HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GARDASIL safely and effectively. See full prescribing information for GARDASIL.

GARDASIL
[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]
Suspension for intramuscular injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES ----------
Indications and Usage (1)
Girls and Women (1.1) 10/2009
Boys and Men (1.2) 10/2009

----------INDICATIONS AND USAGE ----------
GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (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 intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1)

Limitations of GARDASIL Use and Effectiveness:
- GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3) (17)
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. (1.3) (14.3) (14.4)
- GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, and vaginal cancers; CIN; VIN; or VaIN. (1.3)
- GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. (1.3) (14.5)
- Not all vulvar and vaginal cancers are caused by HPV, and GARDASIL protects only against those vulvar and vaginal cancers caused by HPV 16 and 18. (1.3)
- GARDASIL does not protect against genital diseases not caused by HPV. (1.3)
- Vaccination with GARDASIL may not result in protection in all vaccine recipients. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------
0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
- 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3) (11)

----------CONTRAINDICATIONS ----------
- Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. (4) (11)

----------WARNINGS AND PRECAUTIONS----------
- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

---------- ADVERSE REACTIONS----------
The most common adverse reaction was headache. Common adverse reactions (frequency of at least 1.0% and greater than AAHS control or saline placebo) are fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS ----------
GARDASIL may be administered concomitantly with RECOMBIVAX HB (7.1) or with Menactra and Adacel. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------
Safety and effectiveness of GARDASIL have not been established in the following populations:
- Pregnant women. Physicians are encouraged to register pregnant women exposed to GARDASIL by calling 1-800-986-8999 so that Merck can monitor maternal and fetal outcomes. (8.1)
- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL may be diminished. (8.6)
- Individuals 27 years of age and older. (8.1) (14.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Girls and Women

GARDASIL®[1] is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (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 intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

1.2 Boys and Men

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

1.3 Limitations of GARDASIL Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care. *[See Patient Counseling Information (17).]*

GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. *[See Clinical Studies (14.3, 14.4).]*

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

GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. *[See Clinical Studies (14.5).]*

Not all vulvar and vaginal cancers are caused by HPV, and GARDASIL protects only against those vulvar and vaginal cancers caused by HPV 16 and 18.

GARDASIL does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL may not result in protection in all vaccine recipients.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

GARDASIL should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months. *[See Clinical Studies (14.7).]*

2.2 Method of Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL should not be diluted or mixed with other vaccines. After thorough

agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

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

Syncope has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. *[See Warnings and Precautions (5.1).]*

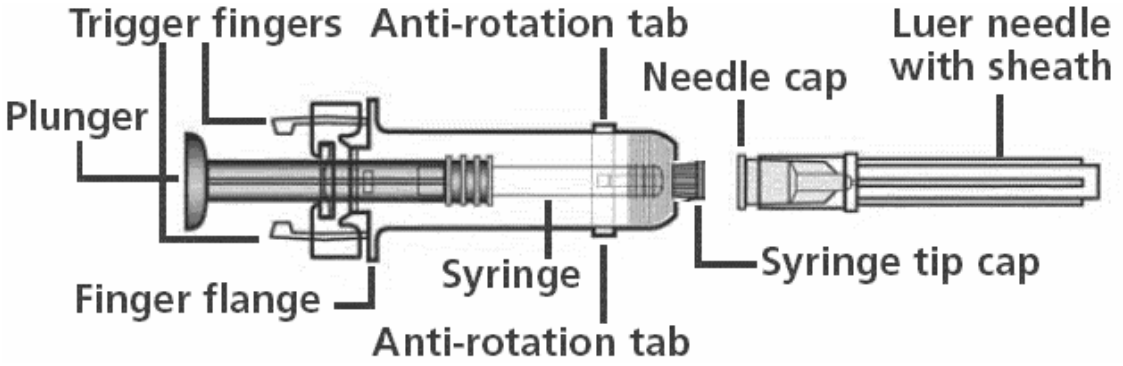
Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

Prefilled Syringe Use With and Without Needle Guard (Safety) Device

Prefilled Syringe With Needle Guard (Safety) Device

Instructions for using the prefilled single-dose syringes preassembled with needle guard (safety) device



NOTE: Please use the enclosed needle for administration. If a different needle is chosen, it should fit securely on the syringe and be no longer than 1 inch to ensure proper functioning of the needle guard device. Two detachable labels are provided which can be removed after the needle is guarded.

At any of the following steps, avoid contact with the Trigger Fingers to keep from activating the safety device prematurely.

Remove Syringe Tip Cap and Needle Cap. Attach Luer Needle by pressing both Anti-Rotation Tabs to secure syringe and by twisting the Luer Needle in a clockwise direction until secured to the syringe. **Remove Needle Sheath. Administer injection** per standard protocol as stated above under DOSAGE AND ADMINISTRATION. Depress the Plunger while grasping the Finger Flange **until the entire dose has been given**. The Needle Guard Device will **NOT** activate to cover and protect the needle unless the **ENTIRE** dose has been given. While the Plunger is still depressed, remove needle from the vaccine recipient. Slowly release the Plunger and allow syringe to move up until the entire needle is guarded. For documentation of vaccination, remove detachable labels by pulling slowly on them. **Dispose in approved sharps container.**

Prefilled Syringe Without Needle Guard (Safety) Device

This package does not contain a needle guard (safety device) or a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

3 DOSAGE FORMS AND STRENGTHS

GARDASIL is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. *[See Description (11).]*

5 WARNINGS AND PRECAUTIONS

5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL.

