Product Monograph

Including Patient Medication Information

GARDASIL®9

[Human Papillomavirus 9-valent Vaccine, Recombinant]
Each 0.5 mL sterile 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
20 mcg of HPV 58 L1 protein

Suspension for intramuscular injection

Active Immunizing Agent

ATC code: J07BM03

GARDASIL®9, is a vaccine indicated for:

- individuals 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:
  - Oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for GARDASIL®9 please refer to Health Canada's https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

GARDASIL®9, is a vaccine indicated for:

- individuals 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:
  - Cervical, vulvar, vaginal, and 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:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

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

has been issued market authorization **without conditions**.

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Date of Authorization:
2025-09-19

Submission Control Number: 296670

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this vaccine on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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Sections or subsections that are not applicable at the time of authorization are not listed.

Part 1: Healthcare Professional Information

1 Indications

GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a vaccine indicated in individuals 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:

- Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers 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:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

1.1 Pediatrics (≥ 9 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of GARDASIL®9 in pediatric patients from 9 years of age has been established. Therefore, Health Canada has authorized an indication for pediatric use in individuals 9 years and above (see 1 Indications, 8 Adverse Reactions and 14 Clinical Trials).

1.2 Geriatrics (≥ 65 years of age)

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

2 Contraindications

- GARDASIL®9 is contraindicated in patients who are hypersensitive to either GARDASIL® or GARDASIL®9 or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL®9 or GARDASIL® should not receive further doses of GARDASIL®9.

4 Dosage and Administration

4.1 Dosing Considerations

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.

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 14 Clinical Trials).

4.2 Recommended Dose and Dosage Adjustment

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. 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 14 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.

4.4 Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL®9 should not be diluted or mixed with other vaccines. 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. Do not use the product if particulates are present or if it appears discolored.

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.

Instructions for Use

Prefilled Syringe Use
Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

Needles
A sterile 22 to 25-gauge needle, 1 to 1-½ inch (2.5 cm – 3.8 cm) length for IM injection should be used. It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

4.5 Missed Dose

If a planned dose of GARDASIL®9 is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 Overdose

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

For the most recent information in the management of a suspected vaccine overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, healthcare professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Syringes

GARDASIL®9 is supplied in single-dose Type I glass prefilled Luer Lock syringes, containing 0.5 mL dose of liquid vaccine.

Available in 1 and 10 single dose syringe packages.

The components of the prefilled syringes are latex free.

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Suspension for injection / Each 0.5 mL sterile 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 20 mcg of HPV 58 L1 protein	Each 0.5-mL sterile dose of the vaccine contains approximately 500 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, 9.56 mg of sodium chloride, and water for injection. The product does not contain a preservative or antibiotics.

7 Warnings and Precautions

General

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, anal, oropharyngeal and other head and neck cancers; CIN, VIN, VaIN, or AIN.

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

GARDASIL®9 has not been shown to protect against diseases due to HPV types not contained in the vaccine.

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.

Routine monitoring and Pap test in women should continue to be performed as indicated, regardless of GARDASIL®9 administration. Recipients of GARDASIL®9 should not discontinue screening for cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers if it has been recommended by a healthcare professional. Appropriate precautions against sexually transmitted diseases should continue to be used.

Febrile Illness

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.

Hematologic
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.

Immune
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 9 Drug Interactions).

Reproductive Health: Female and Male Potential

- **Fertility**

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 (see 7.1.1 Pregnancy, 16 Non-Clinical Toxicology).

7.1 Special Populations
The safety, immunogenicity, and efficacy of GARDASIL®9 have not been evaluated in HIV-infected individuals.

7.1.1 Pregnancy
There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response (see 16 Nonclinical Toxicology). As a precautionary measure, the administration of GARDASIL®9 during pregnancy should be avoided. Women who become or plan to become pregnant during the vaccination series should be advised to interrupt or postpone the vaccination regimen until completion of pregnancy.

A six-year pregnancy registry for GARDASIL®9 enrolled 185 women who were inadvertently exposed to GARDASIL®9 within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 180 of whom were prospectively followed. After excluding elective terminations (n=1), ectopic pregnancies (n=0) and those lost to follow-up (n=110), there were 69 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 4.3% of pregnancies (3/69) and 4.5% of live born infants (3/67), respectively. These frequencies of the assessed outcomes in the prospective population were consistent with estimated background frequencies (see 8.2 Adverse Reactions, Clinical Trials Experience of GARDASIL®9 in Pregnancy).

Pregnant women exposed to GARDASIL®9 are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594.

7.1.2 Breastfeeding
It is not known whether vaccine antigens are excreted in human milk.

A total of 92 women were breast feeding during the vaccination period of the clinical studies for GARDASIL®9 in women aged 16 to 26 years. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period.

7.1.3 Pediatrics (< 9 years of age)
The safety and efficacy of GARDASIL®9 have not been evaluated in children younger than 9 years.

7.1.4 Geriatrics (≥ 65 years of age)
The safety and efficacy of GARDASIL®9 have not been evaluated in individuals aged 65 years and over.

8 Adverse Reactions

8.1 Adverse Reaction Overview
Headache, fever, nausea, dizziness, fatigue, diarrhea, oropharyngeal pain, upper abdominal pain, and local injection site reactions (pain, swelling, erythema, pruritus, bruising, hematoma, mass, hemorrhage, induration) occurred after administration with GARDASIL®9.

8.2 Clinical Trial Adverse Reactions
Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another vaccine.
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®. The race distribution of the integrated safety population for Protocols 001, 002, 005, 006, 007 and 009 for GARDASIL®9 was similar between women (56.2% White; 25.4% Other Races or Multiracial; 14.7% Asian; 3.7% Black) and girls and boys (61.2% White; 18.9% Other Races or Multiracial; 14.6% Asian; 5.3% Black). For Protocol 003, the race distribution for boys and men was 61.9% White; 22.7% Other Races or Multiracial; 9.8% Asian; 5.5% Black. The race distribution of the safety population for GARDASIL® was determined in two studies (Protocol 001 and Protocol 009) that had different profiles. In Protocol 001, the race distribution was similar to the integrated database for GARDASIL®9: 55.3% White; 26.9% Multiracial; 14.2% Asian; 3.3% Black; 0.2% Unknown; 0.1% American Indian or Alaskan Native; and 0.1% Native Hawaiian or other Pacific Islander. Protocol 009 race distribution was 98.0% White; 1.3% Multiracial; 0.3% Asian; and 0.3% Black.

Safety of GARDASIL®9 in women 27 through 45 years of age was evaluated in a clinical trial comparing 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age. The race distribution was similar between women 27 through 45 years of age (97.7% White, 1.6% Asian, 0.3% Other or Multiracial, 0.5% Black) and girls and women 16 through 26 years of age (94.6% White, 3.0% Asian, 1.6% Other or Multiracial, 0.9% Black).

Safety of GARDASIL®9 in men 27 through 45 years of age is inferred from the safety data of GARDASIL® and GARDASIL®9 in boys and men 9 through 26 years of age and girls and women 9 through 45 years of age.

Systemic and Injection-Site Adverse Reactions in Girls and Women

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 Table 2. Few individuals (GARDASIL®9 = 0.1% vs. GARDASIL® < 0.1%) discontinued due to adverse experiences after receiving either vaccine.

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

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL®9 (N = 7 071) %	GARDASIL® (N = 7 078) %	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 with safety follow-up.

