77.7, 99.9)

*There was 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy. The remaining 9 cases in the PPE group were persistent infection endpoints.
CI = Confidence Interval
ASC-US = Atypical Squamous Cells of Undetermined Significance

Long-term follow-up studies

A subset of subjects who received 3 doses were followed up for 10 to 14 years after GARDASIL® vaccination for safety, immunogenicity and protection against clinical diseases related to HPV types 6/11/16/18.

Persistence of antibody response was observed for 10 years in adolescents who were 9 through 15 years of age at time of vaccination; 14 years in girls and women, 16 through 23 years of age at time of vaccination; and 9.5 years in women, 24 through 45 years of age at time of vaccination.

Clinical protection was observed in all subjects in the PPE population: no cases of HPV diseases were observed after a follow-up of approximately 10.7 years (median duration of follow-up of 10.0 years) in girls who were 9 through 15 years of age at time of vaccination; 10.6 years (median duration of follow-up of 9.9 years) in boys, 9 through 15 years of age at time of vaccination; 14 years (median duration of follow-up of 11.9 years) in girls and women, 16 through 23 years of age at time of vaccination; 11.5 years (median duration of follow-up of 9.5 years) in boys and men, 16 through 26 years of age at time of vaccination, and 10.1 years (median duration of follow-up of 8.7 years) in women, 24 through 45 years of age at time of vaccination.

Persistence of antibody response to GARDASIL® was also assessed in a clinical trial using a 2-dose regimen. One month after the last dose, antibody responses to the 4 HPV types

were non-inferior among girls 9 through 13 years of age who received 2 doses of GARDASIL® 6 months apart compared with girls and women 16 through 26 years of age who received 3 doses of the vaccine within 6 months. In post hoc analyses at 3 and 10 years of follow-up, non-inferiority criteria were also met for all 4 HPV types.

Clinical Trials for GARDASIL®9

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL®9 were assessed in six clinical studies. Clinical studies evaluating the efficacy of GARDASIL®9 against placebo were not acceptable because HPV vaccination represents the standard of care for protection against HPV infection and disease in many countries. Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of GARDASIL®9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL® as a comparator.

Efficacy against HPV Types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrates comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of GARDASIL®9 compared with GARDASIL® (Protocols 001, 002, and 009).

The analysis of efficacy for GARDASIL®9 was evaluated in the PPE population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma *in situ* (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar, and vaginal disease of any grade; persistent infection; cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types in GARDASIL®9 (31, 33, 45, 52, and 58) was evaluated compared to GARDASIL®.

The efficacy is further extended to 9- through 15-year-old adolescents, for all endpoints studied, using immunological bridging. The immunogenicity bridging analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocols 001 and 002) and seronegative (Protocols 001, 002, 005, 007 and 009)] to the relevant HPV type(s) prior to dose 1 and through Month 7.

Protocol 001 evaluated efficacy and immunogenicity of GARDASIL®9 to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women (N = 14,204: 7,099 receiving GARDASIL®9; 7,105 receiving GARDASIL®). Two immunological bridging studies evaluated HPV types 6, 11, 16 and 18 (Protocols 002 and 009) and HPV types 31, 33, 45, 52, and 58 (Protocol 002). Protocol 002 evaluated immunogenicity of GARDASIL®9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age (N=3,066: 1,932 girls; 666 boys; and 468 women receiving GARDASIL®9). Protocol 009 evaluated immunogenicity in girls 9 through 15 years of age (N=600; 300 receiving GARDASIL®9 and 300 receiving GARDASIL®). Protocol 006 evaluated administration of GARDASIL®9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL® (N=921; 615 receiving GARDASIL®9 and 306 receiving placebo). Protocols 005 and 007 evaluated GARDASIL®9 concomitantly administered with vaccines recommended routinely in girls and boys 11 through 15 years of

age (N=2,295). Together, these six studies evaluated 13,360 individuals who received GARDASIL®9 (8,053 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 3,498 girls 9 through 15 years of age at enrollment with a mean age of 12.0 years; and 1,809 boys 9 through 15 years of age at enrollment with a mean age of 12.1 years.

