PRODUCT MONOGRAPH

GARDASIL®

[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

Suspension for injection

Active Immunizing Agent

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GARDASIL®

[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intramuscular injection	Each 0.5 mL dose contains approximately: 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein.	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

GARDASIL® [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] is a recombinant, quadrivalent vaccine that protects against Human Papillomavirus (HPV). It is a sterile liquid suspension prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* (yeast) CANADE 3C-5 (Strain 1895) and self-assembled into VLPs.

INDICATIONS AND CLINICAL USE

GARDASIL® is a vaccine indicated in girls and women 9- through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, and 18 and the following diseases associated with the HPV types included in the vaccine:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- 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, and 18:

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

GARDASIL® is indicated in girls and women 9- through 26 years of age for the prevention of:
- Anal cancer caused by HPV types 16 and 18
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18

GARDASIL® is indicated in boys and men 9 through 26 years of age for the prevention of infection caused by HPV types 6, 11, 16, and 18 and the following diseases associated with the HPV types included in the vaccine:
- Anal cancer caused by HPV types16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18

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

Geriatrics (> 65 years of age):
The safety and efficacy of GARDASIL® have not been evaluated in adults above the age of 45 years.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substances or to any of the excipients of the vaccine. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL® should not receive further doses of GARDASIL®.

WARNINGS AND PRECAUTIONS

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

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

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

GARDASIL® has not been shown to protect against diseases due to all HPV types.

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 vaccination with GARDASIL®. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL® (See ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Routine monitoring and Pap test in women should continue to be performed as indicated, regardless of GARDASIL® administration. Recipients of GARDASIL® should not discontinue anal cancer screening if it has been recommended by a health care provider. 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.

Immunocompromised individuals
Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization (see DRUG INTERACTIONS). No specific data are available from the use of GARDASIL® in these individuals.

Individuals with Bleeding Disorders
This vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder only if the benefit clearly outweighs the risk of bleeding following an intramuscular administration in these individuals.

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

Pregnant Women:
Studies in Female Rats
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. GARDASIL® induced a specific antibody response against HPV Types 6, 11, 16, and 18 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 4 HPV types were transferred to the offspring during gestation and possibly during lactation (see TOXICOLOGY, ANIMAL TOXICOLOGY, Reproductive Toxicology and Development Toxicology).

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

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL®. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL® were instructed to defer completion of their vaccination regimen until resolution of the pregnancy. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2 and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

Pregnant women exposed to GARDASIL® are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594 or the Vaccine Safety Section at Public Health Agency of Canada at 1-866-844-0018 or www.phac-aspc.gc.ca/im/vs-sv/index-eng.php.

During clinical trials, 3819 women (vaccine N = 1894 vs placebo N = 1925) reported at least one pregnancy. The overall proportions of pregnancies 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), were 22.6% (446/1973) in individuals who received GARDASIL® and 23.1% (460/1994) in individuals who received placebo.

Overall, 55 and 65 individuals in the group that received GARDASIL® or placebo, respectively (2.9% and 3.4% of all individuals who reported a pregnancy in the respective vaccination groups), experienced a serious adverse experience during pregnancy. The most common events reported were conditions that can result in Caesarean section (e.g., failure of labor, malpresentation, cephalopelvic disproportion), premature onset of labor (e.g., threatened abortions, premature rupture of membranes), and pregnancy-related medical problems (e.g., pre-eclampsia, hyperemesis). The proportions of pregnant individuals who experienced such events were comparable between the groups receiving GARDASIL® and placebo.

There were 45 cases of congenital anomaly in pregnancies that occurred in individuals who received GARDASIL® and 34 cases of congenital anomaly in pregnancies that occurred in individuals who received placebo.

Further sub-analyses were done to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL® or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL® compared to 1 case of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received GARDASIL® compared with 33 cases of congenital anomaly in the group that received placebo.

The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women aged 16 through 45 years.

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

GARDASIL® may be administered to lactating women.

GARDASIL® or AAHS control were given to a total of 1133 women (vaccine N = 582, placebo N = 551) during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

Overall, 27 and 13 infants of individuals who received GARDASIL® or placebo, respectively (representing 4.6% and 2.4% of the total number of individuals who were breast-feeding during the period in which they received GARDASIL® or placebo, respectively), experienced a serious adverse experience. None was judged by the investigator to be vaccine related.

In clinical studies, a higher number of breast-fed infants (n = 7) whose mothers received GARDASIL® had acute respiratory illnesses within 30 days post-vaccination of the mother as compared to infants (n = 2) whose mothers received AAHS placebo.

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

Geriatrics (> 65 years of age):
The safety and efficacy of GARDASIL® have not been evaluated in adults above the age of 45 years.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical trials, GARDASIL® was generally well tolerated when compared to placebo (Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS) Adjuvant or saline).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse drug reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

In 7 clinical trials (6 placebo-controlled), individuals were administered GARDASIL® or placebo on the day of enrollment, and approximately 2 and 6 months thereafter. In those clinical trials, a total of 15,706 individuals received GARDASIL® and 13,617 individuals received placebo. GARDASIL® demonstrated a favorable safety profile when compared with placebo (AAHS Adjuvant or saline). Few individuals (0.2%) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL® or placebo. The individuals who were monitored using VRC-aided surveillance included 10,088 individuals (6995 girls and women 9 through 45 years of age and 3093 boys and men 9 through 26 years of age at enrollment) who received GARDASIL® and 7995 individuals who received placebo.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are shown in Tables 1-2.

Table 1 - Vaccine-Related Injection-Site and Systemic Adverse Experiences in 9- Through 45-Year-Old Girls and Women*

Adverse Experience (1 to 5 Days Postvaccination)	**GARDASIL®** (N = 6995) %	**AAHS** Adjuvant-containing Placebo** (N = 5372) %	**Saline Placebo** (N = 320) %
Injection Site			
Pain	81.5	70.6	48.6
Swelling	23.5	14.2	7.3
Erythema	21.9	15.6	12.1
Pruritus	2.7	2.3	0.6
Hematoma	2.9	2.8	1.6
Adverse Experience (1 to 15 Days Postvaccination)	**GARDASIL®** (N = 6995) %	**Placebo** (N = 5692) %	
Systemic			
Headache	20.5	20.3	
Fever	10.1	8.7	
Nausea	3.7	3.4	
Dizziness	2.9	2.7	
Pain in extremity	1.5	1.0	

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.
**Amorphous aluminum hydroxyphosphate sulfate.

Of those girls and women who reported an injection site reaction, 94.2% judged their injection-site adverse reaction to be mild or moderate in intensity.

In addition, bronchospasm was reported very rarely as a serious adverse experience.

Table 2 - Vaccine-Related Injection-Site and Systemic Adverse Experiences in 9- Through 26-Year-Old Boys and Men*

Adverse Experience (1 to 5 Days Postvaccination)	**GARDASIL®** (N = 3,093) %	**AAHS** Adjuvant-containing Placebo** (N = 2,029) %	**Saline Placebo** (N = 274) %
Injection Site			
Pain	61.4	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2
Hematoma	1.0	0.3	3.3
Adverse Experience (1 to 15 Days Postvaccination)	**GARDASIL®** (N = 3,093) %	**Placebo** (N = 2,303) %	
Systemic			
Headache	7.5	6.7	
Fever	6.3	5.1	

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.
**Amorphous aluminum hydroxyphosphate sulfate.

Of those boys and men who reported an injection site reaction, 96.4% judged their injection-site adverse reaction to be mild or moderate in intensity.

All-cause Common Systemic Adverse Experiences
All-cause systemic adverse experiences for recipients of GARDASIL®, that were observed at a frequency of greater than or equal to 1% where the incidence in the vaccine group was greater than or equal to the incidence in the placebo group, are shown in Tables 3-4.

Table 3 - All-cause Common Systemic Adverse Experiences in Girls and Women 9 Through 45 Years of Age (GARDASIL® ≥ Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL®** (N = 6995) %	**AAHS control** or Saline Placebo** (N = 5692) %
Headache	28.1	28.1
Pyrexia	12.7	11.6
Nausea	5.9	5.5
Nasopharyngitis	5.8	5.8
Dizziness	4.0	3.9
Diarrhea	3.4	3.3
Pain in extremity	2.7	2.4
Abdominal pain upper	2.6	2.5
Vomiting	2.0	1.7
Cough	1.7	1.5
Myalgia	1.8	1.6
Upper respiratory tract infection	1.6	1.5
Toothache	1.5	1.4
Malaise	1.3	1.3
Arthralgia	1.1	0.9
Migraine	1.0	1.0
Nasal congestion	0.9	0.7
Insomnia	0.9	0.8

*The adverse reactions in this table are those that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Table 4: All-cause Common Systemic Adverse Experiences in Boys and Men 9 Through 26 Years of Age (GARDASIL® ≥ Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL®** (N = 3093) %	**AAHS control** or Saline Placebo** (N = 2303) %
Headache	12.3	11.2
Pyrexia	8.3	6.5
Oropharyngeal pain	2.8	2.1
Diarrhea	2.7	2.2
Nasopharyngitis	2.6	2.6
Nausea	2.0	1.0
Upper respiratory tract infection	1.5	1.0
Abdominal pain upper	1.4	1.4
Myalgia	1.3	0.7
Dizziness	1.2	0.9
Vomiting	1.0	0.8

*The adverse reactions in this table are those that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Serious Adverse Experiences in the Entire Study Population
A total of 258 individuals out of 29,323 total individuals (9- through 45-year-old girls and women, and 9- through 26-year-old boys and men) who received both GARDASIL® and placebo reported a serious systemic adverse experience following any vaccination visit during the clinical trials for GARDASIL®. Out of the entire study population (29,323 individuals), only 0.04% of the reported serious systemic adverse experiences were judged to be vaccine related by the study investigator. The most frequently reported serious systemic adverse experiences for GARDASIL® compared to placebo and regardless of causality were:

Headache	[0.02% GARDASIL® (3 cases) vs. 0.02% Placebo (2 cases)],
Gastroenteritis	[0.02% GARDASIL® (3 cases) vs. 0.02% Placebo (2 cases)],
Appendicitis	[0.03% GARDASIL® (5 cases) vs. 0.01% Placebo (1 case)],
Pelvic inflammatory disease	[0.02% GARDASIL® (3 cases) vs. 0.03% Placebo (4 cases)],
Urinary tract infection	[0.01% GARDASIL® (2 cases) vs. 0.02% Placebo (2 cases)],
Pneumonia	[0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)],
Pyelonephritis	[0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (3 cases)],
Pulmonary embolism	[0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)].

One case (0.006% GARDASIL®: 0.0% Placebo) of bronchospasm and 2 cases (0.01% GARDASIL®: 0.0% Placebo) of asthma were reported as serious systemic adverse experiences that occurred following any vaccination visit.

In addition, there was 1 individual in the clinical trials, in the group that received GARDASIL®, who reported two injection-site serious adverse experiences (injection-site pain and injection-site joint movement impairment).

Deaths in the Entire Study Population
Across the clinical studies, 39 deaths were reported in 29,323 (GARDASIL® N = 15,706; Placebo N = 13,617) individuals (9- through 45-year-old girls and women, and 9- through 26-year-old boys and men). The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident (5 individuals who received GARDASIL® and 4 individuals who received placebo), followed by drug overdose/suicide (2 individuals who received GARDASIL® and 6 individuals who received placebo), gun shot wound (1 individual who received GARDASIL® and 3 individuals who received placebo), and pulmonary embolus/deep vein thrombosis (1 individual who received GARDASIL® and 1 individual who received placebo). In addition, there were 2 cases of sepsis, 1 case of pancreatic cancer, 1 case of arrhythmia, 1 case of pulmonary tuberculosis, 1 case of hyperthyroidism, 1 case of post-operative pulmonary embolism and acute renal failure, 1 case of traumatic brain injury/cardiac arrest, 1 case of systemic lupus erythematosus, 1 case of cerebrovascular accident, 1 case of breast cancer, and 1 case of nasopharyngeal cancer in the group that received GARDASIL®; and 1 case of asphyxia, 1 case of acute lymphocytic leukemia, 1 case of chemical poisoning, and 1 case of myocardial ischaemia in the placebo group.