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 - Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL®9 Compared with GARDASIL® (Protocols 001 and 009)

	GARDASIL®9				GARDASIL®			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	**N = 7 069**	**N = 6 997**	**N = 6 909**	**N = 7 071**	**N = 7 076**	**N = 6 992**	**N = 6 909**	**N = 7 078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
Systemic Adverse Reactions	**n = 6 995**	**n = 6 913**	**n = 6 743**	**n = 7 022**	**n = 7 003**	**n = 6 914**	**n = 6 725**	**n = 7 024**
Temperature ≥37.8°C	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥38.9°C	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	**N = 300**	**N = 297**	**N = 296**	**N = 299**	**N = 299**	**N = 299**	**N = 294**	**N = 300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	**n = 300**	**n = 294**	**n = 295**	**n = 299**	**n = 299**	**n = 297**	**n = 291**	**n = 300**
Temperature ≥37.8°C	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥38.9°C	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Protocol 001, and the data for girls 9 through 15 years of age are from Protocol 009.
N = number of subjects vaccinated with safety follow-up
n = number of subjects with temperature data
Pain, Any = mild, moderate, severe or unknown intensity
Pain, Severe = incapacitating with inability to work or do usual activity
Swelling, Any = any size or size unknown
Swelling, Severe = maximum size greater than 2 inches (5 cm)
Erythema, Any = any size or size unknown
Erythema, Severe = maximum size greater than 2 inches (5 cm)

An uncontrolled clinical trial with 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age who received GARDASIL®9 (Protocol 004) was also conducted. Solicited and unsolicited adverse reactions reported by women 27 through 45 years of age in this study are shown in Table 4.

Table 4 - Rates (%) of Injection-Site and Systemic Adverse Reactions among Women 27 through 45 years of age and among Girls and Women 16 through 26 years of age Who Received GARDASIL®9

Adverse Reaction	Women 27 Through 45 Years of Age N = 640	Girls and Women 16 Through 26 Years of Age N = 570
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain	82.8	86.1
Swelling	23.3	23.3
Erythema†	16.9	19.5
Pruritus	1.6	1.8
Hematoma	1.3	1.1
Discomfort	0.8	1.2
Bruising	0.8	1.1
Systemic Adverse Reactions (1 to 15 Days Post-Vaccination)		
Headache	13.6	12.6
Fatigue	3.4	2.8
Pyrexia	1.7	3.0
Nausea	1.7	1.8
Oropharyngeal pain	1.1	0.7
Myalgia	0.8	1.4
Abdominal pain	0.3	1.1
Elevated Temperature (1 to 5 Days Postvaccination)		
Oral Temperature ≥ 37.8°C†	2.5	3.5
The data are from Protocol 004. N = number of subjects vaccinated with safety follow-up †For oral temperature: number of subjects with temperature data for women 27 through 45 years of age N = 640; for girls and women 16 through 26 years of age, N = 569		

Systemic and Injection-Site Adverse Reactions in Boys and Men

An uncontrolled clinical trial with 662 boys and 1 923 girls 9 through 15 years of age (Protocol 002) was conducted. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 5.

An uncontrolled clinical trial with 1 394 boys and men and 1 075 girls and women 16 through 26 years of age (Protocol 003) was also conducted. Solicited and unsolicited adverse reactions reported by boys and men 16 through 26 years of age in this study are shown in Table 5.

Table 5 - Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 years of Age who Received GARDASIL®9

	GARDASIL®9
Boys and Men 16 through 26 years of age	**N = 1 394**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain	63.4
Injection-Site Erythema	20.7
Injection-Site Swelling	20.2
Oral Temperature ≥37.8°C†	4.4
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hypersensitivity	1.0
Injection-Site Pruritus	1.0
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	7.3
Pyrexia	2.4
Fatigue	1.4
Dizziness	1.1
Nausea	1.0
Boys 9 through 15 years of age	**N = 662**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain	70.2
Injection-Site Erythema	24.2
Injection-Site Swelling	26.0
Oral Temperature ≥37.8°C†	10.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hematoma	1.2
Injection-Site Induration	1.1
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	9.1
Pyrexia	8.6
Nausea	1.2

The data for GARDASIL®9 boys 9 through 15 years of age are from Protocol 002. The data for boys and men 16 through 26 years of age for GARDASIL®9 are from Protocol 003.

*Unsolicited adverse reactions reported by ≥1% of individuals

N = number of subjects vaccinated with safety follow-up

†For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N = 660; for boys and men 16 through 26 years of age, N = 1 386.

Serious Adverse Events in Clinical Studies of GARDASIL®9

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. The vaccine-related serious adverse events that occurred during the study period were pyrexia, allergy to vaccine, asthmatic crisis, and headache. No vaccine-related deaths were reported.

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. Three (0.5%) individuals who received GARDASIL®9 discontinued due to adverse reactions. No individuals who received placebo 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 6.

Table 6 - 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 with safety follow-up

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 Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)]; or Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] and Menactra* [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.

Clinical Trials Experience of GARDASIL®9 in Pregnancy
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 24 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.

For pregnancies with estimated onset within 30 days of vaccination, the proportion of pregnancies that resulted in a spontaneous abortion out of the total number of pregnancies with a known outcome (excluding elective terminations) was 27.4% (17/62) and 12.7% (7/55) in women who received GARDASIL®9 or GARDASIL®, respectively. For pregnancies with estimated onset more than 30 days following vaccination, that proportion was 10.9% (105/960) and 14.6% (136/933) in women who received GARDASIL®9 or GARDASIL®, respectively.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics
The safety profile of GARDASIL®9 is consistent between children and adults (see 8.2 Clinical Trial Adverse Reactions).

8.5 Post-Market Adverse Reactions

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

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

Gastrointestinal disorders
Vomiting

General disorders and administration site conditions
Injection-site nodule

Nervous system disorders
Syncope sometimes accompanied by tonic-clonic movements

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL® and remain relevant to GARDASIL®9:

Blood and lymphatic system disorders
Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy

Gastrointestinal disorders
Pancreatitis

General disorders and administration site conditions
Asthenia, chills, death, malaise

Immune system disorders
Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria

Infections and infestations
Cellulitis

Musculoskeletal and connective tissue disorders
Arthralgia, myalgia

Nervous system disorders
Acute disseminated encephalomyelitis, Guillain-Barré syndrome, motor neuron disease, paralysis, transverse myelitis

Respiratory, thoracic and mediastinal disorders
Pulmonary embolus

Vascular disorders

Deep venous thrombosis

9 Drug Interactions

9.2 Drug Interactions Overview

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] and 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) (Tdap-IPV)] (see 14 Clinical Trials).

Use with Hormonal Contraceptives
In 7 269 women (aged 16 through 26 years, 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 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 Warnings and Precautions, 7.1 Special Populations).

9.5 Drug-Food Interactions
Interactions with food have not been established.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action
Efficacy of GARDASIL® 9 against anogenital diseases related to the vaccine HPV types is thought to be mediated by humoral immune responses induced by the vaccine. The exact mechanism of protection is unknown.

HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (vs. types 6, 11, 16, and 18) cause approximately 90% (vs. 70%) of cervical cancers, 75 - 85% (vs. 50%) of cervical precancerous lesions, and 50 - 60% (vs. 30 - 35%) of low-grade cervical lesions, respectively. Among HPV-related cases, these HPV types also cause 85 - 90% (vs. 70 - 75%) of vulvar cancers, 80 - 85% (vs. 65%) of vaginal cancers, 90 - 95% (vs. 85 - 90%) of anal cancers, and at least 75% (vs. 60%) of these cancers' precursor lesions as well as 95% (vs 85%) of oropharyngeal cancers.