One clinical trial (Protocol 010) assessed the 2-dose regimen of GARDASIL®9. Protocol 010 evaluated the immunogenicity of 2 doses of GARDASIL®9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL®9 in girls 9 through 14 years of age and girls and women 16 through 26 years of age; (N=1,516; 751 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years.

The totality of results from the clinical studies support that GARDASIL®9 was efficacious against HPV disease and persistent infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Therefore the efficacy for cervical, vulvar, vaginal, and anal diseases, genital warts and persistent infection that was demonstrated in the original clinical studies for GARDASIL® can be extended to GARDASIL®9. In clinical studies, protective efficacy has been shown to last up to 5.6 years postdose 3 in duration for GARDASIL®9.

The decision to vaccinate an individual should take into account the risk for previous HPV exposure and potential benefit from vaccination.

Comparison of Immune Responses Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the Clinical Studies for GARDASIL®9

Studies Supporting the Efficacy of GARDASIL®9 *Against HPV Types 6, 11, 16, 18*
Because of the high efficacy of GARDASIL®, there is no known immune correlate of protection. The minimal anti-HPV response associated with protection against HPV 6-, 11-, 16-, and 18-related infection and disease has not been established. In addition, the existence of HPV Types 6, 11, 16, and 18 antigens in both the formulations for GARDASIL®9 and the active comparator vaccine (GARDASIL®) should result in no or few infection and disease endpoints associated with these HPV types. A low number of efficacy endpoints in both vaccination groups preclude a direct measurement of efficacy using disease endpoints associated with these HPV types.

GARDASIL®9 efficacy against HPV 6-, 11-, 16-, and 18-related infection and disease was inferred from comparative studies to the quadrivalent HPV (Types 6, 11, 16 18) vaccine, GARDASIL®, in which GARDASIL®9 elicited immune responses as measured by GMT. These studies were designed to evaluate immunologic non-inferiority of GARDASIL®9 to GARDASIL®. Therefore, the efficacy findings from the pivotal clinical studies for GARDASIL® against HPV Type 6-, 11-, 16-, and 18-related disease were extended to GARDASIL®9 by demonstrating that the immune responses elicited by GARDASIL®9 were non-inferior to the immune responses elicited by GARDASIL®.

Comparison of GARDASIL®9 with GARDASIL® immunogenicity with respect to HPV types 6, 11, 16, and 18 were conducted in a population of 16- through 26-year-old women from Protocol 001 and 9- through 15-year-old girls from Protocol 009. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocol 001) and seronegative (Protocols 001 and 009) prior to dose one] to the relevant

HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age; Protocol 001) to the relevant HPV type(s) through Month 7.

A statistical analysis of non-inferiority was performed based on Month 7 cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs between individuals administered GARDASIL®9 and individuals administered GARDASIL®. Immune responses, measured by GMT, for GARDASIL®9 were non-inferior to immune responses for GARDASIL® (Table 8). Therefore, efficacy for GARDASIL®9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of GARDASIL®.

Table 8: Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the Per Protocol Immunogenicity (PPI)* Population of 9- through 26-Year-Old Girls and Women