6 ADVERSE REACTIONS

Overall Summary of Adverse Reactions

Headache, fever, nausea, and dizziness; and local injection site reactions (pain, swelling, erythema, pruritus, and bruising) occurred after administration with GARDASIL.

Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. *[See Warnings and Precautions (5.1).]*

Anaphylaxis has been reported following vaccination with GARDASIL.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Studies in Girls, Women, Boys, and Men 9 Through 26 Years of Age

In 6 clinical trials (4 Amorphous Aluminum Hydroxyphosphate Sulfate [AAHS]-controlled, 1 saline placebo-controlled, and 1 uncontrolled), 14,273 individuals were administered GARDASIL or AAHS control or saline placebo on the day of enrollment, and approximately 2 and 6 months thereafter, and safety was evaluated using vaccination report cards (VRC)-aided surveillance for 14 days after each injection of GARDASIL or AAHS control or saline placebo in these individuals. The individuals who were monitored using VRC-aided surveillance included 8180 individuals 9 through 26 years of age at enrollment who received GARDASIL and 6093 individuals who received AAHS control or saline placebo. Few individuals (0.2%) discontinued due to adverse reactions. The race distribution of the girls and women in the safety population was as follows: 62.3% White; 17.6% Hispanic (Black and White); 6.8% Asian; 6.7% Other; 6.4% Black; and 0.3% American Indian. The race distribution of the boys and men in the safety population was as follows: 42.0% White; 19.7% Hispanic (Black and White); 11.0% Asian; 11.2% Other; 15.9% Black; and 0.1% American Indian.

Common Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age

The injection site adverse reactions 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 AAHS control or saline placebo recipients are shown in Table 1.

Table 1
Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	**GARDASIL** (N = 5088) %	**AAHS Control**** (N = 3470) %	**Saline Placebo** (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Pruritus	3.2	2.8	0.6
Bruising	2.8	3.2	1.6

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Common Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age

The injection site adverse reactions 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 AAHS control or saline placebo recipients are shown in Table 2.

Table 2
Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	**GARDASIL** (N = 3092) %	**AAHS Control **** (N = 2029) %	**Saline Placebo** (N = 274) %
Injection Site			
Pain	61.5	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Evaluation of Injection-Site Adverse Reactions by Dose in Girls and Women 9 Through 26 Years of Age

An analysis of injection-site adverse reactions in girls and women by dose is shown in Table 3. Of those girls and women who reported an injection-site reaction, 94.3% judged their injection-site adverse reaction to be mild or moderate in intensity.

Table 3
Postdose Evaluation of Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age
(1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			**AAHS Control*** (% occurrence)			**Saline Placebo** (% occurrence)		
Adverse Reaction	Postdose 1 N** = 5011	Postdose 2 N = 4924	Postdose 3 N = 4818	Postdose 1 N = 3410	Postdose 2 N = 3351	Postdose 3 N = 3295	Postdose 1 N = 315	Postdose 2 N = 301	Postdose 3 N = 300
Pain	63.4	60.7	62.7	57.0	47.8	49.6	33.7	20.3	27.3
Mild/Moderate	62.5	59.7	61.2	56.6	47.3	48.9	33.3	20.3	27.0
Severe	0.9	1.0	1.5	0.4	0.5	0.6	0.3	0.0	0.3
Swelling***	10.2	12.8	15.1	8.2	7.5	7.6	4.4	3.0	3.3
Mild/Moderate	9.6	11.9	14.2	8.1	7.2	7.3	4.4	3.0	3.3
Severe	0.6	0.8	0.9	0.2	0.2	0.2	0.0	0.0	0.0
Erythema***	9.2	12.1	14.7	9.8	8.4	8.9	7.3	5.3	5.7
Mild/Moderate	9.0	11.7	14.3	9.5	8.4	8.8	7.3	5.3	5.7
Severe	0.2	0.3	0.4	0.3	0.1	0.1	0.0	0.0	0.0

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**N = Number of individuals with follow-up
***Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Evaluation of Injection-Site Adverse Reactions by Dose in Boys and Men 9 Through 26 Years of Age

An analysis of injection-site adverse reactions in boys and men by dose is shown in Table 4. 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.