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 infection can also cause non-malignant lesions. HPV types 6 and 11 cause 90% of genital warts (condyloma acuminata) and 90% of recurrent respiratory papillomatosis (RRP) cases. These conditions rarely progress to cancer, but are associated with significant morbidity and psychosocial impacts, including a low health related quality of life.

10.2 Pharmacodynamics

Duration of Effect

Duration of effectiveness of GARDASIL®9 has been observed up to 8.2 years and 9.5 years in 9 to 15-year-olds and 16 to 26-year-olds postdose 3, respectively. Persistence of immune response has been observed for up to 7 years and 5 years in 9 to 15-year-olds and 16 to 26-year-olds postdose 3, respectively.

11 Storage, Stability, and Disposal

Store refrigerated at 2° to 8°C. 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.

12 Special Handling Instructions

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART 2: Scientific Information

13 Pharmaceutical Information

Drug Substance
Human Papillomavirus 9-valent Vaccine, Recombinant

Product Characteristics:
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 preformed 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 and the final purification buffer.

After thorough agitation, GARDASIL®9 is a white, cloudy liquid.

14 Clinical Trials

14.1 Clinical Trials by Indication

Study Results
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®
Efficacy of GARDASIL® 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, and 3 817 women 24 through 45 years of age).

Individuals 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 (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 7). In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination appears to be 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) appears to be protected from reinfection or recurrence of infection leading to clinical disease with the same HPV type. There was no evidence of protection from disease caused by vaccine HPV types for which individuals were PCR positive and seropositive at baseline.

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 7). 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 7).

Table 7 - Analysis of Efficacy of GARDASIL® in the PPE* Population of 16- through 26-Year-Old Subjects 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	8 493	2	8 464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7 772	0	7 744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7 772	0	7 744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7 864	9	7 865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7 900	2	7 902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6 932	2	6 856	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	1 394	3	1 404	32	90.6 (70.1, 98.2)
Condyloma	1 394	3	1 404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1 394	0	1 404	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)

*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 7 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.

Individuals 24 through 45 Years of Age

GARDASIL® was highly efficacious in reducing the combined incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18, which was primarily driven by prevention of persistent infection (Table 8). 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 (Table 8).

Table 8 - Analysis of Efficacy of GARDASIL® in the PPE* Population of 24- Through 45-Year-Old Women for Vaccine HPV Types

Endpoint		GARDASIL®		AAHS Control		% Efficacy (95% CI)
		N	Number of cases	N	Number of cases	
HPV 6-, 11-, 16-, or 18-related Persistent Infection, CIN (any grade), or EGL		1 601	10**	1 599	86	88.7 (78.1, 94.8)
HPV 6-, 11-, 16-, or 18-related	Persistent Infection	1 581	9	1 586	85	89.6 (79.3, 95.4)
	CIN 1	1 581	0	1 584	15	100.0 (72.1, 100.0)
	CIN 2/3 or AIS	1 581	1	1 584	6	83.3 (-37.6, 99.6)
	Condyloma	1 600	0	1 599	7	100.0 (30.8, 100.0)
	VIN 1 or VaIN 1	1 600	0	1 599	1	100.0 (-3 796.0, 100.0)
	VIN 2/3 or VaIN 2/3	1 600	0	1 599	0	not applicable
HPV 16- or 18-related Persistent Infection, CIN (any grade), or EGL		1 587	8**	1 571	51	84.7 (67.5, 93.7)

*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).
**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.
N = Number of individuals with at least 1 follow-up visit after Month 7.
CI = Confidence Interval.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Effectiveness of GARDASIL® in men 27 through 45 years of age is inferred from efficacy data in women 24 through 45 years of age as described above. In addition, a published study provided immunogenicity data in 150 men, 27 through 45 years of age who received a 3-dose regimen of GARDASIL® (0, 2, 6 months)[1].

[1] Giuliano AR, Isaacs-Soriano K, Torres BN, Abrahamsen M, Ingles DJ, Sirak BA, et al. Immunogenicity and safety of Gardasil among mid-adult aged men (27-45 years) - The MAM Study. Vaccine. 2015 Oct 13;33(42):5640-6.

Long-term follow-up studies

A subset of subjects who received 3 doses were followed up for an extended period 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; 9.5 years in boys and men, 16 through 26 years of age at time of vaccination, and 9.5 years in women, 24 through 45 years of age at time of vaccination.

In a selection of subjects in the PPE population of a registry-based extension of a base clinical trial, no cases of HPV 16/18-related high grade CIN were reported postdose 3 of GARDASIL® during a period with a median length of 11.8 years (range from 3.7 to 14 years) in 16-23 year old females (N = 2,121; 24,099 person-years at risk). In a selection of subjects in the PPE population of long-term extension of clinical studies, no cases of HPV 6-, 11-, 16-, or 18-related high-grade anogenital dysplasia and/or external genital lesions were observed postdose 3 of GARDASIL® during a period with a median length of 9.5 years (range from 3.1 to 11.4 years) in 16-26 year old men (N = 732; 6,538 person-year at risk); no cases of HPV 6-, 11-, 16-, or 18-related cervical dysplasia or external genital warts during a period with a median length of 9.1 years (range from 5.5 to 10.1 years) in 24-45 year old women (N = 601; 5,390 person-years at risk).

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

Table 9 - Summary of patient demographics from clinical trials that contributed efficacy data

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
001	Randomized, double-blind, multicenter, international, controlled with GARDASIL®, dose-ranging safety, immunogenicity and efficacy study of GARDASIL®9	(1) GARDASIL®9 (N = 7 099) (2) GARDASIL® (N = 7 105) Intramuscular injection 3 doses of 0.5 mL	14 215	Females: 21.9 years (16 to 26 years)	Females N = 14 215

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL®9 were assessed in eight 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 demonstrated comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of GARDASIL®9 compared with GARDASIL® (Protocol 001 and 009).

The analysis of efficacy for GARDASIL®9 was evaluated in the per-protocol efficacy population (PPE) 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 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 girls and boys 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 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 1 month postdose 3 Month 7.

P001 evaluated immunogenicity of GARDASIL®9 and efficacy 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. P002 evaluated immunogenicity of GARDASIL®9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Protocol 009 evaluated immunogenicity of GARDASIL®9 compared with GARDASIL® in girls 9 through 15 years of age. 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 (N = 2 515: 1 103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1 099 women receiving GARDASIL®9). P006 evaluated administration of GARDASIL®9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL®. Protocol 005 and Protocol 007 evaluated GARDASIL®9 concomitantly administered with Menactra* and Adacel*; or Repevax*, respectively, in girls and boys 11 through 15 years of age. Together, these seven clinical trials 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 race distribution of the 16 through 26-year-old girls and women in the clinical trials was as follows: 56.2% White; 25.4%

Other; 14.7% Asian; and 3.7% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 63.2% White; 16.2% Other; 14.6% Asian; and 5.9% Black. The race distribution of the 9- through 15 year-old boys in the clinical trials was as follows: 57.2% White; 24.0% Other; 14.6% Asian; and 4.1% Black. In Protocol 003, the race distribution was as follows: 16- through 26-year-old boys and men: 61.9% White; 22.7% Other; 9.8% Asian; and 5.5% Black; 16-through 26-year-old girls and women: 60.4% White; 23.7% Other; 10.0% Asian; and 5.9% Black.