POPULATION	GARDASIL®9			GARDASIL®			GARDASIL®9 / GARDASIL®	
	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio	(95% CI)#
Anti-HPV 6								
9- through15-year-old girls	300 (273)	100 (98.7, 100)	1679.4 (1518.9, 1856.9)	300 (261)	100 (98.6, 100)	1565.9 (1412.2, 1736.3)	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	99.8 (99.6, 99.9)	893.1 (871.7, 915.1)	6795 (3975)	99.8 (99.7, 99.9)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06)¶
Anti-HPV 11								
9- through 15-year-old girls	300 (273)	100 (98.7, 100)	1315.6 (1183.8, 1462.0)	300 (261)	100 (98.6, 100)	1417.3 (1274.2, 1576.5)	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	100 (99.9, 100)	666.3 (649.6, 683.4)	6795 (3982)	99.9 (99.8, 100)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83)¶
Anti-HPV 16								
9- through 15-year-old girls	300 (276)	100 (98.7, 100)	6739.5 (6134.5, 7404.1)	300 (270)	100 (98.6, 100)	6887.4 (6220.8, 7625.5)	0.97	(0.85, 1.11)¶
16- through 26-year-old girls and women	6792 (4032)	100 (99.9, 100)	3131.1 (3057.1, 3206.9)	6795 (4062)	100 (99.8, 100)	3156.6 (3082.3, 3232.7)	0.99	(0.96, 1.03)¶
Anti-HPV 18								
9- through 15-year-old girls	300 (276)	100 (98.7, 100)	1956.6 (1737.3, 2203.7)	300 (269)	100 (98.6, 100)	1795.6 (1567.2, 2057.3)	1.08	(0.91, 1.29)¶
16- through 26-year-old girls and	6792 (4539)	99.8 (99.7, 99.9)	804.6 (782.7, 827.1)	6795 (4541)	99.7 (99.5, 99.8)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23)¶

women								

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data for 16- through 26- year-old girls and women are from Protocol 001, and the data for 9- through 15-year-old girls are from Protocol 009.

†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck units
¶p-value <0.001
CI=Confidence Interval
GMT=Geometric Mean Titers
cLIA= Competitive Luminex Immunoassay
#Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

Prophylactic Efficacy of GARDASIL®9 for HPV Types 31, 33, 45, 52, and 58 in Girls and Women 16 through 26 Years of Age

Studies Supporting Efficacy of GARDASIL®9 *Against HPV Types 31, 33, 45, 52, and 58*
The efficacy of GARDASIL®9 in 16- through 26- year-old women was assessed in an active comparator-controlled, double-blind, randomized clinical study (Protocol 001) that included a total of 14,204 women (GARDASIL®9 = 7,099; GARDASIL® = 7,105), who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up to 67 months postdose 3, with a median duration of follow-up of 43 months.

The primary efficacy is based on evaluation of a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58- related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. The efficacy is further supported by evaluation of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL®9 on the rates of HPV 31-, 33-, 45-, 52-, and 58- related abnormal Pap tests, cervical and external genital procedures (i.e., biopsies) and cervical definitive therapy procedures.

Efficacy was evaluated in the PPE population of 16- through 26-year-old women, who were naïve to the relevant HPV type(s) prior to dose one and through Month 7. Efficacy was measured starting after the Month 7 visit. GARDASIL®9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58- related persistent infection and disease (Table 9). GARDASIL®9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58- related Pap test abnormalities, cervical and external genital procedures (i.e., biopsies), and cervical definitive therapy procedures (including loop electrosurgical excision procedure [LEEP] or conization). See (Table 9).

Table 9: Analysis of Efficacy of GARDASIL®9 Against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population 16- through 26-Year-old Women

Disease Endpoint	GARDASIL® 9 N†=7099		GARDASIL® N†=7105		%Efficacy (95% CI)¶
	n‡	Number of cases§	n‡	Number of cases§	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS#	5949	1	5943	35	97.1 (83.5, 99.9)
CIN2	5949	1	5943	32	96.9 (81.5, 99.8)
CIN3	5949	0	5943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5949	1	5943	87	98.9 (94.1, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal DiseaseÞ	6009	1	6012	18	94.4 (67.7, 99.7)
VIN2/3# and VaIN2/3	6009	0	6012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Monthsß	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Monthsà	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Papè Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Biopsy	6013	6	6014	253	97.7 (95.1, 99.0)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Definitive Therapy Procedureð	6013	4	6014	41	90.2 (75.0, 96.8)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7). The data are from Protocol 001.