Table 4
Postdose Evaluation of Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age
(1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			**AAHS Control*** (% occurrence)			**Saline Placebo** (% occurrence)		
Adverse Reaction	Postdose 1 N** = 3002	Postdose 2 N = 2897	Postdose 3 N = 2825	Postdose 1 N = 1950	Postdose 2 N = 1853	Postdose 3 N = 1799	Postdose 1 N = 269	Postdose 2 N = 263	Postdose 3 N = 259
Pain	44.7	36.9	34.4	38.4	28.2	25.8	27.5	20.5	16.2
Mild/Moderate	44.5	36.5	34.1	37.9	28.2	25.5	27.5	20.2	16.2
Severe	0.2	0.5	0.3	0.4	0.1	0.3	0.0	0.4	0.0
Swelling***	5.6	6.6	7.7	5.6	4.5	4.1	4.8	1.5	3.5
Mild/Moderate	5.3	6.2	7.1	5.4	4.5	4.0	4.8	1.5	3.1
Severe	0.2	0.3	0.5	0.2	0.0	0.1	0.0	0.0	0.4
Erythema***	7.2	8.0	8.7	8.3	6.3	5.7	7.1	5.7	5.0
Mild/Moderate	6.8	7.7	8.3	8.0	6.2	5.6	7.1	5.7	5.0
Severe	0.3	0.2	0.3	0.2	0.1	0.1	0.0	0.0	0.0

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**N = Number of individuals with follow-up
***Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 28.2% and AAHS control or saline placebo = 28.4%). Fever was the next most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 13.0% and AAHS control or saline placebo = 11.2%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the GARDASIL group was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 5.

Table 5
Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age (GARDASIL ≥Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL** (N = 5088) %	**AAHS Control** or Saline Placebo** (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.5
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

*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

Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 12.3% and AAHS control or saline placebo = 11.2%). Fever was the next most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 8.2% and AAHS control or saline placebo = 6.5%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the group that received GARDASIL was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 6.

Table 6
Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age (GARDASIL ≥Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL** (N = 3092) %	**AAHS Control** or Saline Placebo** (N = 2303) %
Headache	12.3	11.2
Pyrexia	8.2	6.5
Pharyngolaryngeal 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

Evaluation of Fever by Dose in Girls and Women 9 Through 26 Years of Age

An analysis of fever in girls and women by dose is shown in Table 7.

Table 7
Postdose Evaluation of Fever in Girls and Women 9 Through 26 Years of Age
(1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N** = 4945	Postdose 2 N = 4804	Postdose 3 N = 4671	Postdose 1 N = 3681	Postdose 2 N = 3564	Postdose 3 N = 3467
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.2	0.4	0.5

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**N = Number of individuals with follow-up

Evaluation of Fever by Dose in Boys and Men 9 Through 26 Years of Age

An analysis of fever in boys and men by dose is shown in Table 8.

Table 8
Postdose Evaluation of Fever in Boys and Men 9 Through 26 Years of Age
(1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N** = 2971	Postdose 2 N = 2847	Postdose 3 N = 2791	Postdose 1 N = 2194	Postdose 2 N = 2079	Postdose 3 N = 2046
≥100 to <102	2.4	2.5	2.3	2.1	2.1	1.6
≥102	0.6	0.5	0.5	0.6	0.3	0.3

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**N = Number of individuals with follow-up

Serious Adverse Reactions in the Entire Study Population

Across the clinical studies, 255 individuals (GARDASIL N = 126 or 0.8%; placebo N = 129 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men) reported a serious systemic adverse reaction.

Of the entire study population (29,323 individuals), 0.04% of the reported serious systemic adverse reactions were judged to be vaccine related by the study investigator. The most frequently (frequency of 4 cases or greater with either GARDASIL, AAHS control, saline placebo, or the total of all three) reported serious systemic adverse reactions, regardless of causality, were:

Headache [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],
Gastroenteritis [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],
Appendicitis [0.03% GARDASIL (5 cases) vs. 0.01% AAHS control (1 case)],
Pelvic inflammatory disease [0.02% GARDASIL (3 cases) vs. 0.03% AAHS control (4 cases)],
Urinary tract infection [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (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% AAHS control or saline placebo) of bronchospasm; and 2 cases (0.01% GARDASIL; 0.0% AAHS control or saline placebo) of asthma were reported as serious systemic adverse reactions 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 reactions (injection-site pain and injection-site joint movement impairment).

Deaths in the Entire Study Population

Across the clinical studies, 37 deaths (GARDASIL N = 18 or 0.1%; placebo N = 19 or 0.1%) were reported in 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023, saline placebo N = 594) 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 AAHS control), followed by drug overdose/suicide (2 individuals who received GARDASIL and 6 individuals who received AAHS control), gun shot wound (1 individual who received GARDASIL and 3 individuals who received AAHS control), and pulmonary embolus/deep vein thrombosis (1 individual who received GARDASIL and 1 individual who received AAHS control). 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, and 1 case of systemic lupus erythematosus in the group that received GARDASIL; 1 case of asphyxia, 1 case of acute lymphocytic leukemia, 1 case of chemical poisoning, and 1 case of myocardial ischemia in the AAHS control group; and 1 case of medulloblastoma in the saline placebo group.