One additional immunological bridging study was conducted. Protocol 004 evaluated immunogenicity of GARDASIL®9 in girls and women 16 through 26 years of age compared to women 27 through 45 years of age (N = 1 210: 640 women 27 through 45 years and 570 girls and women 16 through 26 years). In Protocol 004, the race distribution was as follows: women 27 through 45 years of age: 97.7% White, 1.6% Asian, 0.3% Other or Multiracial, 0.5% Black; girls and women 16 through 26 years of age : 94.6% White, 3.0% Asian, 1.6% Other or Multiracial, 0.9% Black.

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 9 through 14 years of age; 451 boys 9 through 14 years of age; and 314 girls and women 16 through 26 years of age). 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.

Anogenital Indication

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

Studies Supporting the 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 with a median duration of follow-up of 40 months post-dose 3 (range 0 to 64 months) after the last vaccination.

The primary efficacy was 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 CIN 1, 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 10). 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 10.

Table 10 - 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[†] = 7 099		GARDASIL® N[†] = 7 105		%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	6 016	1	6 017	30	96.7[Þ] (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5 948	1	5 943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5 948	1	5 943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6 009	1	6 012	16	93.8 (61.5, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months[§]	5 939	35	5 953	810	96.0 (94.4, 97.2)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months[¶]	5 939	21	5 953	544	96.3 (94.4, 97.7)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap[#] Abnormality	5 881	35	5 882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6 016	7	6 017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapy	6 012	4	6 014	32	87.5 (65.7, 96.0)

*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 who remained PCR negative to the relevant HPV type(s) and 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
[‡]Number of individuals contributing to the analysis
[§]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
[Þ]p-value<0.0001
CI = Confidence Interval
ASC-US = Atypical squamous cells of undetermined significance
HR = High-Risk

At the end of study, efficacy analyses were conducted in the efficacy substudy cohort with a median follow-up time of 3.5 years post-dose 3 (with a range of 0.0 to 5.6 years). For the HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer, there was 1 case in the GARDASIL®9 group and 38 cases in the GARDASIL® group representing an efficacy of 97.4%. With respect to 12 month persistent infection, there were 23 cases in the GARDASIL®9 group and 657 cases in the GARDASIL® group representing an efficacy of 96.7%. There were 37 cases in the GARDASIL®9 group and 506 cases in the GARDASIL® group of HPV31-, 33-, 45-, 52- and 58-related Pap test abnormalities representing an efficacy of 92.9%. There were 4 cases in the GARDASIL®9 group and 41 cases in the GARDASIL® group of HPV 31-, 33-, 45-, 52- and 58-related cervical definitive therapy representing an efficacy of 90.2%.

Immunogenicity

Table 11 - Summary of patient demographics from clinical trials that contributed immunogenicity data

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
001	Randomized, double-blind, multicenter, international, controlled with GARDASIL®, dose-ranging safety, immunogenicity and efficacy study of GARDASIL®9	(1) GARDASIL®9 (N = 7 099) (2) GARDASIL® (N = 7 105) Intramuscular injection 3 doses of 0.5 mL	14 215	Females: 21.9 years (16 to 26 years)	Females N = 14 215
002	International, multicentered, immunogenicity, safety, and manufacturing consistency study of GARDASIL®9	All subjects received GARDASIL®9 N = 3 066 Intramuscular injection 3 doses of 0.5 mL	3 074	Females: 11.6 years (9 to 15 years) Males: 11.7 years (9 to 15 years) Females: 21.3 years (16 to 26 years)	Females: 2 405 Males: 669
003	Open-label, international, multicenter, immunogenicity and safety of GARDASIL®9	All subjects received GARDASIL®9 N = 2 515 Intramuscular injection 3 doses of 0.5 mL	2 520	Females: 21.3 years (16 to 26 years) Males (HM and MSM): 21.1 years (16 to 26 years) 20.8 years (HM) (16 to 26 years) 22.2 years (MSM) (16 to 26 years)	Females: 1 101 Males: 1 419 (HM: 1 106; MSM: 313)
004	Open-label, immunogenicity and safety study of GARDASIL®9 in Adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds).	All subjects received GARDASIL®9 (N = 1 210) 27 to 45-year-olds (N = 640) 16 to 26-year-olds (N = 570) Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9	1 212	Females: 21.6 years (16 to 26 years) Females: 35.8 years (27 to 45 years)	Females: 1 212 27 to 45-year-olds: (642) 16 to 26-year-olds: (570)

005	Open-label, randomized, immunogenicity and safety study of GARDASIL®9 given concomitantly with Menactra* and Adacel*	All subjects received GARDASIL®9 (N = 1 237) Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9	1 241	Females: 12.1 years (11 to 15 years) Males: 12.2 years (11 to 15 years)	Females: 620 Males: 621
006	Randomized, placebo-controlled, double-blind safety and immunogenicity study of GARDASIL®9 in prior GARDASIL® recipients	GARDASIL®9 (N = 615) Placebo (N = 306) Intramuscular injection 3 doses of 0.5 mL	924	Females: 19.0 years (12 to 26 years)	Females: 924
007	Open-label, randomized, immunogenicity and safety study of GARDASIL®9 given concomitantly with Repevax*	All subjects received GARDASIL®9 N = 1 053 Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9	1 054	Females: 12.4 years (11 to 15 years) Males: 12.4 years (11 to 15 years)	Females: 528 Males: 526
009 /GDS01 C	Randomized, GARDASIL®-controlled, double-blind immunogenicity and safety study of GARDASIL®9	GARDASIL®9 (N = 300) GARDASIL® (N = 300) Intramuscular injection 3 doses of 0.5 mL	600	Females: 12.6 years (9 to 15 years)	Females: 600
010	Open label, randomized, safety and immunogenicity of GARDASIL®9 (2-dose versus 3 dose)	All subjects received GARDASIL®9 N = 1 516 Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9 2 doses of 0.5 mL of GARDASIL®9	1 516	Females: 11.4 years (9 to 14 years) 21.0 years (16 to 26 years) Males: 11.5 (9 to 14 years)	Females: 1 065 Males: 451
HM = heterosexual men; MSM = men who have sex with men					

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.

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).

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre-specified serostatus cutoff for a given HPV type (Table 12). The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of Competitive Luminex Immunoassay (cLIA).

Table 12 - Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL®9 HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/mL)	cLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8
*mMU = milli-Merck Units		

Studies Supporting the Efficacy of GARDASIL®9 Against HPV Types 6, 11, 16, 18

GARDASIL®9 efficacy against HPV 6-, 11-, 16-, and 18-related infection and disease was inferred from comparative studies to the quadrivalent (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 (N = 13 587), and 9- through 15-year-old girls from Protocol 009 (N = 600). The primary analyses were conducted in the per-protocol immunogenicity population.