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

‡n=Number of individuals contributing to the analysis

§Number of cases= number of individuals with at least one follow-up visit after Month 7

¶Subjects were followed for up to 67 months postdose 3 (median 43 months postdose 3)

#No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.

Þincludes VIN1/2/3, VaIN1/2/3, condyloma

ðloop electrosurgical excision procedure (LEEP) or conization

ßPersistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart

àPersistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart

èPapanicolaou test

CI=Confidence Interval
ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk

Additional Efficacy Evaluation of Gardasil®9 Against HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58
Since the efficacy of Gardasil®9 could not be evaluated against placebo, the following exploratory analyses were conducted.

Efficacy Evaluation of Gardasil®9 Against Cervical High Grade Diseases Caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE
The efficacy of Gardasil®9 against CIN 2 and worse related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to Gardasil® was 94.4% (95% CI 78.8; 99.0) with 2/5,952 versus 36/5,947 cases. The efficacy of Gardasil®9 against CIN 3 related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to Gardasil® was 100% (95% CI 46.3; 100.0) with 0/5,952 versus 8/5,947 cases. These results reflect efficacy of Gardasil®9 versus Gardasil® against disease caused by HPV types 31, 33, 45, 52, and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Impact of Gardasil®9 Against Cervical Biopsy and Definite Therapy Related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE
The efficacy of Gardasil®9 against cervical biopsy related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to Gardasil® was 95.9% (95% CI 92.7; 97.9) with 11/6,016 versus 262/6,018 cases. The efficacy of Gardasil®9 against cervical definitive therapy (including loop electrosurgical excision procedure [LEEP] or conization) related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to Gardasil® was 90.7% (95% CI 76.3; 97.0) with 4/6,016 versus 43/6,018 cases. These results reflect efficacy of Gardasil®9 versus Gardasil® against procedures associated with HPV types 31, 33, 45, 52, and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Long-term Effectiveness Studies
A subset of subjects who received 3 doses is being followed up for 10 to 14 years after GARDASIL®9 vaccination for safety, immunogenicity, and effectiveness against clinical diseases related to the HPV types 6/11/16/18/31/33/45/52/58.

Clinical protection has been observed in all subjects in the long-term extension of Protocol 001 registry study in the PPE population. No cases of high-grade CIN were observed through 9.5 years postdose 3 (median duration of follow-up of 6.3 years) in girls and women who were 16 through 26 years of age at time of vaccination.

In the long-term extension of Protocol 002, no cases of high-grade intraepithelial neoplasia or genital warts were observed through 11 years postdose 3 (median duration of follow-up of 10.0 years) in girls and through 10.6 years postdose 3 (median duration of follow-up of 9.9 years) in boys who were 9 through 15 years of age at time of vaccination with GARDASIL®9. In girls and boys, incidence rates of 6-month persistent infections related to vaccine HPV types observed during the study were 52.4 and 54.6 per 10,000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of GARDASIL®9 and GARDASIL® vaccine).

Immunogenicity of GARDASIL®9

Assays to Measure Immune Response
The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL®9 it has not been possible to establish minimum antibody levels that protect against clinical disease caused by vaccine HPV types.

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

Immune Response to GARDASIL®9 *at Month 7 in Clinical Studies*

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age) and seronegative prior to dose one] to the relevant HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age) to the relevant HPV type(s) through Month 7.

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

GARDASIL®9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses measured at Month 7 (Table 10). In clinical studies 99.6% to 100% who received GARDASIL®9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GMTs were higher in girls and boys than in 16- through 26-year-old women and higher in boys than in girls and women.