Systemic Autoimmune Disorders
In the clinical studies, male (ages 9 through 26) and female (ages 9 through 45) individuals were evaluated for new medical conditions that occurred over the course of follow up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL® or placebo are shown in Tables 5-6. This population includes all individuals who received at least one dose of GARDASIL® or placebo, and had safety data available.

Table 5 - Summary of Girls and Women 9 Through 45 Years of Age Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL® Regardless of Causality

Conditions	GARDASIL® (N = 12,613)	AAHS Control* or Saline Placebo (N = 11,314)
	n (%)	n (%)
Arthralgia/Arthritis/Arthropathy**	149 (1.2)	129 (1.1)
Autoimmune Thyroiditis	4 (0.0)	1 (0.0)
Coeliac Disease	10 (0.1)	6 (0.1)
Diabetes Mellitus Insulin-dependent	2 (0.0)	2 (0.0)
Erythema Nodosum	3 (0.0)	4 (0.0)
Hyperthyroidism***	33 (0.3)	28 (0.2)
Hypothyroidism†	51 (0.4)	63 (0.6)
Inflammatory Bowel Disease‡	10 (0.1)	10 (0.1)
Multiple Sclerosis	2 (0.0)	5 (0.0)
Nephritis¶	2 (0.0)	5 (0.0)
Optic Neuritis	2 (0.0)	0 (0.0)
Pigmentation Disorder§	5 (0.0)	3 (0.0)
Psoriasis#	13 (0.1)	15 (0.1)
Raynaud's Phenomenon	3 (0.0)	4 (0.0)
Rheumatoid Arthritis††	9 (0.1)	4 (0.0)
Scleroderma/Morphea	3 (0.0)	1 (0.0)
Stevens-Johnson Syndrome	1 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	1 (0.0)	3 (0.0)
Uveitis	4 (0.0)	1 (0.0)
All Conditions	307 (2.4)	284 (2.5)

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

**Arthralgia/Arthritis/Arthropathy includes the following terms: Arthralgia, Arthritis, Arthritis reactive, and Arthropathy

***Hyperthyroidism includes the following terms: Basedow's disease, Goitre, Toxic nodular goitre, and Hyperthyroidism

†Hypothyroidism includes the following terms: Hypothyroidism and thyroiditis

‡Inflammatory bowel disease includes the following terms: Colitis ulcerative, Crohn's disease, and Inflammatory bowel disease

¶Nephritis includes the following terms: Nephritis, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative

§Pigmentation disorder includes the following terms: Pigmentation disorder, Skin depigmentation, and Vitiligo

#Psoriasis includes the following terms: Psoriasis, Pustular psoriasis, and Psoriatic arthropathy

††Rheumatoid arthritis includes Rheumatoid arthritis and juvenile rheumatoid arthritis. One individual counted in the rheumatoid arthritis group reported rheumatoid arthritis as an adverse experience at Day 130.

N = Number of individuals enrolled

n = Number of individuals with specific new Medical Conditions

NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Table 6: Summary of Boys and Men 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL® Regardless of Causality

Conditions	GARDASIL® (N = 3093) n (%)	AAHS Control* or Saline Placebo (N = 2303) n (%)
Alopecia Areata	2 (0.1)	0 (0.0)
Ankylosing Spondylitis	1 (0.0)	2 (0.1)
Arthralgia/Arthritis/Reactive Arthritis	30 (1.0)	17 (0.7)
Autoimmune Thrombocytopenia	1 (0.0)	0 (0.0)
Diabetes Mellitus Type 1	3 (0.1)	2 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.0)
Hypothyroidism**	3 (0.1)	0 (0.0)
Inflammatory Bowel Disease***	1 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	4 (0.2)
Skin Depigmentation	1 (0.0)	0 (0.0)
Vitiligo	2 (0.1)	5 (0.2)
All Conditions	46 (1.5)	34 (1.5)

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**Hypothyroidism includes the following terms: Hypothyroidism and Autoimmune thyroiditis
***Inflammatory bowel disease includes the following terms: Colitis ulcerative and Crohn's disease
N = Number of individuals who received at least one dose of either vaccine or placebo.
n = Number of individuals with specific new Medical Conditions
NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Post-Market Adverse Drug Reactions

The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL®. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Infections and infestations: cellulitis

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

Respiratory, thoracic and mediastinal disorders: pulmonary embolus.

Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, syncope sometimes accompanied by tonic-clonic movements, transverse myelitis.

Gastrointestinal disorders: nausea, pancreatitis, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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

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

DRUG INTERACTIONS

Drug-Drug Interactions

Use with Other Vaccines
Results from clinical studies indicate that GARDASIL® may be administered concomitantly (at a separate injection site) with Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] (see CLINICAL TRIALS, Studies with Other Vaccines).

The frequency of adverse experiences observed, in a placebo-controlled study with concomitant administration with hepatitis B vaccine (recombinant), was similar to the frequency when GARDASIL® was administered alone.

In another placebo-controlled study, there was an increase in injection-site swelling when GARDASIL® was given concomitantly with Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap). The majority of injection-site swelling adverse experiences were reported as being mild to moderate in intensity.

Use with Common Medications
In clinical studies for girls and women (aged 16 to 26 years), 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. In a clinical study in women (aged 24 to 45 years), 30.6%, 20.2%, 11.6%, and 7.5% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. Conversely in a clinical study in boys and men (aged 16 to 26 years), 10.3%, 7.8%, 6.8%, 3.4% and 2.6% of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives
In clinical studies, 50.2% of women (aged 16 to 45 years) who received GARDASIL® used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL®.

Use with Steroids
In clinical studies for girls and women (aged 16 to 26 years), 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively. In a clinical study in women (aged 24 to 45 years), 1.4% (n = 27) used corticosteroids for systemic use. In a clinical study in boys and men (aged 16 to 26 years), 1.0% (n = 21) used corticosteroids for systemic use. The corticosteroids for all individuals were administered close to the time of administration of a dose of GARDASIL®. These medicines did not appear to affect the immune responses to GARDASIL®. Very few individuals in the clinical studies were taking steroids, and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications
There are no data on the concomitant use of potent immunosuppressants with GARDASIL®. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization (See WARNINGS AND PRECAUTIONS, General).

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

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

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established. There was no evidence from the clinical studies database of impact of GARDASIL® administration on the performance characteristics of the Pap test and some commercially available HPV tests.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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

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

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

Alternatively, in individuals 9 through 13 years of age, GARDASIL® can be administered according to a 2-dose (0, 6 months or 0, 12 months) schedule. The administration of the second dose at an interval of less than 6 months after the first dose has not been formally evaluated. If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should be considered.

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

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

The need for a booster dose has not been established.

Administration

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

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

The prefilled syringe is for single use only and should not be used for more than one individual. For single-use vials, a separate sterile syringe and needle must be used for each individual.

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

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

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

Instructions for Use

Single-Dose Vial Use

Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use

Inject the entire contents of the syringe.

OVERDOSAGE

There have been occasional reports of administration of higher than recommended doses of GARDASIL®.

In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL®.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Disease Burden

Cervical cancer is caused by different types of Human Papillomavirus (HPV) infection.[1,2,3,4,5] HPV causes squamous cell cervical cancer (and its histologic precursor lesions Cervical Intraepithelial Neoplasia [CIN] 1 or low grade dysplasia and CIN 2/3 or moderate to high grade dysplasia) and cervical adenocarcinoma (and its precursor lesion adenocarcinoma *in situ* [AIS]). HPV also causes approximately 35-50% of vulvar and vaginal cancers. Vulvar Intraepithelial Neoplasia (VIN) Grade 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) Grade 2/3 are immediate precursors to these cancers.[6,7,8]

HPV infection is very common.[9] Most HPV infections clear without sequelae but some progress to cervical cancer and/or other HPV-related diseases. It is estimated that 75% of sexually active Canadians will have at least one HPV infection during their lifetime,[10] with the highest prevalence observed in women aged 20-24 years.[11,12] Women remain at high risk for HPV acquisition and disease caused by HPV 6, 11, 16 and 18 up to the age of 45.[11,13,14] Men play an important role in transmission of HPV to their sexual partners. Several prospective studies have shown a high level of HPV concordance between couples who recently became infected, indicating transmission of HPV between the couples (male to female, and female to male). These data consistently support the sexually transmitted nature of HPV and the role of men in infecting women, who subsequently can develop HPV-related anogenital cancers and warts. Based on these various lines of evidence it is expected that decreasing the risk of HPV infection in men through vaccination should decrease the risk of infection in their sexual partners, thereby providing additional public health benefit.

Cervical cancer prevention focuses on routine screening and early intervention. This strategy has reduced cervical cancer rates by approximately 75% in compliant individuals by monitoring and removing premalignant dysplastic lesions.[12,15,16] In 2001, more than 1350 Canadian women were diagnosed with cervical cancer and 400 women died from it.[17] After breast cancer, cervical cancer is the most common cancer in Canadian women between the ages of 20 and 44.[18]

HPV also causes genital warts (condyloma acuminata) which are growths of the cervicovaginal, vulvar, perianal and intra-anal mucosa, and the external genitalia that rarely progress to cancer, but cause significant psychosocial impact and disease recurrence.[19] The lifetime risk for acquisition of genital warts has been estimated to exceed 10%.[20,21] The risk of acquisition of genital warts for both males and females is highest between the ages of 15-34, but the risk of incident infection remains throughout life.[22]

Based on two recent epidemiologic studies from BC and Manitoba, anogenital warts (AGWs) are associated with a significant burden of illness and costs to the Canadian healthcare system.[22,23] Of note is the similarity in findings between the two studies with respect to the incidence of genital warts. In BC overall incidence was found to be 1.26 per 1000 population, at an average cost of $190 per episode for treatment which, translates into approximately $1million in annual, direct medical costs.[23] Similarly, in Manitoba the incidence of genital warts in males was found to be 1.54 per 1000, whilst for females it was 1.23 per 1000,[22] resulting in an average cost of $200 per individual treated.[24] If the Manitoba rates are generalizable to Canada, then in 2006 (based 2004 Manitoba rates and the 2006 Canadian census population) there would have been 41,450 incident cases, 48,600 prevalent cases, and 617,950 people who had been diagnosed with AGWs since 1985.[22]

HPV infection is strongly associated with anal cancer. The great majority of anal cancers are squamous cell carcinoma (SCC). Anal canal SCC are HPV positive in 80 to 90% of cases in men and women. HPV 16 (73%) and HPV 18 (5%) are the most common associated types. Approximately 100,000 new cases of anal cancer are estimated to occur annually around the world and the rate of anal cancer cases has been increasing. There are no routine screening tests for this cancer in healthy people.

HPV is accepted as an important cause of head and neck cancer, and emerging data show an increase over the past several decades in the proportion of head and neck cancers caused by HPV. The majority of HPV-related head and neck cancers occur in the oropharynx, specifically in the tonsillar area of Waldeyer's Ring. Of oropharyngeal cancers, 60-70% are caused by HPV, and of these, approximately 90% are associated with HPV 16. Overall, approximately 2/3 of these cases occur in men. Oral HPV infection and seropositivity for HPV 16 have been associated with a significantly elevated risk for development of head and neck cancer.

HPV 6, 11, 16, and 18 are common HPV types.

HPV types 16 and 18 cause approximately:

- 70% of cervical cancer, AIS, and CIN 3 cases;
- 50% of CIN 2 cases;
- 70% of HPV-related vulvar and vaginal cancer, VIN 2/3, and VaIN 2/3 cases;
- 90% of HPV-related anal cancers;
- 70% of HPV-related AIN 2/3; and
- 60% of HPV-related penile cancers.

HPV types 6, 11, 16, and 18 cause approximately:

- 35 to 50% of all CIN 1, VIN 1, and VaIN 1 cases.

HPV types 6 and 11 cause approximately:

- 90% of genital wart cases; [2,25,26,27,28] and
- 9 to 12% of CIN 1 cases.

HPV type 16 causes approximately:

- 90% of HPV-related Oropharyngeal squamous cell carcinomas.

HPV 31, 33, 52, 56, 58, and 59 are high-risk HPV types. These types are responsible for:

- 11.6% of cervical cancer cases;
- 32.2% of CIN 1 cases;
- 39.3% of CIN 2 cases; and
- 24.3% of CIN 3 or AIS cases.