Systemic Autoimmune Disorders in Girls and Women 9 Through 26 Years of Age

In the clinical studies, 9- through 26-year-old girls and women 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 AAHS control or saline placebo are shown in Table 9. This population includes all girls and women who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

Table 9
Summary of Girls and Women 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 10,706)	AAHS Control* or Saline Placebo (N = 9412)
	n (%)	n (%)
Arthralgia/Arthritis/Arthropathy**	120 (1.1)	98 (1.0)
Autoimmune Thyroiditis	4 (0.0)	1 (0.0)
Celiac Disease	10 (0.1)	6 (0.1)
Diabetes Mellitus Insulin-dependent	2 (0.0)	2 (0.0)
Erythema Nodosum	2 (0.0)	4 (0.0)
Hyperthyroidism***	27 (0.3)	21 (0.2)
Hypothyroidism†	35 (0.3)	38 (0.4)
Inflammatory Bowel Disease‡	7 (0.1)	10 (0.1)
Multiple Sclerosis	2 (0.0)	4 (0.0)
Nephritis¶	2 (0.0)	5 (0.1)
Optic Neuritis	2 (0.0)	0 (0.0)
Pigmentation Disorder§	4 (0.0)	3 (0.0)
Psoriasis#	13 (0.1)	15 (0.2)
Raynaud's Phenomenon	3 (0.0)	4 (0.0)
Rheumatoid Arthritis††	6 (0.1)	2 (0.0)
Scleroderma/Morphea	2 (0.0)	1 (0.0)
Stevens-Johnson Syndrome	1 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	1 (0.0)	3 (0.0)
Uveitis	3 (0.0)	1 (0.0)
All Conditions	245 (2.3)	218 (2.3)

*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, Goiter, Toxic nodular goiter, 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 juvenile rheumatoid arthritis. One woman 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.

Systemic Autoimmune Disorders in Boys and Men 9 Through 26 Years of Age

In the clinical studies, 9- through 26-year-old boys and men 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 AAHS control or saline placebo are shown in Table 10. This population includes all boys and men who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

Table 10
Summary of Boys and Men 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 3092)	AAHS Control* or Saline Placebo (N = 2303)
	n (%)	n (%)
Alopecia Areata	1 (0.0)	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***	0 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	2 (0.1)
Vitiligo	2 (0.1)	5 (0.2)
All Conditions	43 (1.4)	32 (1.4)

*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.

Safety in Concomitant Use with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] in Girls and Women 16 Through 23 Years of Age

The safety of GARDASIL when administered concomitantly with RECOMBIVAX HB®[1] [hepatitis B vaccine (recombinant)] was evaluated in an AAHS-controlled study of 1871 girls and women with a mean age of 20.4 years *[see Clinical Studies (14.8)]*. The race distribution of the study individuals was as follows: 61.6% White; 23.8% Other; 11.9% Black; 1.6% Hispanic (Black and White); 0.8% Asian; and 0.3% American Indian. The rates of systemic and injection-site adverse reactions were similar among girls and women who received concomitant vaccination as compared with those who received GARDASIL or RECOMBIVAX HB [hepatitis B vaccine (recombinant)].

Safety in Concomitant Use 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 of GARDASIL when administered concomitantly 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)] was evaluated in a randomized study of 1040 boys and girls with a mean age of 12.6 years *[see Clinical Studies (14.9)]*. The race distribution of the study subjects was as follows: 77.7% White; 1.4% Multi-racial; 12.3% Black; 6.8% Hispanic (Black and White); 1.2% Asian; 0.4% American Indian, and 0.2% Indian.

There was an increase in injection-site swelling reported at the injection site for GARDASIL (concomitant = 10.9%, non-concomitant = 6.9%) when GARDASIL was administered concomitantly with Menactra and Adacel as compared to non-concomitant (separated by 1 month) vaccination. The majority of injection-site swelling adverse experiences were reported as being mild to moderate in intensity.

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during post-approval use of GARDASIL. Because these events 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.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Nausea, pancreatitis, vomiting.

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

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

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Vascular disorders: Deep venous thrombosis.

7 DRUG INTERACTIONS

7.1 Use with RECOMBIVAX HB

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] *[see Clinical Studies (14.8)]*.

7.2 Use with Menactra and Adacel

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] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] *[see Clinical Studies (14.9)]*.

7.3 Use with Hormonal Contraceptives

In clinical studies, 13,293 women (GARDASIL N = 6644; AAHS control or saline placebo N = 6649) who had post-Month 7 follow-up used hormonal contraceptives for a total of 17,597 person-years (65.1% of the total follow-up time in the studies). Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not alter immune response in the per protocol efficacy (PPE) population.

7.4 Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines *[see Use in Specific Populations (8.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rats at doses equivalent to the recommended human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, GARDASIL should be used during pregnancy only if clearly needed.

An evaluation of the effect of GARDASIL on embryo-fetal, pre- and postweaning development was conducted using rats. One group of rats was administered GARDASIL twice prior to gestation, during the period of organogenesis (gestation Day 6) and on lactation Day 7. A second group of pregnant rats was administered GARDASIL during the period of organogenesis (gestation Day 6) and on lactation Day 7 only. GARDASIL was administered at 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to the recommended human dose) by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring.

Clinical Studies in Humans

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.

GARDASIL is not indicated for women 27 years of age or older. However, safety data in women 16 through 45 years of age was collected, and 3620 women (GARDASIL N = 1796 vs. AAHS control or saline placebo N = 1824) reported at least 1 pregnancy each.