A statistical analysis of non-inferiority was performed based on Month 7 comparing 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® (Tables 13 and 14). 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 13 - Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the PPI* Population of 9- through 15-Year-Old Girls

9- through15-year-old girls	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	300 (273)	100 (98.7, 100)	1 679.4 (1 518.9, 1 856.9)	300 (261)	100 (98.6, 100)	1 565.9 (1 412.2, 1 736.3)	1.07	(0.93, 1.23)
Anti-HPV 11	300 (273)	100 (98.7, 100)	1 315.6 (1 183.8, 1 462.0)	300 (261)	100 (98.6, 100)	1 417.3 (1 274.2, 1 576.5)	0.93	(0.80, 1.08)
Anti-HPV 16	300 (276)	100 (98.7, 100)	6 739.5 (6 134.5, 7 404.1)	300 (270)	100 (98.6, 100)	6 887.4 (6 220.8, 7 625.5)	0.97	(0.85, 1.11)
Anti-HPV 18	300 (276)	100 (98.7, 100)	1 956.6 (1 737.3, 2 203.7)	300 (269)	100 (98.6, 100)	1 795.6 (1 567.2, 2 057.3)	1.08	(0.91, 1.29)

*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, and 18) prior to dose 1. 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

#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

Table 14 - Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the PPI* Population of 16- through 26-Year-Old Girls and Women

16- through 26-year-old girls and women	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	6 792 (3 993)	99.8 (99.6, 99.9)	893.1 (871.7, 915.1)	6 795 (3 975)	99.8 (99.7, 99.9)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06)
Anti-HPV 11	6 792 (3 995)	100 (99.9, 100)	666.3 (649.6, 683.4)	6 795 (3 982)	99.9 (99.8, 100)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83)
Anti-HPV 16	6 792 (4 032)	100 (99.9, 100)	3 131.1 (3 057.1, 3 206.9)	6 795 (4 062)	100 (99.8, 100)	3 156.6 (3 082.3, 3 232.7)	0.99	(0.96, 1.03)
Anti-HPV 18	6 792 (4 539)	99.8 (99.7, 99.9)	804.6 (782.7, 827.1)	6 795 (4 541)	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, 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 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.

†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

#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

In addition, a published study provided immunogenicity data in 500 heterosexual men, 16 through 26 years of age who received a 3-dose regimen of GARDASIL® or GARDASIL®9 (0, 2, 6 months)[2].

Study Supporting the Effectiveness of GARDASIL®9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys

Effectiveness of GARDASIL®9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison in Protocol 002 of GMTs following vaccination with GARDASIL®9 among 9- through 15-year-old girls and boys with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 15).

[2] Van Damme P, Meijer CJ, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, et al. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-12.

Table 15 - Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old, Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL®9 Vaccine HPV Types

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT ratio¶ relative to 16-through 26-year-old girls and women (95% CI)
Anti-HPV 6					
9- through 15-year-old girls	646	517	99.8 (98.9,100)	1 715.4 (1 595.1, 1 844.7)	1.90 (1.70, 2.14)
9- through 15-year-old boys	666	559	99.8 (99.0, 100)	2 084.7 (1 944.0, 2 235.7)	2.31 (2.07, 2.59)
16- through 26-year-old women	468	328	99.7 (98.3, 100)	900.8 (822.3, 986.9)	1
Anti-HPV 11					
9- through 15-year-old girls	646	517	100 (99.3, 100)	1 295.1 (1 204.1, 1 393.0)	1.83 (1.63, 2.06)
9- through 15-year-old boys	666	559	100 (99.3, 100)	1 487.1 (1 386.5, 1 595.0)	2.10 (1.88, 2.36)
16- through 26-year-old women	468	332	100 (98.9, 100)	706.6 (645.2, 773.8)	1
Anti-HPV 16					
9- through 15-year-old girls	646	529	100 (99.3, 100)	6 979.8 (6 508.1, 7 485.8)	1.98 (1.77, 2.22)
9- through 15-year-old boys	666	569	100 (99.4, 100)	8 628.9 (8 065.9, 9 231.3)	2.45 (2.19, 2.74)
16- through 26-year-old women	468	329	100 (98.9, 100)	3 522.6 (3 223.5, 3 849.5)	1
Anti-HPV 18					
9- through 15-year-old girls	646	531	99.8 (99.0, 100)	2 153.7 (1 980.4, 2 342.1)	2.44 (2.13, 2.80)
9- through 15-year-old boys	666	567	100 (99.4, 100)	2 822.8 (2 602.8, 3 061.5)	3.20 (2.80, 3.65)
16- through 26-year-old women	468	345	99.7 (98.4, 100)	882.7 (795.4, 979.5)	1
Anti-HPV 31					
9- through 15-year-old girls	646	522	100 (99.3, 100)	1 891.6 (1 745.7, 2 049.7)	2.51 (2.21, 2.85)
9- through 15-year-old boys	666	564	100 (99.3, 100)	2 221.2 (2 056.1, 2 399.5)	2.95 (2.60, 3.34)
16- through 26-year-old women	468	340	99.7 (98.4, 100)	753.9 (682.5, 832.7)	1
Anti-HPV 33					
9- through 15-year-old girls	646	534	100 (99.3, 100)	980.4 (911.7, 1 054.3)	2.10 (1.87, 2.36)
9- through 15-year-old boys	666	567	100 (99.4, 100)	1 198.7 (1 117.1, 1 286.2)	2.57 (2.29, 2.88)
16- through 26-year-old women	468	354	99.7 (98.4, 100)	466.8 (426.9, 510.3)	1
Anti-HPV 45					
9- through 15-year-old girls	646	534	99.8 (99.0, 100)	714.4 (651.9, 782.8)	2.62 (2.27, 3.03)
9- through 15-year-old boys	666	570	100 (99.4, 100)	907.0 (830.2, 991.0)	3.33 (2.89, 3.84)
16- through 26-year-old women	468	368	99.5 (98.1, 99.9)	272.2 (243.8, 303.9)	1
Anti-HPV 52					
9- through 15-year-old girls	646	533	100 (99.3, 100)	932.9 (864.8, 1 006.4)	2.22 (1.97, 2.51)
9- through 15-year-old boys	666	568	100 (99.4, 100)	1 037.8 (964.4, 1 116.9)	2.47 (2.19, 2.79)
16- through 26-year-old women	468	337	99.7 (98.4, 100)	419.6 (381.4, 461.5)	1
Anti-HPV 58					
9- through 15-year-old girls	646	531	100 (99.3, 100)	1 286.7 (1 195.7, 1 384.6)	2.18 (1.93, 2.45)
9- through 15-year-old boys	666	566	100 (99.4, 100)	1 567.7 (1 460.2, 1 683.1)	2.66 (2.37, 2.98)
16- through 26-year-old women	468	332	100 (98.9, 100)	590.5 (538.2, 647.9)	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 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] PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data are from Protocol 002.

†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 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- through 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. Anti-HPV GMTs at Month 7 among 16- through 26-year-old boys and men (HM) appeared non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 16). 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.

Table 16 - 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

	Comparison Group				Estimated Fold Difference Group A/ Group B (95% CI)
	16-26 year old males (HM) (Comparison Group A) (N = 1 103)		16-26 year old females (Comparison Group B) (N = 1 099)		
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	
Anti-HPV 6	847	782.0	708	703.9	1.11 (1.02, 1.21)
Anti-HPV 11	851	616.7	712	564.9	1.09 (1.00, 1.19)
Anti-HPV 16	899	3 346.0	781	2 788.3	1.20 (1.10, 1.30)
Anti-HPV 18	906	808.2	831	679.8	1.19 (1.08, 1.31)
Anti-HPV 31	908	708.5	826	570.1	1.24 (1.13, 1.37)
Anti-HPV 33	901	384.8	853	322.0	1.19 (1.10, 1.30)
Anti-HPV 45	909	235.6	871	185.7	1.27 (1.14, 1.41)
Anti-HPV 52	907	386.8	849	335.2	1.15 (1.05, 1.26)
Anti-HPV 58	897	509.8	839	409.3	1.25 (1.14, 1.36)

*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.

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

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

n = Number of subjects contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex Immunoassay.

HM = Heterosexual men.