A recent Canadian study evaluated the prevalence of HPV in liquid-based specimens from a sample of 8700 women throughout British Columbia who were attending for routine cytology screening at high-volume primary care screening sites. This study found that HPV types 31, 33, 52 and 58 were responsible for:

- 9.8% of LSILs (Low grade Squamous Intraepithelial Lesion, encompassing: HPV/mild dysplasia/CIN I);
- 18.8% of HSILs (High grade Squamous Intraepithelial Lesion, encompassing: moderate and severe dysplasia, carcinoma in situ, CIN II and CIN III).[29]

Mechanism of Action

GARDASIL® contains L1 VLPs, which are proteins that resemble wild-type virions. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

HPV only infects humans, but animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

In preclinical studies, induction of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to the unvaccinated animals. These data suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.[30,31,32]

STORAGE AND STABILITY

Store refrigerated at 2°C to 8°C. Do not freeze. Protect from light.

GARDASIL® should be administered as soon as possible after being removed from refrigeration. GARDASIL® 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 discoloured.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GARDASIL® is a sterile preparation for intramuscular administration supplied as a 0.5-mL single-dose vial or a 0.5 mL single-dose prefilled Luer Lock syringe. After thorough agitation, GARDASIL® is a white, cloudy liquid.

COMPOSITION

Active Ingredients
GARDASIL® is a sterile preparation for intramuscular administration. Each 0.5 mL dose contains approximately 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, and 20 µg of HPV 18 L1 protein.

Inactive Ingredients
Each 0.5 mL dose of the vaccine contains approximately 225 µg of aluminum (as amorphous aluminum hydroxyphosphate sulfate [AAHS] adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.

PACKAGING

Vials
GARDASIL® is supplied in 3 mL single-dose Type I glass vials containing one 0.5 mL dose of liquid vaccine.

GARDASIL® is available in packages of 1 and 10 single-dose vials.

Syringes
GARDASIL® is supplied in 1.5 mL single-dose Type I glass prefilled Luer Lock syringes, containing one 0.5 mL dose of liquid vaccine in a carton. One needle is provided separately in the carton.

Vials and prefilled syringes components are latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

Product Characteristics

The quadrivalent Human Papillomavirus Virus-Like Particle vaccine (HPV VLP vaccine) is a sterile liquid suspension prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* (yeast) CANADE 3C-5 (Strain 1895) and self-assembled into VLPs. The VLPs for each type are purified and adsorbed on AAHS-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate). The quadrivalent HPV VLP vaccine is prepared by combining the adsorbed VLPs of each HPV type, the AAHS-containing adjuvant formulation, and a buffer.

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

CLINICAL TRIALS

Study demographics and trial design

Table 7 - Summary of patient demographics for clinical trials in HPV Disease Efficacy

Study #	Trial design	Dosage, route of administration and duration	Study individuals (N = number)	Mean age (Range)	Gender
005	Randomized, double-blind, multicenter, placebo-controlled trial	(1) HPV 16 L1 VLP vaccine (40 µg/0.5 mL) (2) Placebo Intramuscular injection 3 doses of 0.5 mL	Vaccine N = 1193 Placebo N = 1198	21.5 years (16 to 25 years)	Female
007	Part A: Randomized, double-blind, multicenter, placebo-controlled, dose-escalating trial	Part A: (1) placebo (225 µg/0.5 mL) (2) placebo (450 µg/0.5 mL) (3) GARDASIL® (20/40/40/20 µg/0.5 mL) (4) Quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine (40/40/40/40 µg/0.5 mL) (5) Quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine (80/80/40/80 µg/0.5 mL) Intramuscular injection 3 doses of 0.5 mL	Part A Placebo (225 µg/dose) N = 11 Placebo (450 µg/dose) N = 6 Vaccine (20/40/40/20 µg/dose) N = 13 Vaccine (40/40/40/40 µg/dose) N = 10 Vaccine (80/80/40/80 µg/dose) N = 12	Part A 20.5 years (18 to 23 years)	Female

Study #	Trial design	Dosage, route of administration and duration	Study individuals (N = number)	Mean age (Range)	Gender
007 (Cont'd)	Part B: Randomized, double-blind, multicenter, placebo-controlled, dose-ranging trial	Part B: (1) placebo (225 µg/0.5 mL) (2) placebo (450 µg/0.5 mL) (3) GARDASIL® (20/40/40/20 µg/0.5 mL) (4) Quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine (40/40/40/40 µg/0.5 mL) (5) Quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine (80/80/40/80 µg/0.5 mL) Intramuscular injection 3 doses of 0.5 mL	Part B Placebo (225 µg/dose) N = 135 Placebo (450 µg/dose) N = 140 Vaccine (20/40/40/20 µg/dose) N = 276 Vaccine (40/40/40/40 µg/dose) N = 272 Vaccine (80/80/40/80 µg/dose) N = 280	Part B 20.0 years (13 to 24 years)	Female
013 (FUTURE I)	Randomized, double-blind, placebo-controlled, multicenter, multinational trial	(1) GARDASIL® (20/40/40/20 µg/0.5 mL) (2) Placebo Intramuscular injection 3 doses of 0.5 mL	Vaccine N = 2717 Placebo N = 2725	20.3 years (16 to 24 years)	Female
015 (FUTURE II)	Randomized, double-blind, placebo-controlled, multicenter, multinational trial	(1) GARDASIL® (20/40/40/20 µg/0.5 mL) (2) Placebo Intramuscular injection 3 doses of 0.5 mL	Vaccine N = 6082 Placebo N = 6075	19.9 years (15 to 26 years)	Female

Study #	Trial design	Dosage, route of administration and duration	Study individuals (N = number)	Mean age (Range)	Gender
019 (FUTURE III)	Randomized, double-blind, placebo-controlled, multicenter, multinational trial	(1) GARDASIL® (20/40/40/20 µg/0.5 mL) (2) Placebo Intramuscular injection 3 doses of 0.5 mL	Vaccine N = 1910 Placebo N = 1907	34.3 years (21 to 46 years)	Female
020	Randomized, Double-blind, Placebo-controlled, Multicenter	(1) GARDASIL® (20/40/40/20 µg/0.5 mL) (2) Placebo Intramuscular injection 3 doses of 0.5 mL	Vaccine N = 2032 Placebo N = 2033	20.5 years (15-27 years)	Male

Study Results

Clinical Studies

In females, cervical intraepithelial neoplasia 2/3 (CIN 2/3) and cervical adenocarcinoma *in situ* (AIS) are the immediate and necessary precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, they serve as surrogate markers for the prevention of cervical cancer.

Vulvar intraepithelial neoplasia 2/3 (VIN 2/3) and vaginal intraepithelial neoplasia 2/3 (VaIN 2/3) are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.[33]

In men, up to 84% of penile/perineal/perianal intraepithelial neoplasia (PIN) 1 (low grade) and over 90% of PIN 3 (high grade) has been associated with HPV. HPV 16 is the most common type detected. Erythoplasia of Queyrat (EQ), Bowen's disease (BD), and bowenoid papulosis (BP) are clinical presentations of high-grade PIN. As high as 33% of BD and EQ have been associated with invasive cancer. BP rarely progresses to malignancy.

The efficacy of GARDASIL® was assessed in 6 placebo-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL® (Protocol 005, N = 2391 girls and women) and the second evaluated all components of GARDASIL® (Protocol 007, N = 551 girls and women). Two Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL® in 5442 (FUTURE I) and 12,157 (FUTURE II) 16- through 26-year-old girls and women. A third Phase III study, Protocol 020, evaluated GARDASIL® in 4055 16- through 26-year-old boys and men, including a subset of 598 (GARDASIL® = 299; placebo =

299) men who self-identified as having sex with men (MSM population). A fourth Phase III study (FUTURE III) evaluated GARDASIL® in 3817 24- through 45-year-old women. Together, these six studies evaluated 28,413 individuals (20,541 girls and women 16 through 26 years, 4055 boys and men 16 through 26 years, and 3817 women 24 through 45 years of age at enrollment). The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, 2.9, and 4.0 years for Protocol 005, Protocol 007, FUTURE I, FUTURE II, Protocol 020, and FUTURE III, respectively. Individuals received vaccine or placebo on the day of enrollment, and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies conducted in girls and women combined.

Overall, 73% of 16- through 26-year-old girls and women, 67% of 24- through 45-year-old women, and 83% of 16- through 26-year-old boys and men were naïve (i.e., PCR negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment. The naïve individuals continued to be at risk for infection and disease caused by all 4 vaccine HPV types.

A total of 27% of 16- through 26-year-old girls and women, 33% of 24- through 45-year-old women, and 17% of 16-through 26-year-old-boys and men had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types. Among these individuals, 74% of 16- through 26-year-old girls and women, 71% of 24- through 45-year-old women, and 78% of 16- through 26-year-old boys and men had evidence of prior exposure to or ongoing infection with only 1 of the 4 vaccine HPV types and were naïve (PCR negative and seronegative) to the remaining 3 types. Among 24- through 45-year-old subjects, only 0.4% had been exposed to all 4 vaccine HPV types. Among the 16- through 26-year-old boys and men, only 0.2% had been exposed to all 4 vaccine HPV types.

In individuals who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN, VaIN, PIN, and persistent infection caused by any of the 4 vaccine HPV types were counted as endpoints.

Among individuals who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy. Endpoints related to the remaining types for which the individual was naïve (PCR negative and seronegative) were counted.

For example, in individuals who were HPV 18 positive (PCR positive and/or seropositive) at Day 1, lesions caused by HPV 18 were not counted in the prophylactic efficacy evaluations. Lesions caused by HPV 6, 11, and 16 were included in the prophylactic efficacy evaluations. The same approach was used for the other types.

Definition of Clinical Trial Populations

The primary analyses of efficacy was conducted in the "per-protocol efficacy (PPE) population", consisting of individuals who received all 3 vaccinations within 1 year of enrollment, did not

have major deviations from the study protocol and were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit. In individuals who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, AIN, VIN and VaIN caused by any of the 4 vaccine HPV types were counted as endpoints. Among individuals who were positive (HPV positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy.

The "MITT-2 population" and the "HNRT population" consisted of individuals who were naïve to the relevant HPV types(s) (Types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and also individuals who became infected with a vaccine HPV type during the vaccination period. Cases were counted starting after Day 30 for MITT2 and Day 1 for HNRT.

The "HPV-naïve population" of 16- through 26-year-old girls and women consisted of individuals who received at least one dose of vaccine or placebo, had at least one follow-up visit post-Day 30, and were negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1, approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut. Cases were counted starting after Day 30. The "HPV-naïve population" of 16- through 26-year-old boys and men consisted of individuals who received at least one dose of vaccine or placebo, had at least one follow-up visit post-Day 30, and were negative to 14 common HPV types, approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut. Cases were counted starting after Day 1.

The "general study population" consisted of individuals who received at least one dose of vaccine or placebo and had at least one follow-up visit post-Day 30, regardless of baseline HPV status. Some individuals in this population had HPV-related disease at vaccination onset. Of the 16- through 26-year-old girls and women in this population, 12.5% had a positive Pap test; 15.0% were PCR positive; and 19.8% were seropositive to HPV types 6, 11, 16, or 18. Of the 16- through 26-year-old boys and men in this population, 12.2% were PCR positive and 7.6% were seropositive to HPV types 6, 11, 16, or 18. Cases were counted starting after Day 30 for the general study population of girls and women and after Day 1 for the general study population of boys and men.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Girls and Women

GARDASIL® is primarily designed to prevent cervical, vulvar, and vaginal cancers; cervical dysplasias; vulvar or vaginal dysplasias; or genital warts caused by HPV types 6, 11, 16, and 18. GARDASIL® was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of individuals regardless of baseline HPV status (i.e.,

Polymerase Chain Reaction [PCR] status or serostatus). Individuals who were infected with a particular vaccine HPV type (and who may already have had disease due to that infection) were not eligible for prophylactic efficacy evaluations for that type.

The primary analyses of efficacy with respect to HPV types 6, 11, 16, and 18 were conducted in the per-protocol efficacy (PPE) population, consisting 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 in cervicovaginal specimens 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). Efficacy was measured starting after the Month 7 visit.

