GARDASIL® 9

[Human Papillomavirus 9-valent Vaccine, Recombinant]

[Suspension for Injection]

1. INDICATIONS AND USAGE

GARDASIL 9 is a vaccine indicated in girls and women from 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer; premalignant genital lesions (cervical, vulvar and vaginal); premalignant anal lesions; HPV infections; cervical adenocarcinoma in situ (AIS); and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 is indicated in boys and men from 9 through 26 years of age for the prevention of premaglinant lesions and HPV infections caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts (condyloma acuminata) caused by HPV types 6 and 11.

2. DOSAGE AND ADMINISTRATION

2.1 General

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. If an alternate vaccination schedule is necessary, 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.

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

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

The need for a booster dose has not been established. The duration of protection is currently unknown.

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.

2.2 Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL.

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

Safety and immunogenicity of GARDASIL 9 were assessed in individuals who previously completed a three-dose vaccination series with GARDASIL [see 8 ADVERSE REACTIONS and 10 CLINICAL STUDIES].

3. 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.

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.

4. CONTRAINDICATIONS

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.

5. 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.

Vaccination does not substitute for routine cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care.

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, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. Vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9 [See 8 ADVERSE REACTIONS, 8.2 Post-marketing Experience].

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 6 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 6.3 Use with Steroids and 7 USE IN SPECIFIC POPULATIONS, 7.5 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.

6. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

6.1 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).

6.2 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.

6.3 Use with Systemic Immunosuppressive Medications

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 7 USE IN SPECIFIC POPULATIONS, 7.5 Immunocompromised Individuals.]*

7. USE IN SPECIFIC POPULATIONS

7.1 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 12.9% (174/1,353) in women who received GARDASIL 9 and 14.4% (187/1,303) 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, 30 and 23 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.

7.2 Nursing Mothers

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk. However, since many drugs are excreted in human milk, caution should be exercised when GARDASIL 9 is administered to a nursing woman.

A total of 92 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.

7.3 Pediatric Use

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

7.4 Geriatric Use

The safety and efficacy of GARDASIL 9 have not been evaluated in individuals aged 65 years and over.

7.5 Immunocompromised Individuals

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals *[see 6 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 6.3 Use with Steroids]*.

8. ADVERSE REACTIONS

8.1 Clinical Trials Experience

Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety of GARDASIL 9 was evaluated in 7 clinical studies (Protocols 001, 002, 003, 005, 006, 007, 009) that included 15,776 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 9,102 girls and women 16 through 26 years of age, 1,394 boys and men 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 girls and 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, men, 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	Subjects 9 Through 26 Years of Age
	GARDASIL 9 (N=15,776) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)	
Pain†	83.2
Swelling†	36.1
Erythema†	30.8
Pruritus	4.0
Bruising	1.6
Systemic Adverse Reactions (1 to 15 Days Postvaccination)	
Headache	13.2
Pyrexia	6.1
Nausea	3.2
Dizziness	2.3
Fatigue	1.9

*Data from Protocols 001,002, 003, 005, 006, 007, 009

†Designates a solicited adverse reaction

N=number of subjects vaccinated with safety follow-up

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=15,614 %	Dose 2 N=15,243 %	Dose 3 N=15,062 %	Any Dose N=15,676 %
Temperature	< 37.8 °C (100.0 °F)	97.1	97.4	96.9	92.5
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.5	2.3	2.5	6.3
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.3	0.3	0.5	1.1
	≥ 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=15,773**	**Dose 2 N=15,549**	**Dose 3 N=15,378**	**Any Dose N=15,776**
Pain	Mild	52.3	46.7	44.4	51.1
	Moderate	10.8	15.1	16.7	28.5
	Severe	0.6	1.4	2.1	3.5
Swelling†	Mild	9.6	14.7	17.9	24.8
	Moderate	1.7	3.7	4.6	7.3
	Severe	0.8	1.6	2.5	4.0
Erythema†	Mild	8.7	13.6	16.1	24.7
	Moderate	0.9	2.0	2.5	4.4
	Severe	0.2	0.5	1.1	1.7

*Data from Protocols 001, 002, 003, 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 safety follow-up

Serious Adverse Events in Clinical Trials

Serious adverse events were collected throughout the entire study period for the seven integrated clinical studies for GARDASIL 9. Out of the 15,778 individuals who were administered GARDASIL 9 and had safety follow-up, 356 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.

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, with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL.

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.

8.2 Post-marketing Experience

The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL and may also be seen in post-marketing experience with GARDASIL 9. The post-marketing safety 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. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Infections and infestations: cellulitis.

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

Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders:arthralgia, myalgia.