Table 10: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9- through 15-year-old girls	2805	2349	99.7 (99.4, 99.9)	1744.6 (1684.7, 1806.7)
9- through 15-year-old boys	1239	1055	99.9 (99.5, 100)	2085.3 (1984.2, 2191.6)
16- through 26-year-old women	7260	4321	99.8 (99.6, 99.9)	893.7 (873.5, 914.3)
Anti-HPV 11				
9- through 15-year-old girls	2805	2350	99.9 (99.7, 100)	1289.7 (1244.3, 1336.8)
9- through 15-year-old boys	1239	1055	100 (99.7, 100)	1469.2 (1397.7, 1544.4)
16- through 26-year-old women	7260	4327	100 (99.9, 100)	669.3 (653.6, 685.4)
Anti-HPV 16				
9- through 15-year-old girls	2805	2405	99.9 (99.7, 100)	7159.9 (6919.7, 7408.5)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	8444.9 (8054.2, 8854.5)

16- through 26-year-old women	7260	4361	100 (99.9, 100)	3159.0 (3088.6, 3231.1)
Anti-HPV 18				
9- through 15-year-old girls	2805	2420	99.9 (99.6, 100)	2085.5 (2002.2, 2172.3)
9- through 15-year-old boys	1239	1074	100 (99.7, 100)	2620.4 (2474.3, 2775.2)
16- through 26-year-old women	7260	4884	99.8 (99.7, 99.9)	809.9 (789.2, 831.1)
Anti-HPV 31				
9- through 15-year-old girls	2805	2397	100 (99.8, 100)	1883.3 (1811.3, 1958.1)
9- through 15-year-old boys	1239	1069	100 (99.7, 100)	2173.5 (2057.0, 2296.6)
16- through 26-year-old women	7260	4806	99.8 (99.6, 99.9)	664.8 (647.4, 682.6)
Anti-HPV 33				
9- through 15-year-old girls	2805	2418	99.9 (99.7, 100)	960.6 (927.5, 994.9)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	1178.6 (1120.9, 1239.4)
16- through 26-year-old women	7260	5056	99.7 (99.5, 99.8)	419.2 (409.6, 429.1)
Anti-HPV 45				
9- through 15-year-old girls	2805	2430	99.8 (99.6, 100)	728.7 (697.6, 761.2)
9- through 15-year-old boys	1239	1079	100 (99.7, 100)	841.7 (790.0, 896.7)
16- through 26-year-old women	7260	5160	99.6 (99.4, 99.7)	254.1 (247.0, 261.5)
Anti-HPV 52				
9- through 15-year-old girls	2805	2426	99.9 (99.7, 100)	978.2 (942.8, 1015.0)
9- through 15-year-old boys	1239	1077	100 (99.7, 100)	1062.2 (1007.2, 1120.2)
16- through 26-year-old women	7260	4792	99.8 (99.6, 99.9)	382.4 (373.0, 392.0)
Anti-HPV 58				
9- through 15-year-old girls	2805	2397	99.9 (99.7, 100)	1306.0 (1259.8, 1354.0)
9- through 15-year-old boys	1239	1072	100 (99.7, 100)	1545.8 (1470.6, 1624.8)
16- through 26-year-old women	7260	4818	99.8 (99.6, 99.9)	489.2 (477.5, 501.2)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) prior to dose 1 and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7).

†Number of individuals randomized to the respective vaccination group who received at least 1 injection

‡Number of individuals contributing to the analysis
§mMU=milli-Merck Units
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titers

Table 10 displays the Month 7 immunogenicity data for girls and women and boys. Anti-HPV responses at Month 7 among 9- through 15-year-old girls were comparable to anti-HPV responses in 16- through 26-year-old women in the combined database of immunogenicity studies for GARDASIL®9. Anti-HPV responses at Month 7 among 9- through 15-year-old boys were comparable to anti-HPV responses in both 16- through 26-year-women and 9-through 15-year-old girls.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL®9 in 9- through 15-year-old girls and boys is inferred.