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

Study Supporting the Effectiveness of GARDASIL®9 against Vaccine HPV Types in 27 -through 45-Year-Old Women

Effectiveness of GARDASIL®9 against persistent infection and disease related to vaccine HPV types in 27- through 45-year-old women was inferred based on non-inferiority of GMTs following vaccination with GARDASIL®9 in 27- through 45-year-old women compared to 16- through 26-year-old girls and women and demonstration of efficacy of GARDASIL® in girls and women 16 through 45 years of age.

Protocol 004 provided immunogenicity bridging between 27 through 45-year-old women and 16 through 26-year-old girls and women who received GARDASIL®9. Non-inferiority (defined as less than 2-fold decrease) was demonstrated at Month 7 for each of HPV 16, 18, 31,33, 45, 52 and 58 anti-HPV GMTs in women 27 through 45 years of age compared with girls and women 16 through 26 years of age, with GMT ratios between 0.66 and 0.73 (Table 17). These results support the efficacy of GARDASIL®9 in women 27 through 45 years of age.

Table 17 - Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 27 through 45-Year-Old Women and 16- through 26-Year-Old Girls and Women for 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				
27- through 45-year-old women	640	448	638.4 (594.9, 685.0)	N.D#
16- through 26-year-old girls and women	570	421	787.8 (732.5, 847.2)	N.D#
Anti-HPV 11				
27- through 45-year-old women	640	448	453.5 (424.1, 485.0)	N.D#
16- through 26-year-old girls and women	570	421	598.7 (558.7, 641.6)	N.D#
Anti-HPV 16				
27- through 45-year-old women	640	448	2 147.5 (2 001.1, 2 304.5)	0.70 (0.63, 0.77)
16- through 26-year-old girls and women	570	436	3 075.8 (2 863.4, 3 303.9)	1
Anti-HPV 18				
27- through 45-year-old women	640	471	532.1 (491.8, 575.7)	0.71 (0.64, 0.80)
16- through 26-year-old girls and women	570	421	744.5 (685.0, 809.1)	1
Anti-HPV 31				
27- through 45-year-old women	640	488	395.7 (367.0, 426.6)	0.66 (0.60, 0.74)
16- through 26-year-old girls and women	570	447	596.1 (551.1, 644.9)	1
Anti-HPV 33				
27- through 45-year-old women	640	493	259.0 (242.9, 276.1)	0.73 (0.67, 0.80)
16- through 26-year-old girls and women	570	457	354.5 (331.7, 378.9)	1
Anti-HPV 45				
27- through 45-year-old women	640	515	145.6 (134.4, 157.7)	0.68 (0.60, 0.76)
16- through 26-year-old girls and women	570	470	214.9 (197.7, 233.7)	1
Anti-HPV 52				
27- through 45-year-old women	640	496	244.7 (229.4, 261.0	0.71 (0.64, 0.78)
16- through 26-year-old girls and women	570	456	346.5 (324.0, 370.5)	1
Anti-HPV 58				
27- through 45-year-old women	640	478	296.4 (277.1, 317.0)	0.69 (0.63, 0.76)
16- through 26-year-old girls and women	570	451	428.0 (399.4, 458.6)	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 004.
†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 for HPV types 16, 18, 31, 33, 45, 52 and 58 required that the lower bound of the 95% CI of the GMT ratio be greater than 0.50 The Type I error of the non-inferiority comparisons across the seven HPV types was controlled to not exceed 0.025 (one-sided) without multiplicity adjustment since successful non-inferiority demonstration for all seven HPV types was required to declare the comparisons successful.
#N.D = Not Determined. GMT ratios were not calculated because non-inferiority comparison was not specified in the study protocol for HPV types 6 and 11.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers

Men 27 Years of Age and Older

GARDASIL®9 has not been studied in men 27 years of age and older. In men 27 years of age and older, efficacy of GARDASIL®9 is inferred based on (1) efficacy of GARDASIL® in girls and women 16 through 45 years of age, (2) efficacy of GARDASIL® in boys and men 16 through 26 years of age, (3) comparable efficacy of GARDASIL® and GARDASIL®9 in girls and women 16 through 26 years of age, (4) comparable immunogenicity of GARDASIL® and GARDASIL®9 in girls and women 9 through 26 years of age and (5) immunogenicity of GARDASIL® and GARDASIL®9 in boys and men 16 through 26 years of age.

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 18).

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 18). 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 girls and 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 18 - 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	GMT ratio relative to 16- through 26-year-old girls and women (95 % CI)
Anti-HPV 6				
9- through14-year-old girls (0, 6)†	301	258	1 657.9 (1 479.6, 1 857.6)	2.15 (1.83, 2.53)§
9- through 14-year-old boys (0, 6)†	301	263	1 557.4 (1 391.5, 1 743.1)	2.02 (1.73, 2.36)§
9- through14-year-old girls and boys (0, 12)†	300	257	2 678.8 (2 390.2, 3 002.1)	3.47 (2.93, 4.11)§
9- through14-year-old girls (0, 2, 6)†	300	254	1 496.1 (1 334.1, 1 677.8)	1.94 (1.65, 2.29)¶
16- through 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)	1
Anti-HPV 11				
9- through 14-year-old girls (0, 6)†	301	258	1 388.9 (1 240.4, 1 555.3)	2.39 (2.03, 2.82)§
9- through 14-year-old boys (0, 6)†	301	264	1 423.9 (1 273.2, 1 592.3)	2.45 (2.09, 2.88)§
9- through 14-year-old girls and boys (0, 12)†	300	257	2 941.8 (2 626.6, 3 294.9)	5.07 (4.32, 5.94)§
9- through 14-year-old girls (0, 2, 6)†	300	254	1 306.3 (1 165.5, 1 464.0)	2.25 (1.90, 2.66)¶
16- through 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)	1
Anti-HPV 16				
9- through 14-year-old girls (0, 6)†	301	272	8 004.9 (7 160.5, 8 948.8)	2.54 (2.14, 3.00)§
9- through 14-year-old boys (0, 6)†	301	273	8 474.8 (7 582.4, 9 472.3)	2.69 (2.29, 3.15)§
9- through 14-year-old girls and boys (0, 12)†	300	264	14 329.3 (12 796.4, 16 045.9)	4.54 (3.84, 5.37)§
9- through 14-year-old girls (0, 2, 6)†	300	269	6 996.0 (6 254.1, 7 825.8)	2.22 (1.89, 2.61)¶
16- through 26-year-old women (0, 2, 6)†	314	249	3 154.0 (2 807.1, 3 543.7)	1
Anti-HPV 18				
9- through 14-year-old girls (0, 6)†	301	272	1 872.8 (1 651.6, 2 123.6)	2.46 (2.05, 2.96)§
9- through 14-year-old boys (0, 6)†	301	272	1 860.9 (1 641.1, 2 110.2)	2.44 (2.04, 2.92)§
9- through 14-year-old girls and boys (0, 12)†	300	266	2 810.4 (2 474.9, 3 191.3)	3.69 (3.06, 4.45)§
9- through 14-year-old girls (0, 2, 6)†	300	270	2 049.3 (1 806.4, 2 324.8)	2.69 (2.24, 3.24)¶
16- through 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)	1
Anti-HPV 31				
9- through 14-year-old girls (0, 6)†	301	272	1 436.3 (1 272.1, 1 621.8)	2.51 (2.10, 3.00)§
9- through 14-year-old boys (0, 6)†	301	271	1 498.2 (1 326.5, 1 692.0)	2.62 (2.20, 3.12)§
9- through 14-year-old girls and boys (0, 12)†	300	268	2 117.5 (1 873.7, 2 393.1)	3.70 (3.08, 4.45)§
9- through 14-year-old girls (0, 2, 6)†	300	271	1 748.3 (1 548.1, 1 974.5)	3.06 (2.54, 3.67)¶
16- through 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)	1
Anti-HPV 33				
9- through 14-year-old girls (0, 6)†	301	273	1 030.0 (920.4, 1 152.7)	2.96 (2.50, 3.50)§
9- through 14-year-old boys (0, 6)†	301	271	1 040.0 (928.9, 1 164.3)	2.99 (2.55, 3.50)§
9- through 14-year-old girls and boys (0, 12)†	300	269	2 197.5 (1 961.9, 2 461.3)	6.31 (5.36, 7.43)§
9- through 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)	2.29 (1.95, 2.68)¶
16- through 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)	1
Anti-HPV 45				
9- through 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)	1.67 (1.38, 2.03)§
9- through 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)	1.65 (1.37, 1.99)§
9- through 14-year-old girls and boys (0, 12)†	300	268	417.7 (365.9, 476.9)	1.96 (1.61, 2.37)§
9- through 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)	3.10 (2.54, 3.77)¶