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 23.3% (423/1812) in women who received GARDASIL and 24.1% (438/1820) in women who received AAHS control or saline placebo.

Overall, 54 and 63 women in the group that received GARDASIL or AAHS control or saline placebo, respectively (3.0% and 3.5% of all women who reported a pregnancy in the respective vaccination groups), experienced a serious adverse reaction 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 women who experienced such events were comparable between the groups receiving GARDASIL and AAHS control or saline placebo.

There were 40 cases of congenital anomaly in pregnancies that occurred in women who received GARDASIL and 30 cases of congenital anomaly in pregnancies that occurred in women who received AAHS control or saline placebo.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or AAHS control or saline 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 AAHS control or saline placebo. The congenital anomalies seen in pregnancies with estimated onset within 30 days of vaccination included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia, and club foot. Conversely, in pregnancies with onset more than 30 days following vaccination, 35 cases of congenital anomaly were observed in the group that received GARDASIL compared with 29 cases of congenital anomaly in the group that received AAHS control or saline placebo.

Pregnancy Registry for GARDASIL

Merck & Co., Inc. maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to GARDASIL. Patients and health care providers are encouraged to report any exposure to GARDASIL during pregnancy by calling (800) 986-8999.

8.3 Nursing Mothers

Women 16 Through 26 Years of Age

It is not known whether GARDASIL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

A total of 995 nursing mothers (vaccine N = 500, AAHS control N = 495) were given GARDASIL or AAHS control during the vaccination period of the clinical trials.

Overall, 21 and 10 infants of women who received GARDASIL or AAHS control, respectively (representing 4.2% and 2.0% of the total number of women who were breast-feeding during the period in which they received GARDASIL or AAHS control, respectively), experienced a serious adverse reaction.

In a post-hoc analysis of clinical studies, a higher number of breast-feeding infants (n = 6) 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 control. In these studies, the rates of other adverse reactions in the mother and the nursing infant were comparable between vaccination groups.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

8.5 Geriatric Use

The safety and effectiveness of GARDASIL have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

8.6 Immunocompromised Individuals

The immunologic response to GARDASIL may be diminished in immunocompromised individuals *[see Drug Interactions (7.4)]*.

10 OVERDOSAGE

There have been 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.

11 DESCRIPTION

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

GARDASIL is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg

of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

GARDASIL administered to female rats at a dose of 120 mcg total protein, which is equivalent to the recommended human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

The effect of GARDASIL on male fertility has been studied in male rats at an intramuscular dose of 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to the recommended human dose). One group of male rats was administered GARDASIL once, 3 days prior to cohabitation, and a second group of male rats was administered GARDASIL three times, at 6 weeks, 3 weeks, and 3 days prior to cohabitation. There were no treatment-related effects on reproductive performance including fertility, sperm count, and sperm motility. There were no treatment-related gross or histomorphologic and weight changes on the testes.

14 CLINICAL STUDIES

CIN 2/3 and AIS are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer; thus, they serve as surrogate markers for prevention of cervical cancer. In the clinical studies in girls and women aged 16 through 26 years, cases of CIN 2/3 and AIS were the efficacy endpoints to assess prevention of cervical cancer. In addition, cases of VIN 2/3 and VaIN 2/3 were the efficacy endpoints to assess prevention of HPV-related vulvar and vaginal cancers, and observations of external genital lesions were the efficacy endpoints for the prevention of genital warts.

In clinical studies in boys and men aged 16 through 26 years, efficacy was evaluated using the following endpoints: external genital warts and penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer.

Efficacy was assessed in 5 AAHS-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL (Study 1, N = 2391 girls and women) and the second evaluated all components of GARDASIL (Study 2, N = 551 girls and women). Two Phase III studies evaluated GARDASIL in 5442 (Study 3) and 12,157 (Study 4) girls and women. A third Phase III study, Study 5, evaluated GARDASIL in 4055 boys and men. Together, these five studies evaluated 24,596 individuals (20,541 girls and women 16 through 26 years of age at enrollment with a mean age of 20.0 years and 4055 boys and men 16 through 26 years of age at enrollment with a mean age of 20.5 years). The race distribution of the girls and women in the clinical trials was as follows: 70.4% White; 12.2% Hispanic (Black and White); 8.8% Other; 4.6% Black; 3.8% Asian; and 0.2% American Indian. The race distribution of the boys and men in the clinical trials was as follows: 35.2% White; 20.5% Hispanic (Black and White); 14.4% Other; 19.8% Black; 10.0% Asian; and 0.1% American Indian.

The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, and 2.3 years for Study 1, Study 2, Study 3, Study 4, and Study 5, respectively. Individuals received vaccine or AAHS control on the day of enrollment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies in girls and women combined according to a prospective clinical plan.

Overall, 73% of 16- through 26-year-old girls and women and 83% of 16- through 26-year-old boys and men were naïve (i.e., PCR [Polymerase Chain Reaction] negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment.

A total of 27% of 16- through 26-year-old girls and 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 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.

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.