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

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

9. OVERDOSAGE

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

10. CLINICAL STUDIES

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 sulphate 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.

†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 24, 596 individuals (20,541 girls and women 16 through 26 years of age, and 4,055 boys and men 16 through 26 years of age. 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 those girls and women who were PCR negative and seronegative at baseline (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. GARDASIL was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men who were PCR negative and seronegative at baseline. 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 who were PCR negative and seronegative at baseline (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 (FUTURE III, P019) was conducted.

Study P019 evaluated efficacy in 3253 women 27 through 45 years of age based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1: 1 to receive either GARDASIL or amorphous aluminum hydroxyphosphate sulfate (AHHS) control. The efficacy for the combined endpoint was driven primarily by prevention of persistent infection. There was no statistically significant efficacy demonstrated for CIN2/3, AIS or cervical cancer. In post hoc analyses conducted to assess the impact of GARDASIL on the individual components of the combined endpoint, the results in the population of women naïve to the relevant HPV type at baseline were as follows: prevention of HPV 6-, 11-, 16- or 18-related persistent infection (80.5% [95%CI: 68.3, 88.6]), prevention of HPV 6-, 11-, 16- or 18-related CIN (any grade) (85.8% [95%CI: 52.4, 97.3]), and prevention of HPV 6, 11-, 16- or 18-related genital warts (87.6% [95%CI: 7.3, 99.7]).

Efficacy for disease endpoints was diminished in a population impact assessment of women who were vaccinated regardless of baseline HPV status (full analysis set, FAS). In the FAS, efficacy was not demonstrated for the following endpoints; prevention of HPV 16- and 18-related CIN 2/3, AIS, or cervical cancer and prevention of HPV-6 and 11-related condyloma. No efficacy was demonstrated against CIN 2/3, AIS, or cervical cancer in the general population irrespective of HPV type (FAS any type analysis).

Analyses of efficacy were conducted in the PPE population. Efficacy was measured starting after the Month 7 visit (Table 7).

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 is currently being 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.

Currently, persistence of antibody response has been observed for 8 years in adolescents who were 9-15 years of age at time of vaccination; 9 years in girls and women, 16-23 years of age at time of vaccination; 6 years in boys and men, 16-26 years of age at time of vaccination, .

Clinical protection has been observed in all subjects (including those who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18): no cases of HPV diseases were observed after a follow-up of approximately 6.9 years in girls who were 9-15 years of age at time of vaccination; 6.5 years in boys, 9-15 years of age at time of vaccination; 8 years in girls and women, 16-23 years of age at time of vaccination; 6 years in boys and men, 16-26 years of age at time of vaccination.

Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of GARDASIL 9 were assessed in seven 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. Efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine.

The efficacy is further extended to 9- through 15-year-old adolescents and to 16- through 26-year-old boys and men, 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, 003, 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 003 evaluated immunogenicity of Gardasil 9 in boys and men 16 through 26 years of age and in girls and women 16 through 26 years of age (1,103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1,099 women receiving Gardasil 9). 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 seven studies evaluated 15,875 individuals who received GARDASIL 9 (9,152 girls and women 16 through 26 years of age at enrollment with a mean age of 21.7 years; 3,498 girls 9 through 15 years of age at enrollment with a mean age of 12.0 years; 1,416 boys and men 16 through 26 years of age at enrollment with a mean age of 21.1 years; and 1,809 boys 9 through 15 years of age at enrollment with a mean age of 12.1 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 women	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)¶

*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, 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 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

#Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA= Competitive Luminex Immunoassay

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 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 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 Disease♭	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 Months♂	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months♁	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap♀ 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 Procedure♢	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 5.6 years postdose 3 (median 3.5 years)

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

♭includes VIN1/2/3, VaIN1/2/3,condyloma

♢loop electrosurgical excision procedure (LEEP) or conization

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

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

♀Papanicolaou 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.

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.

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). The data are from Protocols 001, 002, 005, 007 and 009.

†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.

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 16- through 26-Year-Old Boys and Men

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority comparison in Protocol 003 of GMTs following vaccination with GARDASIL 9 among 16- to 26-year-old boys and men with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol 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 seronegative to the relevant HPV type(s) prior to dose 1. Anti-HPV GMTs at Month 7 among 16- through 26-year-old boys and men (HM) were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 11). Anti-HPV GMTs at Month 7 among 16- through 26-year-old MSM (HIV-negative) were lower than in 16- through 26-year-old HM. The GMT fold difference in 16- through 26-year-old MSM relative to the HM was 0.6 to 0.8; anti-HPV GMTs for the MSM subjects ranged between 157.5 and 2294.0 mMU/mL. The fold differences observed with GARDASIL 9 for MSM compared to HM were generally similar to those previously observed with GARDASIL. In Protocol 003, 99.6% to 100% in the HM population and 99.4 to 100% in the MSM population who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7.