Table 18 - 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	GMT ratio relative to 16- through 26-year-old girls and women (95 % CI)
16- through 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)	1
Anti-HPV 52				
9- through 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)	1.60 (1.36, 1.87)§
9- through 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)	1.76 (1.51, 2.05)§
9- through 14-year-old girls and boys (0, 12)†	300	268	1 123.4 (1 008.1, 1 251.9)	3.08 (2.64, 3.61)§
9- through 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)	2.50 (2.12, 2.95)¶
16- through 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)	1
Anti-HPV 58				
9- through 14-year-old girls (0, 6)†	301	270	1 251.2 (1 119.6, 1 398.4)	2.55 (2.15, 3.01)§
9- through 14-year-old boys (0, 6)†	301	270	1 325.7 (1 186.2, 1 481.6)	2.70 (2.30, 3.16)§
9- through 14-year-old girls and boys (0, 12)†	300	265	2 444.6 (2 185.2, 2 734.9)	4.98 (4.23, 5.86)§
9- through 14-year-old girls (0, 2, 6)†	300	273	1 229.3 (1 100.7, 1 373.0)	2.50 (2.11, 2.97)¶
16- through 26-year-old women (0, 2, 6)†	314	261	491.1 (438.6, 549.8)	1

*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.
§Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
¶Exploratory analysis; criterion for non-inferiority was not pre-specified
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 Study 1 received all 3 vaccinations within a 1-year period, regardless of the time 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 4 DOSAGE AND ADMINISTRATION).

Persistence of Immune Response to GARDASIL®9

The persistence of antibody response following a complete schedule of vaccination with GARDASIL®9 was studied in two Protocols, Protocol 001 and Protocol 002. In both studies, Anti-HPV cLIA GMTs were highest at 1 month postdose 3 (Month 7) and decreased by approximately 70% at Month 12. In 16 through 26-year-old girls and women (Protocol 001), at Month 42, GMTs were approximately 10-20% of Month 7 GMTs and 78-100% of subjects were seropositive for each of the 9 vaccine HPV types. In 9- through15-year-old boys and girls (Protocol 002), at Month 90, GMTs were approximately 10-20% of Month 7 GMTs and 91-99% of subjects were seropositive for each of the 9 vaccine HPV types.

Administration of GARDASIL®9 to Individuals Previously Vaccinated with 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). 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.

Studies 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)]

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 1,237 boys and girls 11 through 15 years of age at enrollment. The race distribution of the study subjects was as follows: 47.4% White; 35.0% Multiracial; 9.6% American Indian or Alaska Native; 6.4% Black; 1.1% Asian; and 0.6% Native Hawaiian or Other Pacific Islander.

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) (Tdap-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) (Tdap-IPV)] (same visit, injections at separate sites) were evaluated in a study of 1053 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.

Head and Neck Indication

Effectiveness in Prevention of HPV-Related Oropharyngeal and Other Head and Neck Cancers
The effectiveness of GARDASIL®9 against oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, is based on the effectiveness of GARDASIL® and GARDASIL®9 to prevent persistent infection and anogenital disease caused by HPV types covered by the vaccine (see Tables 7, 8, 10 and 14).

Long-term effectiveness studies

A subset of subjects who received 3 doses were followed up for an extended period after GARDASIL® 9 vaccination for safety, immunogenicity and protection against clinical diseases related to HPV types 6/11/16/18/31/33/45/52/58.

In a selection of subjects in the PPE population in the long-term extension of Protocol 001 registry study, 1 case of HPV 16/18/31/33/45/52/58-related high-grade CIN was reported postdose 3 of GARDASIL®9 during a period with a median length of 6.7 years (range from 3.6 to 9.5years) in 16 to 26 year old females (N = 1 509; 9 378 person-years at risk). In a selection of subjects in the PPE population in the long-term extension of Protocol 002, no cases of HPV 16/18/31/33/45/52/58-related high-grade intraepithelial neoplasia or genital warts were identified postdose 3 of GARDASIL®9 during a period with a median length of 7.6 years (range from 3.5 to 8.2 years) in 9-15 year old girls (N = 856; 2 866 person-years at risk). *Note: the age of an individual stated above is the age at time of vaccination for the individual.*

15 Microbiology

No microbiological information is required for this vaccine.

16 Non-Clinical Toxicology

General Toxicology:
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.

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

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

Reproductive and Developmental Toxicology:
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.

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.

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

GARDASIL®9

[Human Papillomavirus 9-valent Vaccine, Recombinant]

This Patient Medication Information is written for the person who will be given **GARDASIL®9**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this vaccine. If you have more questions about this vaccine or want more information about **GARDASIL®9**, talk to a healthcare professional.

What GARDASIL®9 is used for:
GARDASIL®9 is a vaccine (injection/shot) that helps protect against some diseases caused by some types of Human Papillomavirus (HPV). GARDASIL®9 contains the same 4 HPV types (6, 11, 16, 18) as in GARDASIL® with 5 additional HPV types (31, 33, 45, 52, 58).

For the following indication GARDASIL®9 has been approved **with conditions** (Notice of Compliance with conditions (NOC/c)). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the vaccine works the way it should. For more information, talk to your healthcare professional.

GARDASIL®9, a vaccine (injection/shot) indicated for:

- Individuals 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:
    - Certain head and neck cancers, such as throat and back of mouth cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58

For the following indication GARDASIL®9 has been approved **without conditions**. This means it has passed Health Canada's review and can be bought and sold in Canada.

GARDASIL®9, a vaccine (injection/shot) indicated for:

- Individuals 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:
    - Cervical cancer (cancer of the lower end of the uterus or womb) caused by HPV types 16, 18, 31, 33, 45, 52, and 58
    - Vulvar (the outside of the female genital area) and vaginal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
    - 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
    - Abnormal and precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer) as found in a Pap test caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

- Abnormal and precancerous vaginal, vulvar (outside of the female genital area) and anal lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

These diseases have many causes. Most of the time, these diseases are caused by nine types of HPV: HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. GARDASIL®9 only protects against diseases caused by these nine types of HPV.

People cannot get HPV or any of these diseases from GARDASIL®9.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a vaccine in Canada.

Health Canada only gives an NOC/c to a vaccine that treats, prevents, or helps identify a serious or life-threatening illness. The vaccine must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the vaccine must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Vaccine makers must agree in writing to clearly state on the label that the vaccine was given an NOC/c, to complete more testing to make sure the vaccine works the way it should, to actively monitor the vaccine's performance after it has been sold, and to report their findings to Health Canada.