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 in those who were PCR negative and seronegative at baseline (Table 8).

Table 8 - Analysis of Efficacy of GARDASIL® in the PPE* Population of 16- Through 26-Year-Old Girls and Women**

Population	GARDASIL®		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Protocol 005***	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (-3744.9, 100.0)
FUTURE I	2201	0	2222	36	100.0 (89.2, 100.0)
FUTURE II	5306	2†	5262	63	96.9 (88.2, 99.6)
Combined Protocols‡	8493	2†	8464	112	98.2 (93.5,99.8)
HPV 16-related CIN 2/3 or AIS					
Combined Protocols‡	7402	2	7205	93	97.9 (92.3, 99.8)
HPV 18-related CIN 2/3 or AIS					
Combined Protocols‡	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 16- or 18-related VIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2219	0	2239	6	100.0 (14.4, 100.0)
FUTURE II	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols‡	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2219	0	2239	5	100.0 (-10.1, 100.0)
FUTURE II	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols‡	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (-138.4, 100.0)
FUTURE I	2241	0	2258	77	100.0 (95.1, 100.0)
FUTURE II	5388	9	5374	145	93.8 (88.0, 97.2)
Combined Protocols‡	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts					
Protocol 007	235	0	233	3	100.0 (-139.5, 100.0)
FUTURE I	2261	0	2279	58	100.0 (93.5, 100.0)
FUTURE II	5404	2	5390	132	98.5 (94.5,99.8)
Combined Protocols	7900	2	7902	193	99.0 (96.2,99.9)
HPV 6- and 11-related Genital Warts					
Combined Protocols	6932	2	6856	189	99.0 (96.2, 99.9)

*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).

**See Table 13 for analysis of vaccine impact in the general population.

***Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL®.

†There were two cases of CIN 3 that occurred in the group that received GARDASIL®. In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. The possibility of

association with the vaccine HPV types cannot be completely ruled out. However, given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type.
‡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: P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); efficacy against HPV 16/18-related CIN 2/3 is >25% (Combined Protocols); and efficacy against HPV 6-, 11-, 16-, and 18-related CIN is >20% (FUTURE I).
Note 4: FUTURE I refers to Protocol 013; FUTURE II refers to Protocol 015.

In a supplemental analysis, in 16- through 26-year-old girls and women, the efficacy of GARDASIL® was evaluated against HPV 16/18-related FIGO (International Federation of Obstetrics and Gynaecology) Stage 0 cervical cancer (CIN 3 and AIS) and for the immediate precursors to vulvar and vaginal cancer (VIN 2/3 or VaIN 2/3) in the per-protocol efficacy (PPE) population and a modified intention to treat-2 (MITT-2) population. The MITT-2 population consisted of individuals who were naïve to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and who became infected with a vaccine HPV type during the vaccination period. Efficacy was measured starting 30 days Postdose 1 for the MITT-2 population (Table 9).

Table 9 - Supplemental Analyses of Cancer-related Endpoints: Efficacy Against HPV 16/18-related Invasive Cancer Precursors for the Combined Protocols in the PPE* and MITT-2 Populations of 16- Through 26-Year-Old Girls and Women**

Population	GARDASIL®		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 3					
Per-protocol	8493	2	8464	64	96.9 (88.4, 99.6)
MITT-2	9346	3	9407	92	96.7 (90.2, 99.3)
HPV 16- or 18-related AIS					
Per-protocol	8493	0	8464	7	100.0 (30.6, 100.0)
MITT-2	9346	0	9407	11	100.0 (60.0, 100.0)
HPV 16- or 18-related VIN 2/3 or VaIN 2/3					
Per-protocol	7772	0	7744	19	100.0 (78.6, 100.0)
MITT-2	8642	1	8673	34	97.0 (82.4, 99.9)

*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).
**The MITT-2 consisted of individuals who were naïve to the relevant HPV types (s) (Types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine/placebo, and had at least one follow-up visit post-Day 30 (case counting on Day 31).
n = Number of individuals with at least one follow-up visit after Day 1.
CI = Confidence Interval.
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Prophylactic efficacy against overall persistent infection or disease in an extension phase of Protocol 007, that included data through Month 60, was 95.8% (95% CI: 83.8%, 99.5%). In the group that received GARDASIL®, no cases due to waning immunity were observed.

GARDASIL® was efficacious against HPV disease caused by HPV types 6, 11, 16, and 18.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Women 24 Through 45 Years of Age

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 women up to and including age 45 years, an efficacy study (FUTURE III) was conducted. FUTURE III study builds on the efficacy database established in women ages 16 through 26 to extend the indication of efficacy of GARDASIL® to a population of women through age 45.

For women 26- 45 years of age, prevention of vulvar and vaginal lesions and vulvar and vaginal cancers due to vaccine HPV types has not been demonstrated, although prevention of persistent infection was shown (see Table 10).

The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population (Table 10). The efficacy of GARDASIL® against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 88.7% (95% CI: 78.1, 94.8). The efficacy of GARDASIL® against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 84.7% (95% CI: 67.5, 93.7).

Table 10 - 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		1601	10**	1599	86	88.7 (78.1, 94.8)
HPV 6-, 11-, 16-, or 18-related	Persistent Infection	1581	9	1586	85	89.6 (79.3, 95.4)
	CIN 1	1581	0	1584	15	100.0 (72.1, 100.0)
	CIN 2/3 or AIS	1581	1	1584	6	83.3 (-37.6, 99.6)
	Condyloma	1600	0	1599	7	100.0 (30.8, 100.0)
	VIN 1 or VaIN 1	1600	0	1599	1	100.0 (-3796.0, 100.0)
	VIN 2/3 or VaIN 2/3	1600	0	1599	0	not applicable
HPV 16- or 18-related Persistent Infection, CIN (any grade), or EGL		1587	8**	1571	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.

Prophylactic Efficacy – External Genital Disease Associated with HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Boys and Men

In clinical studies in boys and men, efficacy was evaluated using the following endpoints: external genital warts; penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer; and persistent infection. High grade PIN is associated with certain types of penile/perineal/perianal cancers. Persistent infection is a predictor of clinical disease.

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population. This 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). Efficacy was measured starting after the Month 7 visit.

GARDASIL® was efficacious in reducing the incidence of genital warts (Condyloma) caused by HPV types 6 and 11 and infection related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 11).

Table 11 - Analysis of Efficacy of GARDASIL® in the PPE* Population of 16- Through 26-Year-Old Boys and Men for Vaccine HPV Types

Endpoint	GARDASIL®		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Genital Warts (Condyloma)	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
Persistent Infection†					
HPV 6, 11, 16, or 18- related	1390	21	1402	140	85.5 (77.0, 91.3)
HPV 6-related	1238	5	1242	50	90.1 (75.3, 96.9)
HPV 11-related	1238	1	1242	18	94.4 (64.7, 99.9)
HPV 16-related	1288	13	1268	61	79.3 (61.9, 89.6)
HPV 18 -related	1327	2	1350	33	93.9 (76.3, 99.3)

*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).

† Persistent Infection is defined by 2 consecutive samples that are PCR positive for the same HPV type collected at least 6 months (+/- 1 month) apart.

N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 Through 26 Years of Age in the MSM Sub-study

A sub-study of Protocol 020 evaluated the efficacy of GARDASIL® against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 MSM. In this sub-study, efficacy was evaluated using the combined incidence of HPV 6-, 11-, 16-, or 18-related anal intraepithelial neoplasia (AIN, grades 1/2/3) or Anal Cancer. The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population of Protocol 020.

GARDASIL® was efficacious in reducing the combined 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 those boys and men who were PCR negative and seronegative at baseline (Table 12).

Table 12 - Analysis of Efficacy of GARDASIL® for Anal Disease in the PPE* Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types

HPV 6-, 11-, 16-, or 18-related Endpoint	GARDASIL®		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
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).
N = Number of individuals with at least 1 follow-up visit after Month 7.
CI = Confidence Interval.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Several of the AIN 2/3 lesions contained multiple oncogenic types (including non-vaccine HPV types). An additional analysis was conducted to determine vaccine efficacy against lesions likely to be causally associated with vaccine HPV types. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in swab and/or biopsy samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 2 AIN2+ cases (2 in the vaccine group and 0 in the control group) which were not considered to be causally associated with vaccine HPV type infections acquired during the trial. Based on this analysis there was 1 case of HPV 6/11/16/18 AIN 2+ in the vaccine group (AIN 3 attributed to HPV 6) and 13 cases in the control group (Efficacy 91.7%; 95% CI: 44.6%; 99.8%).

Efficacy in 16- Through 45-Year-Old Girls and Women with Current Infection with HPV Types 6, 11, 16, or 18
GARDASIL® is a prophylactic vaccine. There was no evidence of protection from disease caused by vaccine HPV types for which individuals were PCR positive and seropositive at baseline.

Efficacy in women (16 to 45 years) with evidence of a prior infection with a vaccine HPV type (seropositive) that was no longer detectable at vaccination onset (PCR negative)
GARDASIL® appears to prevent reacquisition or recurrence of infection leading to clinical disease among women with evidence of a prior infection that has resolved by vaccination onset. However, a significant difference between GARDASIL® and placebo was only noted for low grade lesions (CIN 1 and benign EGL) for girls and women age 16- 26 years. The efficacy of GARDASIL® against HPV 6-, 11-, 16-, and 18-related persistent infection was 66.8% (95% CI: 3.8, 90.5) in women 24 to 45 years of age.

Individuals of 16- 26 year old who received GARDASIL®, but had ongoing HPV infection at the time of vaccination had a 19.7% (95% CI: -9.5%, 41.2%) lower incidence of CIN (CIN 1 or CIN 2/3) or AIS resulting from this infection as compared with placebo. Ongoing infection was defined as infection with a vaccine HPV type at enrollment, but no evidence of immune response to it (PCR positive and seronegative). However, the decrease was not statistically significant and the clinical significance of this finding has not been determined.

Individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

General Population Impact – HPV 6-, 11-, 16-, or 18-related Disease in 16- Through 26-Year-Old Girls and Women
The general population of individuals includes women who are HPV-naïve (PCR negative and seronegative) and women who are HPV-non-naïve (PCR positive and/or seropositive), some of whom have HPV-related disease. Analyses were conducted to evaluate the overall impact of GARDASIL® with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in the general population. Here, analyses included events arising from HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL® in the general population is shown in Table 13. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in women who are naïve (PCR negative and seronegative) to the relevant HPV types at vaccination onset. General population impact denotes vaccine impact among women regardless of baseline PCR status and serostatus. The majority of CIN and genital warts, VIN, and VaIN detected in the group that received GARDASIL® occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

Table 13 - General Population Impact for Vaccine HPV Types in 16- Through 26-Year-Old Girls and Women

Endpoints	Analysis	GARDASIL® or HPV 16 L1 VLP Vaccine		Placebo		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	MITT2*	9346	4	9407	155	97.4 (93.3,99.3)
	HPV 16 and/or HPV 18 Positive at Day 1	--	142	--	148**	--
	General Population Impact***	9836	146	9904	303	51.8 (41.1, 60.7)†
HPV 16- or 18-related VIN 2/3 or VaIN 2/3	MITT2*	8642	1	8673	34	97.0 (82.4, 99.9)
	HPV 16 and/or HPV 18 Positive at Day 1	--	8	--	4	--
	General Population Impact***	8955	9	8968	38	76.3 (50.0, 89.9)†
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	MITT2*	8630	16	8680	309	94.8 (91.5, 97.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	186‡	--	213‡	--
	General Population Impact***	8819	202	8854	522	61.5 (54.6, 67.4)†
HPV 6-, 11-, 16-, or 18-related Genital Warts	MITT2*	8761	10	8792	252	96.0 (92.6, 98.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	51#	--	55#	--
	General Population Impact***	8955	61	8968	307	80.3 (73.9, 85.3)†
HPV 6-, or 11-, related Genital Warts	MITT2*	7769	9	7792	246	96.4 (93.0, 98.4)
	HPV 6 and/or HPV 11Positive at Day 1	--	51	--	54	--
	General Population Impact***	8955	60	8968	300	80.1 (73.7, 85.2)†

*Includes all individuals who received at least 1 vaccination and who were naïve (PCR negative and seronegative) to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.