Table 11: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men for All GARDASIL 9 Vaccine HPV Types

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16-through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
16 to 26-year-old HM	1103	847	782.0	1.11 (1.02, 1.21)
16- through 26-year-old girls and women	1099	708	703.9	1
Anti-HPV 11				
16 to 26-year-old HM	1103	851	616.7	1.09 (1.00, 1.19)
16- through 26-year-old girls and women	1099	712	564.9	1
Anti-HPV 16				
16 to 26-year-old HM	1103	899	3346.0	1.20 (1.10, 1.30)
16- through 26-year-old girls and women	1099	781	2788.3	1
Anti-HPV 18				
16 to 26-year-old HM	1103	906	808.2	1.19 (1.08, 1.31)
16- through 26-year-old girls and women	1099	831	679.8	1
Anti-HPV 31				
16 to 26-year-old HM	1103	908	708.5	1.24 (1.13, 1.37)
16- through 26-year-old girls and women	1099	826	570.1	1
Anti-HPV 33				
16 to 26-year-old HM	1103	901	384.8	1.19 (1.10, 1.30)
16- through 26-year-old girls and women	1099	853	322.0	1
Anti-HPV 45				
16 to 26-year-old HM	1103	909	235.6	1.27 (1.14, 1.41)
16- through 26-year-old girls and women	1099	871	185.7	1
Anti-HPV 52				
16 to 26-year-old HM	1103	907	386.8	1.15 (1.05, 1.26)
16- through 26-year-old girls and women	1099	849	335.2	1
Anti-HPV 58				
16 to 26-year-old HM	1103	897	509.8	1.25 (1.14, 1.36)
16- through 26-year-old girls and women	1099	839	409.3	1

*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 seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Protocol 003.

†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

¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=Competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titers

On the basis of this immunogenicity bridging, the efficacy of GARDASIL 9 in 16- through 26-year-old boys and men is inferred.

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 2 DOSAGE AND ADMINISTRATION, 2.2 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 9-15 year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 3 years; depending on HPV type, 93 to 99 % of subjects were seropositive.

In 16-26 year-old girls and women (Protocol 001), persistence of antibody response has been demonstrated for at least 3.5 years; depending on HPV type, 78-98% 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.

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. The clinical significance of this observation is not known. 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.

11. CLINICAL PHARMACOLOGY

11.1 Therapeutic Class

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

11.2 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.

12. ANIMAL TOXICOLOGY

12.1 Carcinogenesis

GARDASIL 9 has not been evaluated for the potential to cause carcinogenicity.

12.2 Mutagenesis

GARDASIL 9 has not been evaluated for the potential to cause genotoxicity.

12.3 Reproduction

GARDASIL 9 administered to female rats at a dose approximately 240 times the human dose (mg/kg basis) had no effects on mating performance, fertility, or embryonic/fetal survival.

12.4 Development

GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) had no effects on development, behavior, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during the period of gestation and lactation.

12.5 Repeat Dose Toxicity and Local Tolerance

A repeat dose toxicity study has been performed in rats at a dose approximately 250 times the human dose (mg/kg basis) and revealed no special hazards to humans.

13. NAME OF THE DRUG

Human Papillomavirus 9-valent Vaccine, Recombinant

14. PHARMACEUTICAL FORM

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose prefilled syringes.

15. PHARMACEUTICAL PARTICULARS

15.1 Chemistry

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.

15.2 Composition

Active Ingredient

GARDASIL 9 is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 60 mcg of HPV 16 L1 protein, 40 mcg of HPV 18 L1 protein, 20 mcg of HPV 31 L1 protein, 20 mcg of HPV 33 L1 protein, 20 mcg of HPV 45 L1 protein, 20 mcg of HPV 52 L1 protein, and 20 mcg of HPV 58 L1 protein.

Inactive Ingredients (List of excipients)

Each 0.5-mL dose of the vaccine contains approximately 500 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection. 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 is a white, cloudy liquid.

15.3 Storage

Special Precautions for 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.

16. PRESENTATION

GARDASIL 9 is supplied as a 0.5-mL single-dose prefilled syringe in packs of

1. 1 single-dose prefilled syringe with separate needle
2. 10 single-dose prefilled syringes with separate needles

Not all presentations may be available locally.

17. MARKETING AUTHORIZATION HOLDER

MSD Pharma (Singapore) Pte. Ltd.
150 Beach Road
#31-00, Gateway West
Singapore 189720

18. DATE OF REVISION

March 2016