14.1 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Girls and Women 16 Through 26 Years of Age

GARDASIL was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of girls and women regardless of baseline HPV status (i.e., PCR status or serostatus). Girls and women with current or prior HPV infection with an HPV type contained in the vaccine 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 girls and women 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 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 11).

In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types.

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

Population	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Study 1***	755	0	750	12	100.0 (65.1, 100.0)
Study 2	231	0	230	1	100.0 (-3744.9, 100.0)
Study 3	2201	0	2222	36	100.0 (89.2, 100.0)
Study 4	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					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	6	100.0 (14.4, 100.0)
Study 4	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					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	5	100.0 (-10.1, 100.0)
Study 4	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					
Study 2	235	0	233	3	100.0 (-138.4, 100.0)
Study 3	2241	0	2258	77	100.0 (95.1, 100.0)
Study 4	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					
Study 2	235	0	233	3	100.0 (-139.5, 100.0)
Study 3	2261	0	2279	58	100.0 (93.5, 100.0)
Study 4	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
‡Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 11 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Prophylactic efficacy against overall cervical and genital disease related to HPV 6, 11, 16, and 18 in an extension phase of Study 2, that included data through Month 60, was noted to be 100% (95% CI: 12.3%, 100.0%) among girls and women in the per protocol population naïve to the relevant HPV types.

GARDASIL was efficacious against HPV disease caused by HPV types 6, 11, 16, and 18 in girls and women who were naïve for those specific HPV types at baseline.

14.2 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Boys and Men 16 Through 26 Years of Age

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population. This population consisted of boys and men 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 related to vaccine HPV types 6 and 11 in those boys and men who were PCR negative and seronegative at baseline (Table 12). Efficacy against penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance.

Table 12
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	1397	3	1408	31	90.4 (69.2, 98.1)
Condyloma	1397	3	1408	28	89.4 (65.5, 97.9)
PIN 1/2/3	1397	0	1408	3	100 (-141.2, 100.0)

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

14.3 Population Impact in Girls and Women 16 Through 26 Years of Age

Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

The clinical trials included girls and women regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in these girls and women. Here, analyses included events arising among girls and women regardless of baseline PCR status and serostatus, including 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 girls and women regardless of current or prior exposure to a vaccine HPV type is shown in Table 13. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in girls and women who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in girls and women who were positive for vaccine HPV infection, as well as vaccine impact among girls and women regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of CIN and genital warts, VIN, and VaIN related to a vaccine HPV type 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.

There was no clear evidence of protection from disease caused by HPV types for which girls and women were PCR positive regardless of serostatus at baseline.

Table 13
Effectiveness of GARDASIL in Prevention of HPV 6, 11, 16, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Endpoint	Analysis	GARDASIL or HPV 16 L1 VLP Vaccine		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9346	4	9407	155	97.4 (93.3, 99.3)
	HPV 16 and/or HPV 18 Positive at Day 1	2870	142	2898	148**	--***
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18†	9836	146	9904	303	51.8 (41.1, 60.7)‡
HPV 16- or 18-related VIN 2/3 or VaIN 2/3	Prophylactic Efficacy*	8642	1	8673	34	97.0 (82.4, 99.9)
	HPV 16 and/or HPV 18 Positive at Day 1	1880	8	1876	4	**--***
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18†	8955	9	8968	38	76.3 (50.0, 89.9)‡
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	Prophylactic Efficacy*	8630	16	8680	309	94.8 (91.5, 97.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	2466	186#	2437	213#	**--***
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types†	8819	202	8854	522	61.5 (54.6, 67.4)‡
HPV 6-, 11-, 16-, or 18-related Genital Warts	Prophylactic Efficacy*	8761	10	8792	252	96.0 (92.6, 98.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	2501	51§	2475	55§	**--***
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types†	8955	61	8968	307	80.3 (73.9, 85.3)‡
HPV 6- or 11-related Genital Warts	Prophylactic Efficacy*	7769	9	7792	246	96.4 (93.0, 98.4)
	HPV 6 and/or HPV 11 Positive at Day 1	1186	51	1176	54	**--***
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types†	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 AAHS control cases of 16/18 CIN 2/3, 2 women were missing serology or PCR results for Day 1.
***There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.
†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 AAHS control women with missing serology/PCR data at Day 1.
§Includes 1 woman 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 1, 2, 3, and 4. All other endpoints only included data from studies 2, 3, and 4.
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.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

The impact of GARDASIL against the overall burden of HPV-related cervical, vulvar, and vaginal disease (i.e., disease caused by any HPV type) results from a combination of prophylactic efficacy against vaccine HPV types, disease contribution from vaccine HPV types present at time of vaccination, and the disease contribution from HPV types not contained in the vaccine.