**Out of the 148 placebo cases of 16/18 CIN 2/3, 2 individuals were missing serology or PCR results for Day 1.

***Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

†Percent reduction includes the prophylactic efficacy of GARDASIL® as well as the impact of GARDASIL® on the course of infections present at the start of the vaccination.

‡Includes 2 placebo individuals with missing serology/PCR data at Day 1.

#Includes 1 subject with missing serology/PCR data at Day 1.

CI = Confidence Interval.

N = Number of individuals who have at least one follow-up visit after Day 1.

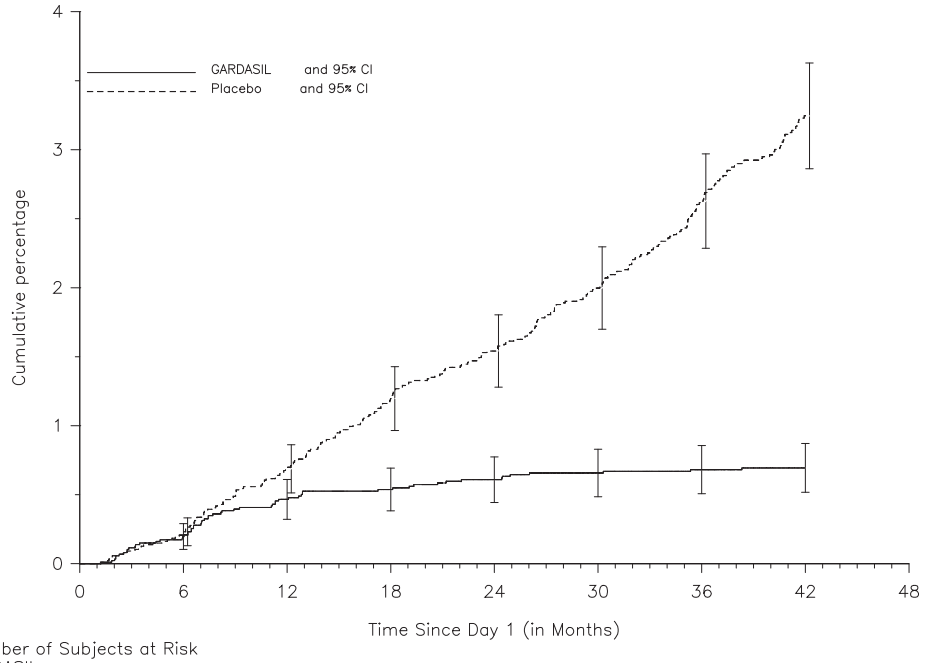
Note 1: The 16- and 18-related CIN 2/3 or AIS composite endpoint included data from studies 005, 007, 013, and 015. All other endpoints only included data from studies 007, 013, and 015.

Note 2: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.

Note 3: Table 13 does not include disease due to non-vaccine HPV types.

The impact of GARDASIL® on the rate of HPV 6- or 11-related genital warts was assessed in the general study population. Administration of GARDASIL® to the general population reduced the incidence of HPV 6- and HPV 11-related genital warts. The benefit of the vaccine with respect to the overall incidence of HPV 6- and HPV 11-related genital warts became more apparent over time (Figure 1).

Figure 1 - Cumulative Incidence of Genital Warts (Caused by HPV Types 6 and 11) Among the General Study Population of Women Including Those with HPV Infection at Vaccination Onset in the Phase III Clinical Trials (FUTURE I and FUTURE II)



General Population Impact – HPV 6-, 11-, 16-, or 18-related Disease in 24- Through 45-Year-Old Women

The impact of GARDASIL® in the general population is shown in Table 14. The efficacy of GARDASIL® against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 47.2% (95% CI: 33.5, 58.2). The efficacy of GARDASIL® against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 41.6% (95% CI: 24.3, 55.2).

Table 14 - Analysis of Efficacy of GARDASIL® in the General Study Population of 24- Through 45-Year-Old Women for Vaccine HPV Types

Endpoints	Analysis	GARDASIL®		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	HNRT*	1799	3	1782	8	62.9 (-54.6, 93.7)
	HPV 16 and/or HPV 18 Positive at Day 1	391	18	400	19	--
	General Population Impact**	1862	21	1861	27	22.4 (-42.5, 58.3)†
HPV 6-, 11-, 16-, or 18-related CIN 1/2/3 or AIS	HNRT*	1817	3	1812	27	89.0 (64.1, 97.9)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	611	27	594	28	--
	General Population Impact**	1862	29	1861	55	47.5 (16.3, 67.7)†
HPV 6-, 11-, 16-, or 18-related VIN 1 or VaIN 1	HNRT*	1839	2	1832	1	-99.4 (-11666.5, 89.6)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	623	1	601	0	--
	General Population Impact**	1884	3	1882	1	-199.8 (-15640.4, 75.9)†
HPV 6-, 11-, 16-, or 18-related VIN 2/3 or VaIN 2/3	HNRT*	1839	0	1832	0	not applicable
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	623	2	601	0	--
	General Population Impact**	1884	2	1882	0	not applicable
HPV 6-, 11-, 16-, or 18-related Genital Warts (Condyloma)	HNRT*	1839	1	1832	11	91.0 (37.9, 99.8)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	623	5	601	1	--
	General Population Impact**	1884	7	1882	12	41.8 (-60.3, 80.6)†

*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at Day 1.
**Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
†Percent reduction includes the prophylactic efficacy of GARDASIL® as well as the impact of GARDASIL® on the course of infections present at the start of the vaccination.
CI = Confidence Interval.
N = Number of individuals who have at least one follow-up visit after Day 1.
Note 1: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.
Note 2: Table 14 does not include disease due to non-vaccine HPV types.

General Population Impact – HPV 6-, 11-, 16-, or 18-related Disease in 16- Through 26-Year-Old Boys and Men

The general population of individuals includes boys and men who are HPV-naïve (PCR negative and seronegative) and boys and men who are HPV-non-naïve (PCR positive and/or seropositive), some of whom have HPV-related disease. Analyses were conducted to evaluate the overall impact of GARDASIL® with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in the general population. Here, analyses included events arising from HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL® in the general population is shown in Table 15. Prophylactic efficacy denotes the vaccine's efficacy in boys and men who are naïve (PCR negative and seronegative) to the relevant HPV types at vaccination onset. General population impact denotes

vaccine impact among boys and men regardless of baseline PCR status and serostatus. The majority of HPV disease detected in the group that received GARDASIL® occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

Table 15 - General Population Impact for Vaccine HPV Types in 16- Through 26-Year-Old Boys and Men

Endpoint	Analysis	GARDASIL®		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	HNRT*	1775	13	1770	54	76.3 (56.0, 88.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	460	14	453	26	--
	General Population Impact**	1943	27	1937	80	66.7 (48.0, 79.3)
Genital Warts (Condyloma)	HNRT*	1775	10	1770	49	80.0 (59.9, 90.9)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	460	14	453	25	--
	General Population Impact**	1943	24	1937	74	68.1 (48.8, 80.7)
PIN 1/2/3	HNRT*	1775	4	1770	5	20.7 (-268.4, 84.3)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	460	2	453	1	--
	General Population Impact**	1943	6	1937	6	0.3 (-272.8, 73.4)
AIN 1/2/3	HNRT*	259	9	261	39	76.9 (51.4, 90.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	103	29	116	38	--
	General Population Impact**	275	38	276	77	50.3 (25.7, 67.2)

*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at Day 1.
**Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
CI = Confidence Interval.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Results of Analysis of Efficacy for HPV Types Other Than the Four Types Included in GARDASIL® in 16- Through 26-Year-Old Girls and Women

The cross-protective efficacy of GARDASIL® was evaluated in the combined database of the FUTURE I and FUTURE II trials (N = 17,599). Efficacy was evaluated for the combined incidence of HPV 31- and HPV 45-related CIN 2/3 or AIS, HPV 31-, 33-, 52-, and 58-related CIN 2/3 or AIS, and HPV 31-, 33-, 45-, 52-, and 58-related CIN 2/3 or AIS (Table 16). Analyses were also conducted to evaluate efficacy with respect to CIN 2/3 or AIS caused by non-vaccine HPV types individually (Tables 17 and 18).

Table 16 - Impact of GARDASIL® on the Rates of CIN 2/3 or AIS for the Combined FUTURE I and FUTURE II Disease Cross Protection Data Set in 16- Through 26-Year-Old Girls and Women

HPV Types	Population	% Reduction	95% CI
HPV 31/45-related**	MITT2* (n = 16,895)	43.2	12.1, 63.9
	General Population (Including HPV-infected*** Individuals) (n = 17,151)	21.4	-5.6, 41.7
HPV 31/33/45/52/58-related†	MITT2 (n = 16,969)	25.8	4.6, 42.5
	General Population (Including HPV-infected Individuals) (n = 17,151)	14.2	-3.3, 28.8
HPV 31/33/52/58-related	MITT2 (n = 16,965)	31.4	10.9, 47.3
	General Population (Including HPV-infected Individuals) (n = 17,151)	16.6	-0.8, 31.1

*The MITT-2 consisted of individuals who were naïve to the relevant HPV type (s) (by serology and PCR for types 6, 11, 16, and 18 or by PCR for types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) prior to dose 1, received at least one dose of vaccine/placebo, and had at least one follow-up visit post-Day 30 (case counting on Day 31).

**Primary pre-specified endpoint of the analysis.

***General population included all individuals with follow-up after Day 30 of the study. Case counting started at Day 30.

†Secondary pre-specified endpoint of the analysis.

CI = Confidence Interval.

Table 17 - Analysis of Efficacy Against CIN 2/3 or AIS Due to Any HPV Type for the Combined FUTURE I and FUTURE II Data Set in the MITT 2 Population* for Individual Vaccine and Non-Vaccine HPV Types in 16- Through 26-Year-Old Girls and Women

Endpoint	GARDASIL®		Placebo		% Efficacy (95% CI)
	n	Cases	n	Cases	
CIN 2/3 or AIS Due to Any HPV Type	8540	204	8575	308	33.8 (20.7, 44.8)
CIN 2/3 or AIS Related to HPV 6/11/16/18	8372	4	8424	146	97.3 (92.8, 99.3)
HPV 6-related CIN 2/3 or AIS	7417	0	7461	15	100.0 (72.1, 100.0)
HPV 11-related CIN 2/3 or AIS	7417	0	7461	4	100.0 (-51.6, 100.0)
HPV 16-related CIN 2/3 or AIS	7111	4	7136	111	96.4 (90.5, 99.0)
HPV 18-related CIN 2/3 or AIS	7903	0	7965	37	100.0 (89.5, 100.0)
CIN 2/3 or AIS Related to Non-vaccine HPV Types	8540	201	8573	240	16.2 (-1.5, 30.9)
HPV 31-related CIN 2/3 or AIS	8065	23	8127	52	55.6 (26.2, 74.1)
HPV 33-related CIN 2/3 or AIS	8281	29	8329	36	19.1 (-35.7, 52.1)
HPV 35-related CIN 2/3 or AIS	8321	13	8379	15	13.0 (-95.9, 61.9)
HPV 39-related CIN 2/3 or AIS	8075	15	8116	24	37.5 (-24.2, 69.5)
HPV 45-related CIN 2/3 or AIS	8273	11	8279	11	0.0 (-154.2, 60.7)
HPV 51-related CIN 2/3 or AIS	7788	34	7888	41	16.3 (-35.2, 48.5)
HPV 52-related CIN 2/3 or AIS	7958	44	8040	52	14.7 (-30.0, 44.2)
HPV 56-related CIN 2/3 or AIS	7786	34	7834	30	-13.7 (-92.4, 32.5)
HPV 58-related CIN 2/3 or AIS	8161	24	8176	35	31.5 (-18.5, 61.0)
HPV 59-related CIN 2/3 or AIS	8151	9	8182	15	39.9 (-46.5, 76.8)

*The MITT-2 consisted of individuals who were naïve to the relevant HPV type (s) (by serology and PCR for types 6, 11, 16, and 18 or by PCR for types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) prior to dose 1, received at least one dose of vaccine/placebo, and had at least one follow-up visit post-Day 30 (case counting on Day 31).
CI = Confidence Interval