A formal immunogenicity bridging has not been conducted in 16- through 26-year-old men or in 27- through 45-year-old women. Efficacy of GARDASIL®9 in these groups is inferred based on high efficacy of GARDASIL® in these groups and comparable immunogenicity of GARDASIL®9 and GARDASIL® in other age groups.

Immune Responses to GARDASIL®9 *Using a 2-dose Schedule in Individuals 9 through 14 Years of Age*

Protocol 010 measured HPV antibody responses to the 9 HPV types after GARDASIL®9 vaccination in the following cohorts: girls and boys 9 through 14 years of age receiving 2 doses at a 6-month or 12-month interval (+/- 1 month); girls 9 through 14 years of age receiving 3 doses (at 0, 2, 6 months); and women 16 through 26 years of age receiving 3 doses (at 0, 2, 6 months).

GMTs were non-inferior in girls and boys who received 2 doses of GARDASIL®9 (at either 0, 6 months or 0, 12 months) to GMTs in 16- through 26-year-old girls and women who received 3 doses of GARDASIL®9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2-dose regimen of GARDASIL®9 in 9- through 14-year-old girls and boys is inferred. One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types (Table 11).

In the same study, in girls and boys 9 through 14 years of age, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years of age after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 11). The clinical relevance of these findings is unknown.

Persistence of antibody response to GARDASIL®9 was observed for 3 years in girls and boys who were 9 through 14 years of age at time of vaccination receiving 2 doses at 6-month or 12-month interval. At Month 36, non-inferiority criteria were also met for GMTs in girls and boys 9 through 14 years of age receiving 2 doses at a 6-month interval (+/-1 month) compared to GMTs in women 16 through 26 years of age receiving 3 doses of GARDASIL®9.

Duration of protection of a 2-dose schedule of GARDASIL®9 has not been established.

Table 11. Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population at

One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses† or 3 Doses† of GARDASIL®9

Population (Regimen)	N	N	GMT (95% CI) mMU§/mL
Anti-HPV 6			
9- through 14-year-old girls (0, 6)†	301	258	1657.9 (1479.6, 1857.6)
9- through 14-year-old boys (0, 6)†	301	263	1557.4 (1391.5, 1743.1)
9- through 14-year-old girls (0, 12)†	150	123	2685.7 (2274.6, 3171.2)
9- through 14-year-old boys (0, 12)†	150	134	2672.4 (2279.1, 3133.5)
9- through 14-year-old girls (0, 2, 6)†	300	254	1496.1 (1334.1, 1677.8)
16- through 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)
Anti-HPV 11			
9- through 14-year-old girls (0, 6)†	301	258	1388.9 (1240.4, 1555.3)
9- through 14-year-old boys (0, 6)†	301	264	1423.9 (1273.2, 1592.3)
9- through 14-year-old girls (0, 12)†	150	123	2915.9 (2475.1, 3435.1)
9- through 14-year-old boys (0, 12)†	150	134	2965.9 (2534.9, 3470.1)
9- through 14-year-old girls (0, 2, 6)†	300	254	1306.3 (1165.5, 1464.0)
16- through 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)
Anti-HPV 16			
9- through 14-year-old girls (0, 6)†	301	272	8004.9 (7160.5, 8948.8)
9- through 14-year-old boys (0, 6)†	301	273	8474.8 (7582.4, 9472.3)
9- through 14-year-old girls (0, 12)†	150	129	13828.1 (11780.6, 16231.5)
9- through 14-year-old boys (0, 12)†	150	135	14825.2 (12675.7, 17339.3)
9- through 14-year-old girls (0, 2, 6)†	300	269	6996.0 (6254.1, 7825.8)
16- through 26-year-old women (0, 2, 6)†	314	249	3154.0 (2807.1, 3543.7)
Anti-HPV 18			
9- through 14-year-old girls (0, 6)†	301	272	1872.8 (1651.6, 2123.6)
9- through 14-year-old boys (0, 6)†	301	272	1860.9 (1641.1, 2110.2)
9- through 14-year-old girls (0, 12)†	150	129	2696.0 (2252.4, 3227.0)
9- through 14-year-old boys (0, 12)†	150	137	2922.5 (2454.7, 3479.5)
9- through 14-year-old girls (0, 2, 6)†	300	270	2049.3 (1806.4, 2324.8)
16- through 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)
Anti-HPV 31			
9- through 14-year-old girls (0, 6)†	301	272	1436.3 (1272.1, 1621.8)
9- through 14-year-old boys (0, 6)†	301	271	1498.2 (1326.5, 1692.0)
9- through 14-year-old girls (0, 12)†	150	132	2086.4 (1761.7, 2471.1)
9- through 14-year-old boys (0, 12)†	150	136	2148.1 (1818.3, 2537.7)
9- through 14-year-old girls (0, 2, 6)†	300	271	1748.3 (1548.1, 1974.5)
16- through 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)
Anti-HPV 33			
9- through 14-year-old girls (0, 6)†	301	273	1030.0 (920.4, 1152.7)
9- through 14-year-old boys (0, 6)†	301	271	1040.0 (928.9, 1164.3)
9- through 14-year-old girls (0, 12)†	150	132	2037.4 (1737.6, 2389.0)
9- through 14-year-old boys (0, 12)†	150	137	2363.6 (2021.6, 2763.3)
9- through 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)
16- through 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)