How GARDASIL®9 works:
When an individual receives the GARDASIL®9 vaccine, his/her immune system produces antibodies against the 9 HPV types contained in the vaccine. If that individual is exposed to one of these types, the antibodies may help defend against developing infection and related diseases.

About HPV
Human Papillomavirus (HPV) is a common virus. Without vaccination, the majority of sexually active people will catch HPV during their lifetime. While most infected people clear the virus, those who do not can develop HPV-related cancers and precancers, or genital warts. Many people who have HPV may not show any signs or symptoms. This means that they can transmit (pass on) the virus to others without knowing it.

HPV causes nearly 100% of cervical cancers. HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 specifically cause approximately 90% of cervical cancers and 75-85% of cervical precancers. These 9 types of HPV also cause at least 25% of HPV-related vulvar, 74% vaginal, 80 – 90% of anal cancers and precancers and 70% of certain head and neck cancers, such as throat and back of mouth cancers. Over 90% of genital warts are caused by HPV types 6 and 11.

Will GARDASIL®9 help me if I already have Human Papillomavirus?
GARDASIL®9 helps prevent the diseases caused by some types of papillomavirus but will not treat them. If you are already infected with one type of HPV contained in the vaccine, GARDASIL®9 will help protect you against the other eight types. Talk to your health-care provider for more information.

Use in children
GARDASIL®9 can be used in children as young as 9 years of age.

Use in pregnancy

Tell the doctor or health care professional if you or your child (the person getting GARDASIL®9), is pregnant or is planning to get pregnant.

You should not get GARDASIL®9 during pregnancy. If you plan to get pregnant or get pregnant, you should wait until you are no longer pregnant to complete your vaccine series.

In more than 1 000 pregnancies, women who were pregnant or became pregnant after getting GARDASIL®9 did not have a higher chance for miscarriages or babies with birth defects.

Pregnant women exposed to GARDASIL®9 are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594.

Use in breastfeeding
It is not known whether GARDASIL®9 is excreted in human milk. If you are breastfeeding, talk to your doctor or health care professional to see if you should be vaccinated with GARDASIL®9.

Use in geriatrics
GARDASIL®9 has not been studied in the elderly.

The ingredients in GARDASIL®9 are:
Medicinal ingredients: The main ingredients are highly purified inactive proteins (L1) that come from HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Non-medicinal ingredients: Amorphous aluminum hydroxyphosphate sulfate (AAHS Adjuvant), L-histidine, polysorbate 80, sodium borate, sodium chloride, and water for injection. GARDASIL®9 does not contain any preservatives.

GARDASIL®9 comes in the following dosage form:
- 0.5 mL single-dose prefilled syringes

Do not use GARDASIL®9 if:
Anyone with an allergic reaction to:
- A previous dose of GARDASIL®9
- A previous dose of GARDASIL®
- Any of the ingredients in the vaccine (listed in "What are the ingredients in GARDASIL®9" section).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child get GARDASIL®9. Talk about any health conditions or problems you may have, including if you:
- Are pregnant or planning to get pregnant. GARDASIL®9 is not recommended for use in pregnant women.
- Have immune problems, like HIV or cancer.
- Take medicines that affect the immune system.
- Have any illness with a fever over 37.8°C.
- Had an allergic reaction to a previous dose of GARDASIL®9 or GARDASIL®.
- Have a bleeding disorder and cannot receive injections in the arm.
- Take any medicines, even those you can buy over the counter.

The healthcare professional will help decide if you or your child should get the vaccine.

Other warnings you should know about:
GARDASIL®9:

- Does not remove the need for screening for cervical, vulvar, vaginal, anal, and certain head and neck cancers, such as throat and back of mouth cancers as recommended by a health care professional; women should still get routine cervical cancer screening.
- Does not protect the person getting GARDASIL®9 from a disease that is caused by other types of HPV, other viruses or bacteria.
- Does not treat HPV infection.
- Does not protect the person getting GARDASIL®9 from HPV types that he/she may already have; but most people do not have all types contained in the vaccine.

GARDASIL®9 may not fully protect each person who gets it.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Can you get GARDASIL®9 if you have already gotten GARDASIL®?
Talk to your health care professional to see if GARDASIL®9 is right for you.

Can you get GARDASIL®9 with other vaccines?
GARDASIL®9 can be given at the same time as:

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

How to take GARDASIL®9:

Usual dose:
GARDASIL®9 is a shot that is usually given in the arm muscle.

You or your child (the person getting GARDASIL®9) will receive 3 doses of the vaccine. Ideally the doses are given as:

- First dose: at a date you and your health-care provider choose
- Second dose: 2 months after the first dose (not earlier than one month after the first dose)
- Third dose: 6 months after the first dose (not earlier than 3 months after the second dose)

All three doses should be given within a 1-year period. Talk to your doctor for more information.

Alternatively, individuals 9 through 14 years of age may receive 2 doses of the vaccine.

- Dose 1: at a date you and your doctor or health care professional choose
- Dose 2: given between 5 and 13 months after first dose.

If the second vaccine dose is given earlier than 5 months after the first dose, a third dose should always be given.

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

course with GARDASIL®9.

Overdose:

If you think you, or a person you are caring for, have received too much GARDASIL®9, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:
Make sure the person getting GARDASIL®9 gets the complete vaccine series. This allows you or your child to get the full benefits of GARDASIL®9. If the person getting GARDASIL®9 misses a dose, tell the doctor or health care professional. Your doctor or health care professional will decide when to give the missed dose.

It is important that you follow the instructions of your doctor or health care professional regarding return visits for follow-up doses.

Possible side effects from using GARDASIL®9:
These are not all the possible side effects you may have when taking GARDASIL®9. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects seen with GARDASIL®9 are:

- pain, swelling, redness, itching, bruising, bleeding and a lump where you got the shot
- headache, fever, nausea, dizziness, tiredness, diarrhea, abdominal pain, sore throat

Fainting can happen after getting a HPV vaccine. Sometimes people who faint can fall and hurt themselves. For this reason, the health care professional may ask the person getting GARDASIL®9 to sit or lie down for 15 minutes after getting the vaccine. Some people who faint might shake or become stiff. The health care professional may need to treat the person getting GARDASIL®9.

Studies show that there was more swelling where the shot was given when GARDASIL®9 was given at the same time with other vaccines such as Repevax*, or Menactra* and/or Adacel*.

Tell the doctor or health care professional if you or your child has these problems because these may be signs of an allergic reaction:

- difficulty breathing
- wheezing (bronchospasm)
- hives
- rash

As with other vaccines, additional side effects that have been reported during general use for GARDASIL®9 are shown below. Side effects reported during the general use of GARDASIL® are also shown below. GARDASIL® side effects are reported as they may be relevant to GARDASIL®9 since the vaccines are similar in composition.

<u>GARDASIL®9</u>

- fainting sometimes accompanied with seizure-like movements
- vomiting

- lump where you got the shot

Additionally, the following side effects have been seen with the general use of GARDASIL®.

- swollen glands (neck, armpit, or groin), Guillain-Barré syndrome, joint pain, aching muscles, unusual tiredness, weakness, or confusion, chills, bad stomach ache, muscle weakness, leg pain, shortness of breath, generally feeling unwell, bleeding or bruising more easily than normal and skin infection.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting suspected side effects for vaccines
For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.
Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:
Store refrigerated at 2°C to 8°C. Do not freeze. Protect from light.
Keep out of reach and sight of children.

If you want more information about GARDASIL®9:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

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