Table 18 - Analysis of Efficacy Against CIN 2/3 or AIS Due to Any HPV Type for the Combined FUTURE I and FUTURE II Data Set in the General Population (Including HPV Infected Girls and Women)* for Individual Vaccine and Non-Vaccine HPV Types in 16- Through 26-Year-Old Girls and Women

Endpoint	GARDASIL®		Placebo		% Efficacy (95% CI)
	n	Cases	n	Cases	
CIN 2/3 or AIS Due to Any HPV Type	8559	421	8592	516	18.4 (7.0, 28.4)
CIN 2/3 or AIS Related to HPV 6/11/16/18	8559	140	8592	286	51.1 (39.9, 60.3)
HPV 6-related CIN 2/3 or AIS	8559	2	8592	22	90.9 (63.0, 99.0)
HPV 11-related CIN 2/3 or AIS	8559	0	8592	6	100.0 (15.0, 100.0)
HPV 16-related CIN 2/3 or AIS	8559	130	8592	237	45.1 (31.8, 56.0)
HPV 18-related CIN 2/3 or AIS	8559	9	8592	59	84.7 (69.0, 93.3)
CIN 2/3 or AIS Related to Non-vaccine HPV Types	8559	340	8592	374	9.0 (-5.6, 21.7)
HPV 31-related CIN 2/3 or AIS	8559	67	8592	92	27.1 (-0.9, 47.6)
HPV 33-related CIN 2/3 or AIS	8559	49	8592	59	16.8 (-23.5, 44.3)
HPV 35-related CIN 2/3 or AIS	8559	21	8592	23	8.6 (-72.7, 51.9)
HPV 39-related CIN 2/3 or AIS	8559	28	8592	33	15.1 (-44.9, 50.6)
HPV 45-related CIN 2/3 or AIS	8559	18	8592	19	5.2 (-90.9, 53.1)
HPV 51-related CIN 2/3 or AIS	8559	53	8592	64	17.1 (-21.2, 43.5)
HPV 52-related CIN 2/3 or AIS	8559	78	8592	87	10.3 (-23.2, 34.8)
HPV 56-related CIN 2/3 or AIS	8559	48	8592	44	-9.2 (-68.3, 29.0)
HPV 58-related CIN 2/3 or AIS	8559	41	8592	59	30.5 (-5.3, 54.5)
HPV 59-related CIN 2/3 or AIS	8559	11	8592	19	42.1 (-28.1, 75.1)

*General population included all individuals with follow-up after Day 30 of the study. Case counting started at Day 30.
CI = Confidence Interval

Impact on the Rates of Pap Test Abnormalities and Cervical, Vulvar, and Vaginal Procedures in 16- Through 26-Year-Old Girls and Women

The impact of GARDASIL® on rates of abnormal Pap tests and cervical procedures (colposcopic biopsy, definitive therapy) regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, FUTURE I and FUTURE II. The impact of GARDASIL® on rates of genital excisional procedures to treat lesions caused by any HPV type was evaluated in 5442 individuals enrolled in FUTURE I. Two populations were considered: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

In both populations, GARDASIL® reduced the proportions of individuals who experienced a Pap test abnormality suggestive of CIN, a colposcopic biopsy, a definitive cervical therapy procedure (Loop Electro-Excision Procedure or Cold-Knife Conization), a vulvar or vaginal biopsy, or a definitive excisional procedure of the vagina or vulva (Table 19).

Table 19 - Impact of GARDASIL® on Rates of Pap Test Abnormalities and Cervical, Vulvar, and Vaginal Procedures in 16- Through 26-Year-Old Girls and Women

Population	Endpoint	GARDASIL®		Placebo		% Reduction (95% CI)
		n	cases	n	cases	
HPV-naïve (Protocols 007, FUTURE I, FUTUREII)	ASC-US (Positive HC2 Probe)	4870	285	4758	359	22.7 (9.4, 34.0)
	ASC-H	4870	59	4758	89	35.2 (8.9, 54.2)
	LSIL	4870	864	4758	1000	16.1 (8.1, 23.5)
	HSIL	4870	24	4758	41	42.7 (2.9, 66.9)
	Colposcopy with Biopsy	4696	741	4759	950	21.8 (13.9, 29.1)
	Definitive Cervical Therapy	4696	132	4759	230	41.9 (27.7, 53.5)
General Study Population (Protocols 007, FUTURE I, FUTUREII)	ASC-US (Positive HC2 Probe)	9359	884	8859	980	14.6 (6.4, 22.1)
	ASC-H	9359	185	8859	254	30.9 (16.1, 43.1)
	LSIL	9359	2255	8859	2399	11.7 (6.4, 16.7)
	HSIL	9359	153	8859	169	14.0 (-7.7, 31.3)
	Colposcopy with Biopsy	8822	2222	8856	2521	12.7 (7.6, 17.6)
	Definitive Cervical Therapy	8822	594	8856	781	23.9 (15.2, 31.7)
HPV-naïve (FUTURE I)	Genital Biopsy	1461	72	1473	128	43.7 (24.3, 58.4)
	Definitive Genital Therapy	1461	43	1473	85	49.3 (26.0, 65.7)
General Study Population (FUTURE I)	Genital Biopsy	2672	213	2671	292	27.8 (13.6, 39.8)
	Definitive Genital Therapy	2672	127	2671	193	34.7 (17.8, 48.2)

ASC-US = Atypical Squamous Cells of Undetermined Significance.

HC2 Probe = Positive Reflex HPV Test (Hybrid Capture 2, Digene Boxborough, MA USA).

ASC-H = Atypical Squamous Cells – Cannot Rule Out HSIL.

LSIL = Low Grade Squamous Intraepithelial Lesion.

HSIL = High Grade Squamous Intraepithelial Lesion.

CI = Confidence interval.

Note 1: Colposcopy with Biopsy denotes a colposcopy in which at least one biopsy was taken.

Note 2: Definitive Cervical Therapy denotes: Loop Electro-Excision Procedure (LEEP); LASER-LEEP; cold-knife conization.

Note 3: Genital Biopsy denotes biopsy of the vagina, vulva, or external genital region.

Note 4: Definitive Genital Therapy denotes definitive surgical excisional procedures.

Note 5: Point estimates and confidence intervals are adjusted for person-time of follow-up.

In addition, administration of GARDASIL® to an HPV naïve population of 16- through 26-year-old individuals reduced the incidence of HPV 16-related and HPV 18-related Pap abnormalities (ASC-US HR positive, LSIL, or worse) by 92.4% (95% CI: 83.7%, 97.0%) and 96.9% (95% CI: 81.6%, 99.9%) in the FUTURE I study. These results should not be interpreted as a reason to reduce or eliminate Pap smear testing.

Immunogenicity

Assays to Measure Immune Response
Type-specific competitive 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.

No minimum anti-HPV 6, 11, 16, 18 antibodies level that protects against clinical disease caused by the HPV types has been established. This was partly due to the few disease cases in naïve individuals (PCR negative and seronegative) to vaccine HPV types, at baseline, in the group that received GARDASIL®.

The immunogenicity of GARDASIL® was assessed in 23,951, 9- through 45-year-old girls and women (GARDASIL® N = 12,634; placebo N = 11,317) and 5417, 9- through 26-year-old boys and men (GARDASIL® N = 3109; placebo N = 2308).

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and PCR negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

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).

Immune Response to GARDASIL®
In clinical studies in 16- through 26-year-old girls and women, 99.8%, 99.8%, 99.8%, and 99.4% who received GARDASIL® became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3 across all age groups tested.

In clinical studies in 27- through 45-year-old women, 98.2%, 97.9%, 98.6%, and 97.1% who received GARDASIL® became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

In clinical studies in 16- through 26-year-old in boys and men, 98.9%, 99.2%, 98.8%, and 97.4% who received GARDASIL® became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

Across all populations, anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs peaked at month 7 (Table 20 and Table 21). GMTs declined through month 24 and then stabilized

through month 36 at levels above baseline. Tables 22 and 23 display the persistence of anti-HPV cLIA geometric mean titers by gender and age group. The duration of immunity following a complete schedule of immunization with GARDASIL® has not been established.

Table 20 - Summary of Month 7Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of 9- Through 45-Year-Old Girls and Women

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
16- through 26-year-old girls and women	9859	3329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
27- through 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
35- through 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
Anti-HPV 11				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	1304.6 (1224.7, 1389.7)
16- through 26-year-old girls and women	9859	3353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
27- through 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
35- through 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
Anti-HPV 16				
9- through 15-year-old girls	1122	915	99.9 (99.4, 100.0)	4918.5 (4556.6, 5309.1)
16- through 26-year-old girls and women	9859	3249	99.8 (99.6, 100.0)	2409.2 (2309.0, 2513.8)
27- through 34-year-old women	667	435	99.3 (98.0, 99.9)	2342.5 (2119.1, 2589.6)
35- through 45-year-old women	957	657	98.2 (96.8, 99.1)	2129.5 (1962.7, 2310.5)
Anti-HPV 18				
9- through 15-year-old girls	1122	922	99.8 (99.2, 100.0)	1042.6 (967.6, 1123.3)
16- through 26-year-old girls and women	9859	3566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
27- through 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
35- through 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

*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 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).
**Number of individuals randomized to the respective vaccination group who received at least 1 injection.
***Number of individuals contributing to the analysis.
cLIA = Competitive Luminex immunoassay.
CI = Confidence interval.
GMT = Geometric mean titers.
†mMU = milli-Merck units.

Table 21 - Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of Boys and Men

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year-old boys	1072	884	99.9 (99.4, 100.0)	1037.5 (963.5, 1117.3)
16- through 26-year-old boys and men	2026	1093	98.9 (98.1, 99.4)	447.8 (418.9, 478.6)
Anti-HPV 11				
9- through 15-year-old boys	1072	885	99.9 (99.4, 100.0)	1386.8 (1298.5, 1481.0)
16- through 26-year-old boys and men	2026	1093	99.2 (98.4, 99.6)	624.3 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year-old boys	1072	882	99.8 (99.2, 100.0)	6056.5 (5601.3, 6548.7)
16- through 26-year-old boys and men	2026	1136	98.8 (97.9, 99.3)	2403.3 (2243.4, 2574.6)
Anti-HPV 18				
9- through 15-year-old boys	1072	887	99.8 (99.2, 100)	1357.4 (1249.4, 1474.7)
16- through 26-year-old boys and men	2026	1175	97.4 (96.3, 98.2)	402.6 (374.6, 432.7)

*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 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).
**Number of individuals randomized to the respective vaccination group who received at least 1 injection.
***Number of individuals contributing to the analysis.
cLIA = Competitive Luminex immunoassay.
CI = Confidence interval.
GMT = Geometric mean titers.
†mMU = milli-Merck units.