Anti-HPV 45			
9- through 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)
9- through 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)
9- through 14-year-old girls (0, 12)†	150	132	439.6 (366.0, 528.0)
9- through 14-year-old boys (0, 12)†	150	136	397.6 (331.9, 476.2)
9- through 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)
16- through 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)
Anti-HPV 52			
9- through 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)
9- through 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)
9- through 14-year-old girls (0, 12)†	150	131	1028.2 (885.0, 1194.7)
9- through 14-year-old boys (0, 12)†	150	137	1222.7 (1055.9, 1415.9)
9- through 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)
16- through 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)
Anti-HPV 58			
9- through 14-year-old girls (0, 6)†	301	270	1251.2 (1119.6, 1398.4)
9- through 14-year-old boys (0, 6)†	301	270	1325.7 (1186.2, 1481.6)
9- through 14-year-old girls (0, 12)†	150	129	2244.7 (1919.2, 2625.3)
9- through 14-year-old boys (0, 12)†	150	136	2650.7 (2275.6, 3087.6)
9- through 14-year-old girls (0, 2, 6)†	300	273	1229.3 (1100.7, 1373.0)
16- through 26-year-old women (0, 2, 6)†	314	261	491.1 (438.6, 549.8)

*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.
†2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).
§mMU=milli-Merck Units.
N = Number of individuals randomized to the respective vaccination group who received at least 1 injection.
n = Number of individuals contributing to the analysis.
CI=confidence interval
cLIA=competitive Luminex immunoassay
GMT=Geometric Mean Titer

Variation in Dosing Regimen in 16-through 26-Year-Old Women
All individuals evaluated for efficacy in the PPE population of Protocol 001 received all 3 vaccinations within a 1-year period, regardless of the interval between doses. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not substantially impact the immune responses to GARDASIL®9 *[see DOSAGE AND ADMINISTRATION, Administration of* GARDASIL®9 *In Individuals Who Have Been Previously Vaccinated With GARDASIL®]*.

Persistence of Immune Response to GARDASIL®9
The persistence of antibody response following a complete schedule of vaccination with GARDASIL® 9 is being studied in a subset of individuals who will be followed up for at least 10 years after vaccination for safety, immunogenicity and effectiveness.

In 9- through 15-year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 10 years; depending on HPV type, 81 to 98% of subjects were seropositive.