Additional efficacy analyses were conducted in 2 populations: (1) a generally 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 girls and women and (2) the general study population of girls and women regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve girls and women and among all girls and women in the study population (including girls and women with HPV infection at Day 1), GARDASIL reduced the overall incidence of CIN 2/3 or AIS; of VIN 2/3 or VaIN 2/3; of CIN (any grade) or AIS; and of Genital Warts (Table 14). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in girls and women naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected girls and women may already have CIN 2/3 or AIS at Day 1 and some will develop CIN 2/3 or AIS during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

Table 14
Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

Endpoints Caused by Vaccine or Non-vaccine HPV Types	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
CIN 2/3 or AIS	Prophylactic Efficacy*	4616	77	4680	136	42.7 (23.7, 57.3)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	8559	421	8592	516	18.4 (7.0, 28.4)***
VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	4688	7	4735	31	77.1 (47.1, 91.5)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	8688	30	8701	61	50.7 (22.5, 69.3)***
CIN (Any Grade) or AIS	Prophylactic Efficacy*	4616	272	4680	390	29.7 (17.7, 40.0)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	8559	967	8592	1189	19.1 (11.9, 25.8)***
Genital Warts	Prophylactic Efficacy*	4688	29	4735	169	82.8 (74.3, 88.8)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	8688	132	8701	350	62.5 (54.0, 69.5)***

*Includes all individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1. Case counting started at 1 month postdose 1.
**Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status or Pap test result 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.
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.4 Population Impact in Boys and Men 16 Through 26 Years of Age

Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Genital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Study 5 included boys and men regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related genital disease in these boys and men. Here, analyses included events arising among boys and men regardless of baseline PCR status and serostatus, including 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 boys and men regardless of current or prior exposure to a vaccine HPV type is shown in Table 15. Impact was measured starting at Day 1. Prophylactic efficacy denotes the vaccine's efficacy in boys and men who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in boys and men who were positive for vaccine HPV infection, as well as vaccine impact among boys and men regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of genital disease related to a vaccine HPV type 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.

There was no clear evidence of protection from disease caused by HPV types for which boys and men were PCR positive regardless of serostatus at baseline.

Table 15
Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Genital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Prophylactic Efficacy*	1775	13	1770	52	75.5 (54.3, 87.7)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	168	14	167	25	--**
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types***	1943	27	1937	77	65.5 (45.8, 78.6)†
Condyloma	Prophylactic Efficacy*	1775	10	1770	48	79.6 (59.1, 90.8)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	168	14	167	24	--**
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types***	1943	24	1937	72	67.2 (47.3, 80.3)†
PIN 1/2/3	Prophylactic Efficacy*	1775	4	1770	4	1.2 (-430.5, 81.6)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	168	2	167	1	--**
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types***	1943	6	1937	5	-19.2 (-393.8, 69.7)†

*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.
**There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.
***Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
†Percent reduction for these analyses 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
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

The impact of GARDASIL against the overall burden of HPV-related genital disease (i.e., disease caused by any HPV type) results from a combination of prophylactic efficacy against vaccine HPV types, disease contribution from vaccine HPV types present at time of vaccination, and the disease contribution from HPV types not contained in the vaccine.

Additional efficacy analyses from Study 5 were conducted in 2 populations: (1) a generally HPV-naïve population that consisted of boys and men who are seronegative and PCR negative to HPV 6, 11, 16, and 18 and PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 at Day 1, approximating a population

of sexually-naïve boys and men and (2) the general study population of boys and men regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve boys and men and among all boys and men in Study 5 (including boys and men with HPV infection at Day 1), GARDASIL reduced the overall incidence of genital disease (Table 16). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in boys and men naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected boys and men may already have genital disease at Day 1 and some will develop genital disease during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

Table 16
Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Generally HPV Naïve*	1275	6	1270	36	83.8 (61.2, 94.4)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	1943	36	1937	89	60.2 (40.8, 73.8)***
Condyloma	Generally HPV Naïve*	1275	5	1270	33	85.3 (62.1, 95.5)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	1943	32	1937	83	62.1 (42.4, 75.6)***
PIN 1/2/3	Generally HPV Naïve*	1275	1	1270	3	67.4 (-306.5, 99.4)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types**	1943	7	1937	6	-15.9 (-317.5, 66.6)***

*Includes all individuals who received at least 1 vaccination and who were seronegative and PCR negative at enrollment to HPV 6, 11, 16 and 18, and PCR negative at enrollment to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Case counting started at Day 1.
**Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
***Percent reduction for these analyses 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
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.5 Overall Population Impact

The subject characteristics (e.g. lifetime sex partners, geographic distribution of the subjects) influence the HPV prevalence of the population and therefore the population benefit can vary widely.

The overall efficacy of GARDASIL will vary with the baseline prevalence of HPV infection and disease, the incidence of infections against which GARDASIL has shown protection, and those infections against which GARDASIL has not been shown to protect.

The efficacy of GARDASIL for HPV types not included in the vaccine (i.e., cross-protective efficacy) is a component of the overall impact of the vaccine on rates of disease caused by HPV. Cross-protective efficacy was not demonstrated against disease caused by non-vaccine HPV types in the combined database of the Study 3 and Study 4 trials.

GARDASIL does not protect against genital disease not related to HPV. One woman who received GARDASIL in Study 3 developed an external genital well-differentiated squamous cell carcinoma at Month 24. No HPV DNA was detected in the lesion or in any other samples taken throughout the study.