Table 22 - Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 45-Year-Old Girls and Women

Assay (cLIA)/ Time Point	9- to 15-year-old Girls (N* = 1122)		16- to 26-year-old Girls and Women (N* = 9859)		27- to 34-year-old Women (N* = 667)		35- to 45-year-old Women (N* = 957)	
	n**	GMT (95% CI) mMU/mL***	n**	GMT (95% CI) mMU/mL***	n**	GMT (95% CI) mMU/mL***	n**	GMT (95% CI) mMU/mL***
Anti-HPV 6								
Month 07	917	929.2 (874.6, 987.3)	3329	545.0 (530.1, 560.4)	439	435.6 (393.4, 482.4)	644	397.3 (365.2, 432.2)
Month 24	214	156.1 (135.6, 179.6)	2788	109.1 (105.2, 113.1)	421	70.7 (63.8, 78.5)	628	69.3 (63.7, 75.4)
Month 36†	356	129.4 (115.6, 144.8)	-	-	399	79.5 (72.0, 87.7)	618	81.1 (75.0, 87.8)
Month 48‡	-	-	2514	73.8 (70.9, 76.8)	391	58.8 (52.9, 65.3)	616	62.0 (57.0, 67.5)
Anti-HPV 11								
Month 07	917	1304.6 (1224.7, 1389.7)	3353	748.9 (726.0, 772.6)	439	577.9 (523.8, 637.5)	644	512.8 (472.9, 556.1)
Month 24	214	218.0 (188.3, 252.4)	2817	137.1 (132.1, 142.3)	421	79.3 (71.5, 87.8)	628	73.4 (67.4, 79.8)
Month 36†	356	148.0 (131.1, 167.1)	-	-	399	81.8 (74.3, 90.1)	618	77.4 (71.6, 83.6)
Month 48‡	-	-	2538	89.4 (85.9, 93.1)	391	67.4 (60.9, 74.7)	616	62.7 (57.8, 68.0)
Anti-HPV 16								
Month 07	915	4918.5 (4556.6, 5309.1)	3249	2409.2 (2309.0, 2513.8)	435	2342.5 (2119.1, 2589.6)	657	2129.5 (1962.7, 2310.5)
Month 24	211	944.2 (804.4, 1108.3)	2721	442.6 (425.0, 460.9)	416	285.9 (254.4, 321.2)	642	271.4 (247.1, 298.1)
Month 36†	353	642.2 (562.8, 732.8)	-	-	399	291.5 (262.5, 323.8)	631	276.7 (254.5, 300.8)
Month 48‡	-	-	2474	326.2 (311.8, 341.3)	394	211.8 (189.5, 236.8)	628	192.8 (176.5, 210.6)
Anti-HPV 18								
Month 07	922	1042.6 (967.6, 1123.3)	3566	475.2 (458.8, 492.1)	501	385.8 (347.6, 428.1)	722	324.6 (297.6, 354.0)
Month 24	214	137.7 (114.8, 165.1)	3002	50.8 (48.2, 53.5)	478	31.8 (28.1, 36.0)	705	26.0 (23.5, 28.8)
Month 36†	357	87.0 (74.8, 101.2)	-	-	453	32.1 (28.5, 36.3)	689	27.0 (24.5, 29.8)
Month 48‡	-	-	2710	33.2 (31.5, 35.0)	444	25.2 (22.3, 28.5)	688	21.2 (19.2, 23.4)

*N = Number of individuals randomized in the respective group who received at least 1 injection.
**n = Number of individuals in the indicated immunogenicity population.
***mMU = milli-Merck units per mL
† Month 37 for 9- to 15-year-old girls. No serology samples were collected at this time point for 16- to 26-year-old girls and women.
‡Month 48/End-of-study visits for 16- to 26-year-old girls and women were generally scheduled earlier than Month 48. Mean visit timing was Month 44. The studies in 9- to 15-year-old girls were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex immunoassay.
CI = Confidence interval.
GMT = Geometric mean titers.

Table 23 - Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 26-Year-Old Boys and Men

Assay (cLIA)/ Time Point	9- to 15-year-old Boys (N* = 1072)		16- to 26-year-old Boys and Men (N* = 2026)	
	n**	GMT (95% CI) mMU/mL***	n**	GMT (95% CI) mMU/mL***
Anti-HPV 6				
Month 07	884	1037.5 (963.5, 1117.3)	1093	447.8 (418.9, 478.6)
Month 24	323	134.1 (119.5, 150.6)	942	79.8 (74.6, 85.4)
Month 36†	385	130.1 (117.1, 144.5)	848	71.5 (66.6, 76.7)
Month 48‡	-	-	-	-
Anti-HPV 11				
Month 07	885	1386.8 (1298.5, 1481.0)	1093	624.3 (588.4, 662.3)
Month 24	324	188.5 (168.3, 211.2)	942	94.6 (88.5, 101.1)
Month 36†	385	156.1 (140.4, 173.6)	848	82.6 (76.9, 88.7)
Month 48‡	-	-	-	-
Anti-HPV 16				
Month 07	882	6056.5 (5601.3, 6548.7)	1136	2403.3 (2243.4, 2574.6)
Month 24	322	938.2 (824.3, 1067.9)	980	342.6 (318.1, 369.0)
Month 36†	384	726.6 (644.4, 819.3)	878	293.1 (270.8, 317.4)
Month 48‡	-	-	-	-
Anti-HPV 18				
Month 07	887	1357.4 (1249.4, 1474.7)	1175	402.6 (374.6, 432.7)
Month 24	324	131.9 (112.1, 155.2)	1012	38.4 (35.0, 42.1)
Month 36†	387	113.3 (97.5, 131.7)	906	33.1 (30.0, 36.5)
Month 48‡	-	-	-	-

*N = Number of individuals randomized in the respective group who received at least 1 injection.
**n = Number of individuals in the indicated immunogenicity population.
***mMU = milli-Merck units per mL
†Month 36 time point for 16- to 26-year-old boys and men; Month 37 for 9- to 15-year-old boys.
‡The studies in 9- to 15-year-old boys and 16- to 26-year-old boys and men were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex immunoassay.
CI = Confidence interval.
GMT = Geometric mean titers.

Tables 20 and 21 display the Month 7 immunogenicity data for girls and women and boys and men. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent girls were non-inferior to anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL®. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent boys were non-inferior to anti-HPV responses in 16- through 26-year-old boys and men in Protocol 020.

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

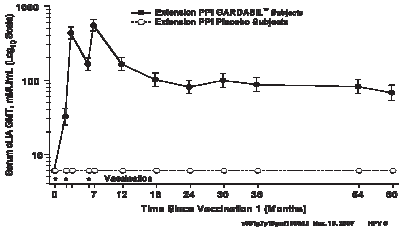
Persistence of the Immune Response to GARDASIL®

The duration of immunity following a complete schedule of immunization with GARDASIL® has not been established. After peaking at Month 7, anti-GMTs for all HPV types decreased through Month 24 and then stabilized at levels above baseline.

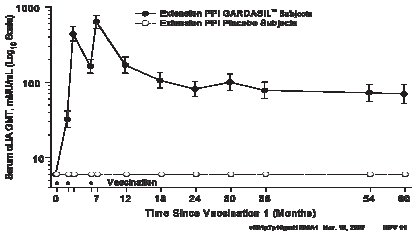
In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then stabilized until at least Month 60 (see Figure 2).

Figure 2 - Persistence of Anti-HPV Responses Following a 3-dose Regimen of GARDASIL®

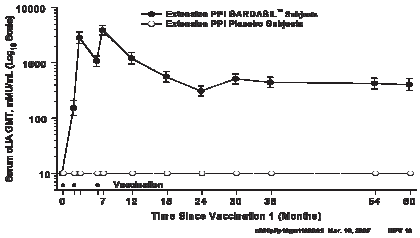
Persistence of Anti-HPV 6 Responses



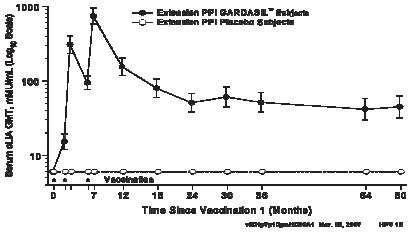
Persistence of Anti-HPV 11 Responses



Persistence of Anti-HPV 16 Responses



Persistence of Anti-HPV 18 Responses



Evidence of Anamnestic (Immune Memory) Response
Evidence of an anamnestic response was seen in vaccinated individuals who were seropositive to relevant HPV type(s) prior to vaccination.

In a study to evaluate the capacity to induce immune memory, individuals who received a 3-dose primary series of vaccine were given a challenge dose of GARDASIL® 5 years after the onset of vaccination. These individuals exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3 (Month 7). The GMTs 1 week post-challenge dose were 0.9-, 2.2-, 1.2-, and 1.4-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18, respectively (Table 24). The GMTs 1 month post-challenge dose were 1.3-, 4.2-, 1.5-, and 1.7-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18 respectively (Table 24). At 1 week post-challenge dose, 87.2%, 94.9%, 86.4% and 95.2% of individuals had anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs higher than those detected at Month 60.

In addition, a subset of individuals that received a 3-dose primary series of vaccine became nominally anti-HPV 18 seronegative by Month 60. Although these individuals were nominally anti-HPV 18 seronegative, no cases of HPV 18-related disease were detected among these individuals. They also showed immune memory: when these individuals were given a challenge dose of GARDASIL® (at Month 60), 93% and 97% became anti-HPV 18 seropositive by 1 week and 1 month post-challenge, respectively; 73% had anti-HPV 18 levels at 1 month post-challenge that were higher than their Month 7 (1 month Postdose 3) anti-HPV 18 level.

Table 24 - Comparison of HPV Antibody Responses At Month 7, Month 60, 1 Week Post-challenge Dose, and 1 Month Post-challenge Dose for GARDASIL® in The Extension Per-protocol Population*

Time Postdose	n	GMT (mMU/mL)	95% Confidence Interval	Fold Change from Month 7
HPV 6				
Month 7	80	549.2	(460.6, 654.7)	-
Month 60 (Pre-challenge)	79	67.7	(53.5, 85.7)	-
Month 60 + 1 Week Post-challenge	79	503.3	(344.2, 736.1)	0.9
Month 61 (Post-challenge)	80	693.2	(451.9, 1063.3)	1.3
HPV 11				
Month 7	80	635.5	(521.3, 774.9)	-
Month 60 (Pre-challenge)	79	70.1	(52.5, 93.7)	-
Month 60 + 1 Week Post-challenge	79	1417.5	(1009.0, 1991.4)	2.2
Month 61 (Post-challenge)	80	2652.4	(1956.7, 3595.3)	4.2
HPV 16				
Month 7	82	3870.0	(3157.0, 4744.0)	-
Month 60 (Pre-challenge)	82	404.2	(312.9, 522.1)	-
Month 60 + 1 Week Post-challenge	81	4466.4	(3095.2, 6445.0)	1.2
Month 61 (Post-challenge)	81	5714.0	(3829.7, 8525.4)	1.5
HPV 18				
Month 7	86	741.2	(576.8, 952.4)	-
Month 60 (Pre-challenge)	85	44.7	(31.8, 62.8)	-
Month 60 + 1 Week Post-challenge	84	1033.2	(753.9, 1415.8)	1.4
Month 61 (Post-challenge)	86	1230.0	(904.5, 1672.5)	1.7

*The extension per-protocol population includes all extension individuals who received 3 primary injections of GARDASIL® and antigen challenge of GARDASIL® at Month 60, were seronegative and Polymerase Chain Reaction (PCR) negative at Day 1 to the respective vaccine HPV types, PCR negative through Month 60 to the respective vaccine HPV types, and had valid serology data 4 weeks post-challenge.
Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Persistence of Immune Response in Phase III Studies of 9- Through 45-Year-Old Girls and Women for GARDASIL®

Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositivity was highest at Month 7, and then declined at persistence time points. At Month 48, anti-HPV seropositivity was highest among 9- through 15-year-olds and lowest among 35- through 45-year-olds for HPV types 6, 11, and 18. Anti-HPV 16 seropositivity was comparable at Month 24 in the 18- through 26-year-olds as compared to the 9- through 17-year-olds.

The decline in the percent seropositivity for anti-HPV 18 responses was greater than the decline in the percent seropositivity for anti-HPV 6, anti-HPV 11, and anti-HPV 16 responses. Despite this decline, the efficacy of the vaccine remained high, across all age groups. In the PPE population of the FUTURE I and FUTURE II studies, efficacy against HPV 18-related CIN 2/3 or AIS was 100.0% (95% CI: 86.6%, 100.0%) and efficacy against HPV 18-related CIN (any grade) or AIS was 98.4% (95% CI: 90.6%, 100.0%). In the PPE population of the FUTURE III study, efficacy against HPV 18-related persistent infection or cervical, vulvar, and vaginal disease was 100.0% (95% CI: 67.4%, 100.0%).

Persistence of Immune Response in Phase III Studies of 9- Through 26-Year-Old Boys and Men for GARDASIL®
Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositivity was highest at Month 7, and then generally declined at persistence time points. At Month 36, anti-HPV seropositivity was highest among 9- through 15-year-olds and lowest among 16- through 26-year-olds.

The decline in the percent seropositivity for anti-HPV 18 responses was greater than the decline in the percent seropositivity for anti-HPV 6, anti-HPV 11, and anti-HPV 16 responses. Despite this decline, the efficacy of the vaccine remained high, across all age groups.

Schedule Flexibility
All individuals evaluated in the PPE populations of the Phase II and III studies received the 3-dose regimen of GARDASIL® within a 1-year period, regardless of the interval between doses. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not substantially impact the immune responses to GARDASIL® (see DOSAGE AND ADMINISTRATION).