In 16- through 26-year-old girls and women (Protocol 001), persistence of antibody response has been demonstrated for at least 5 years; depending on HPV type, 78 to 100% of subjects were seropositive. Efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months postdose 3; median follow-up duration of 43 months).

GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received GARDASIL® or GARDASIL®9 for at least 3.5 years.

Evidence of Anamnestic (Immune Memory) Response

Evidence of an anamnestic response was seen in vaccinated women who were seropositive to relevant HPV type(s) prior to vaccination. In addition, women (n = 150) who received 3 doses of GARDASIL®9 in Protocol 001 and a challenge dose 5 years later, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month postdose 3.

Administration of GARDASIL®9 *to Individuals Previously Vaccinated with GARDASIL®*
Protocol 006 evaluated the immunogenicity of GARDASIL®9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL®. Prior to enrollment in the study, over 99% of subjects had received 3 injections of GARDASIL® within a one year period. The time interval between the last injection of GARDASIL® and the first injection of GARDASIL®9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL®9. The GMTs to HPV Types 31, 33, 45, 52, and 58 were lower than in the population who had not previously received GARDASIL® in Protocols 001, 002, 005, 007 and 009. Efficacy of GARDASIL®9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL® has not been assessed.

Concomitant Use of GARDASIL®9 with Other Vaccines

Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]
In Protocol 005, the safety and immunogenicity of co-administration of GARDASIL®9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in a study of 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL®9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL®9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL®9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL®9).

Concomitant administration of GARDASIL®9 with Menactra and Adacel did not interfere with the antibody response to any of the vaccine antigens when GARDASIL®9 was given concomitantly with Menactra and Adacel or separately.

Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV)]

In Protocol 007, the safety and immunogenicity of co-administration of GARDASIL®9 with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV)] (same visit, injections at separate sites) were evaluated in a study of 1,053 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL®9 in one limb and Repevax in the opposite limb concomitantly on Day 1 (n = 525). The second group received the first dose of GARDASIL®9 on Day 1 in one limb then Repevax at Month 1 in the opposite limb (n = 528). Subjects in both vaccination groups received the second dose of GARDASIL®9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Repevax and 3 doses for GARDASIL®9).

Concomitant administration of GARDASIL®9 with Repevax did not interfere with the antibody response to any of the vaccine antigens when GARDASIL®9 was given concomitantly with Repevax or separately.

Serious Adverse Events in Clinical Trials of GARDASIL®9

Serious adverse events were collected throughout the entire study period for the six integrated clinical studies for GARDASIL®9. Out of the 13,309 individuals who were administered GARDASIL®9 and had safety follow-up, 305 reported a serious adverse event; representing 2.3% of the population. Four individuals administered GARDASIL®9 reported at least one serious adverse event that was determined to be vaccine-related. Four vaccine-related serious adverse events that occurred during the study period were pyrexia, allergy to vaccine, asthmatic crisis, and headache.

EFFECTS ON TO ABILITY DRIVE AND USE MACHINES

GARDASIL®9 has no or negligible influence on the ability to drive or use machines. However, some of the effects mentioned under “Undesirable effects” may temporarily affect the ability to drive or use machines.

SHELF-LIFE

36 Months

PACKAGING INFORMATION

GARDASIL®9 is supplied in vials and pre-syringes.

Carton of one 0.5-mL single-dose vial.

Or

Carton of one 0.5-mL single-dose prefilled Luer Lock syringe with tip cap & needle.

STORAGE AND HANDLING INSTRUCTIONS

Storage

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL®9 should be administered as soon as possible after being removed from refrigeration. GARDASIL®9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

Discard the product if it is frozen, particulates are present, or if it appears discolored.

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08VNW7
(CCDS-V503-I-022016, CCDS-V503-I-032020 & CCDS-V503-I-112022)

If you want to report an adverse experience related to this product, please contact us at: Tel: 18001032642; Fax: +91-124-4647339; dpoc_india@merck.com