Immune Responses to GARDASIL® using a 2-dose schedule
A clinical trial showed that, at Month 7, the immune response in girls aged 9-13 years (n=259) who received 2 doses of GARDASIL® (at 0, 6 months) was not inferior to the immune response in women aged 16-26 years (n=310) who received 3 doses of GARDASIL® (at 0, 2, 6 months). The administration of the second dose at intervals other than 6 or 12 months after the first dose has not been formally evaluated.

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

Studies with Other Vaccines

Studies with RECOMBIVAX HB® [hepatitis B vaccine (recombinant)]
The safety and immunogenicity of co-administration of GARDASIL® with RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized study of 1871 women aged 16 through 24 years at enrollment. Immune response and safety profile to both RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] and GARDASIL® were similar whether they were administered at the same visit or at a different visit.

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)]
The safety and immunogenicity of co-administration of GARDASIL® with Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis

Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in a randomized study of 1040 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL® 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)] does not interfere with the antibody response to any of the components of any of the vaccines. In addition, the safety profile was generally similar (See DRUG INTERACTIONS, Drug-Drug Interactions, Use with Other Vaccines).

TOXICOLOGY

ANIMAL TOXICOLOGY

Acute and Subacute Toxicity

Single-dose (acute) toxicity studies in mice and rats showed no evidence of toxicity. The doses administered were 56 µg total protein for mice which corresponds to approximately 1200-fold the projected human dose and 112 µg total protein for rats which corresponds to approximately 300-fold the projected human dose.

A three-dose (subacute) toxicity study in mice showed a mixed inflammatory response at the injection site and hyperplasia in the draining lymph nodes but no significant changes in the tissues as assessed by histomorphologic examinations. The dose administered for mice was 56 µg total protein which corresponds to approximately 1450-fold excess relative to the projected human dose.

Local Tolerance

An intramuscular irritation (local tolerance) study in rabbits showed that the vaccine caused very slight to moderate irritation at the injection site. The irritation was similar to or slightly greater than the AAHS adjuvant placebo control as assessed by histomorphologic examinations. The dose administered for rabbits ranged from 120 to 280 µg total protein which corresponds to approximately 20- to 40-fold excess relative to the projected human dose.

Carcinogenesis and Mutagenesis

GARDASIL® has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

Reproductive Toxicology

GARDASIL® administered to female rats at a dose of 120 µg total protein, which corresponds to approximately 300-fold excess relative to the projected human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

GARDASIL® administered to male rats at a dose of 120 µg total protein, which corresponds to approximately 200-fold excess relative to the projected human dose, had no effects on reproductive performance including fertility, sperm count, and sperm motility, and there were no vaccine-related gross or histomorphologic changes on the testes and no effects on testes weights.

Developmental Toxicology
GARDASIL® administered to female rats at a dose of 120 µg total protein, which corresponds to approximately 300-fold excess relative to the projected human dose, showed no evidence of developmental toxicity as assessed by embryonic/fetal survival, fetal body weight, and fetal external, visceral, coronal, or skeletal morphology. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring.

Antibodies against all 4 HPV serotypes were transferred to the offspring during gestation and possibly during lactation. The passively transferred antibodies remained up to postnatal day 77, when they were last measured.

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PART III: CONSUMER INFORMATION

GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

This leaflet is part III of a three-part "Product Monograph" published when GARDASIL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GARDASIL®. Contact your physician or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
GARDASIL® is a vaccine (injection/shot) that helps protect girls and women 9 through 45 years of age against the following diseases caused by an infection with Human Papillomavirus (HPV) Types 6, 11, 16, and 18:

- Cervical cancer (cancer of the lower end of the uterus or womb) caused by HPV types 16 and 18
- Vulvar (the outside of the female genital area) and vaginal cancers caused by HPV types 16 and 18
- Genital warts 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, and 18
- Abnormal and precancerous vaginal and vulvar lesions (outside of the female genital area) caused by HPV types 6, 11, 16, and 18

GARDASIL® helps protect girls and women 9 through 26 years of age against:

- Anal cancer caused by HPV types 16 and 18
- Abnormal and precancerous anal lesions caused by HPV types 6, 11, 16, and 18.

GARDASIL® helps protect boys and men 9 through 26 years of age against infection caused by HPV types 6, 11, 16, and 18 and the following diseases caused by HPV:

- Anal cancer caused by HPV types 16 and 18
- Genital warts caused by HPV types 6 and 11
- Abnormal and precancerous anal lesions caused by HPV types 6, 11, 16, and 18.

GARDASIL® helps prevent these diseases—but it will not treat them.

You or your child cannot get HPV or any of the above diseases from GARDASIL®.

What it does:

- As with all vaccines, GARDASIL® may not fully protect everyone who gets the vaccine. Continue to follow your health-care provider's advice on getting Pap tests.
- There are more than 100 HPV types; GARDASIL® will not protect against all types. GARDASIL® helps protect against 4 types (6, 11, 16, and 18). These 4 types have been selected for GARDASIL® because they cause over 70% of cervical cancers, 90% of genital warts, and 80-90% of HPV-related anal cancers worldwide.
- GARDASIL® also will not protect against other diseases that are not caused by HPV.
- GARDASIL® works best when given before you or your child has any contact with certain types of HPV.

What are cervical cancer, precancerous lesions, and genital warts?
Cancer of the cervix is a serious and sometimes life-threatening disease. It starts when a female catches certain types of HPV. These types can cause the cells in the lining of the cervix to change from normal to abnormal or precancerous lesions. These lesions are usually detected by a Pap test. If these lesions are not treated, they can turn cancerous. You or your child cannot get cancer of the cervix without first having an HPV infection.

Genital warts are caused by certain types of HPV. They often appear as skin-colored growths. They are found on the inside or outside of the genitals in both males and females. They can hurt, itch, bleed, and cause discomfort. Sometimes they can come back after treatment.

What are vulvar and vaginal cancers and precancerous lesions?
Approximately 40-50% of vulvar and 65-80% of vaginal cancers are associated with HPV. HPV types 16 and 18 have been associated with 60-95% of all HPV-related vulvar and vaginal cancers. The rates of these cancers have been increasing. There are no routine screening tests for these cancers.

What are anal cancer and anal precancerous lesions?
Human Papillomavirus (HPV) infection is strongly associated with anal cancer and the precancerous anal lesions that precede cancer. The great majority of anal cancers are squamous cell carcinoma (SCC) and 80 to 90% of these cancers are HPV positive. HPV types 16 and 18 are the most commonly associated types. Approximately 100,000 new cases of anal cancer are estimated to occur annually around the world and the rate of anal cancer cases has been increasing. There are no routine screening tests for this cancer in healthy people.

What is Human Papillomavirus (HPV)?
HPV is a common virus. It is estimated that the occurrence of HPV in Canadian women ranges from 20-33%.[34] The highest rates of cancer-causing HPV infection (16-24%) were in young women aged 15 to 29 years.[35] There are many different types of HPV; some cause no harm. Others can cause diseases of the genital area.

While most people clear the virus, those who don't can develop cervical cancer, precancerous lesions, or genital warts.

Every year, there are an estimated 4 million Pap tests performed in Canada and 350,000 of these are abnormal. The majority of abnormal Pap tests are caused by HPV. A Pap test is a procedure by which cells of the cervix are collected by a healthcare professional and examined.[36]

Who is at risk for Human Papillomavirus?
In the absence of vaccination, it is estimated that 75% of sexually active Canadians will catch HPV during their lifetime. A person of any age who takes part in any kind of sexual activity that involves genital contact is at risk. The only way to fully protect yourself from HPV is to avoid this kind of sexual activity.

Many people who have HPV may not show any signs or symptoms. This means that they can pass on the virus to others and not know it.

Will GARDASIL® help me if I already have Human Papillomavirus?
GARDASIL® 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® will help protect you against the other three types. Talk to your health-care provider for more information.

When it should not be used:
Anyone who:
- is allergic to any of the ingredients in the vaccine. A list of ingredients can be found below.
- has an allergic reaction after getting a dose of the vaccine.

What the medicinal ingredient is:
The main ingredients are highly purified inactive proteins (L1) that come from HPV Types 6, 11, 16, and 18.

What the important non-medicinal ingredients are:
It also contains amorphous aluminum hydroxyphosphate sulphate (AAHS Adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection.

What dosage forms it comes in:
GARDASIL® is supplied as:
- 0.5 mL single-dose vials
- 0.5 mL single-dose prefilled syringes

WARNINGS AND PRECAUTIONS

It is very important to tell your health-care provider if you or your child:
- has had an allergic reaction to the vaccine
- has a bleeding disorder and cannot receive injections in the arm
- has a weakened immune system, for example due to a genetic defect or HIV infection, or if you take medicines that affect your immune system
- is pregnant or is planning to get pregnant
- has any illness with a fever more than 37.8°C
- takes or plans to take any medicines, even those you can buy over the counter

Your health-care provider will decide if you or your child should receive the vaccine.

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

Use in pregnancy
It is not known whether the vaccine is harmful to an unborn baby when administered to a pregnant woman. The use of the vaccine is not recommended during pregnancy.

Women who become pregnant before completion of the 3-dose schedule should complete the vaccination schedule after childbirth.

Pregnant women exposed to GARDASIL® are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594 or the Vaccine Safety Section at Public Health Agency of Canada at 1-866-844-0018 or www.phac-aspc.gc.ca/im/vs-sv/index-eng.php.

Use in breast-feeding
GARDASIL® may be given to women who are breast-feeding or intend to breast-feed.

Can I drive or operate machinery following vaccination with GARDASIL®?
There is no information to suggest that GARDASIL® affects your ability to drive or operate machinery.

INTERACTIONS WITH THIS VACCINE

Can other vaccines and medications be given at the same time as GARDASIL®?
GARDASIL® can be given at the same time as RECOMBIVAX HB® [hepatitis B vaccine (recombinant)], 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)]; however the vaccine should not be mixed in the same syringe with any other vaccines or solutions.

Please inform your physician or health-care provider if you or your child are taking or have recently taken any other medicines, even those not prescribed.

PROPER USE OF THIS VACCINE

Usual dose:
GARDASIL® is given as an injection usually in the arm muscle.

You or your child 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
- Third dose: 6 months after the first dose

The second dose should be administered at least one 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. Please speak to your doctor for more information.

Alternatively, individuals 9 through 13 years of age, may receive 2 doses of the vaccine.

First injection: at chosen date
Second injection: ideally 6 months or 12 months after first injection

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

Make sure that you or your child gets all doses. This allows you or your child to get the full benefits of GARDASIL®.

Missed dose:
If you or your child misses a dose, your health-care provider will decide when to give the missed dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all vaccines, there may be some side effects with GARDASIL®. GARDASIL® has been shown to be generally well tolerated in adults and children as young as 9 years of age.

The most commonly reported side effects included:
- pain, swelling, itching, bruising and redness at the injection site
- fever, nausea, dizziness, headache, vomiting, and pain in extremity.

Fainting has been reported. Fainting can occur after vaccination, most commonly among adolescents and young adults. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

Allergic reactions that may include difficulty breathing, wheezing (bronchospasm), hives, and rash have been reported. Some of these reactions have been severe.

There was no increase in side effects when GARDASIL® was given at the same time as hepatitis B vaccine (recombinant).

There was more injection-site swelling when GARDASIL® was given at the same time as Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

As with other vaccines, side effects that have been reported during general use include: swollen glands (neck, armpit, or groin), Guillain-Barré syndrome, headache, joint pain, aching muscles, unusual tiredness, weakness, or confusion, chills, bad stomach ache, muscle weakness, shortness of breath, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection.

If you or your child has any unusual or severe symptoms after receiving GARDASIL®, contact your health-care provider right away.

This is not a complete list of side effects. For any unexpected effects while taking GARDASIL®, contact your physician or pharmacist.

HOW TO STORE IT

Store refrigerated at 2°C to 8°C. Do not freeze. Protect from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory.**

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
Email: CAEFI@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, AL 6502A
Ottawa, ON K1A 0K9

or Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at: 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to: 1-877-428-8675, or
  - Mail to: Merck Canada Inc.
    Medical Information Center
    16750 route Transcanadienne
    Kirkland, QC H9H 4M7

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.merck.ca or by contacting the sponsor, Merck Canada Inc., at: 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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