In 18,150 girls and women enrolled in Study 2, Study 3, and Study 4, GARDASIL reduced definitive cervical therapy procedures by 23.9% (95% CI: 15.2%, 31.7%).

14.6 Other Studies

Data are insufficient to establish effectiveness of GARDASIL in women 27 through 45 years of age.

14.7 Immunogenicity

Assays to Measure Immune Response

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.

The immunogenicity of GARDASIL was assessed in 20,132 9- through 26-year-old girls and women (GARDASIL N = 10,723; AAHS control or saline placebo N = 9409) and 5417 9- through 26-year-old boys and men (GARDASIL N = 3109; AAHS control or saline placebo N = 2308).

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

Immune Response to GARDASIL

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).

In clinical studies in girls and women, at least 99.8%, 99.8%, 99.8%, and 99.5% 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 boys and men, at least 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 17 and Table 18). GMTs declined through Month 24 and then stabilized through Month 36 at levels above baseline. Table 19 displays 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 17
Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of 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	9862	3333	99.8 (99.6, 99.9)	545.2 (530.3, 560.6)
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	9862	3357	99.8 (99.5, 99.9)	749.0 (726.1, 772.7)
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	9862	3253	99.8 (99.6, 100.0)	2411.3 (2311.1, 2515.9)
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	9862	3571	99.4 (99.1, 99.7)	475.6 (459.2, 492.6)

*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 18
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	1094	98.9 (98.1, 99.4)	447.2 (418.4, 477.9)
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	1094	99.2 (98.4, 99.6)	624.5 (588.6, 662.5)
Anti-HPV 16				
9- through 15-year-old boys	1072	882	99.8 (99.2, 100.0)	6056.5 (5601.4, 6548.6)
16- through 26-year-old boys and men	2026	1137	98.8 (97.9, 99.3)	2401.5 (2241.8, 2572.6)
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	1176	97.4 (96.3, 98.2)	402.6 (374.6, 432.6)

*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 19
Persistence of Anti-HPV cLIA Geometric Mean Titers by Gender and Age Group

Assay (cLIA)/ Time Point	9- to 15-year-old Boys (N* = 1072)		16- to 26-year-old Boys and Men (N* = 2026)		9- to 15-year-old Girls (N* = 1122)		16- to 26-year-old Girls and Women (N* = 9859)	
	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	884	1037.5 (963.5, 1117.3)	1094	447.2 (418.4, 477.9)	917	929.2 (874.6, 987.3)	3333	545.2 (530.3, 560.6)
Month 24	323	134.1 (119.5, 150.5)	907	80.3 (74.9, 86.0)	214	156.1 (135.6, 179.6)	2792	109.1 (105.2, 113.1)
Month 36†	342	126.6 (111.9, 143.2)	654	72.4 (68.0, 77.2)	356	129.4 (115.6, 144.8)	-	-
Month 48‡	-	-	-	-	-	-	2375	74.6 (71.6, 77.7)
Anti-HPV 11								
Month 07	885	1386.8 (1298.5, 1481.0)	1094	624.5 (588.6, 662.5)	917	1304.6 (1224.7, 1389.7)	3357	749.0 (726.1, 772.7)
Month 24	324	188.5 (168.4, 211.1)	907	94.6 (88.4, 101.2)	214	218.0 (188.3, 252.4)	2821	137.0 (132.0, 142.2)
Month 36†	342	148.8 (131.1, 169.0)	654	80.3 (75.7, 85.2)	356	148.0 (131.1, 167.1)	-	-
Month 48‡	-	-	-	-	-	-	2399	90.3 (86.6, 94.1)
Anti-HPV 16								
Month 07	882	6056.5 (5601.4, 6548.6)	1137	2401.5 (2241.8, 2572.6)	915	4918.5 (4556.6, 5309.1)	3253	2411.3 (2311.1, 2515.9)
Month 24	322	938.2 (825.0, 1067.0)	938	347.7 (322.5, 374.9)	211	944.2 (804.4, 1108.3)	2725	442.6 (425.0, 460.9)
Month 36†	341	708.8 (613.9, 818.3)	672	306.7 (287.5, 327.1)	353	642.2 (562.8, 732.8)	-	-
Month 48‡	-	-	-	-	-	-	2330	334.6 (319.4, 350.5)
Anti-HPV 18								
Month 07	887	1357.4 (1249.4, 1474.7)	1176	402.6 (374.6, 432.6)	922	1042.6 (967.6, 1123.3)	3571	475.6 (459.2, 492.6)
Month 24	324	131.9 (112.1, 155.3)	967	38.7 (35.2, 42.5)	214	137.7 (114.8, 165.1)	3007	50.8 (48.2, 53.5)
Month 36†	343	113.0 (94.7, 135.0)	690	33.4 (30.9, 36.1)	357	87.0 (74.8, 101.2)	-	-
Month 48‡	-	-	-	-	-	-	2536	33.8 (32.0, 35.7)

*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
†Month 36 time point for 16- to 26-year-old boys and men; Month 37 for 9- to 15-year-old boys and 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 boys and girls 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 17 and 18 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 Study 5.

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

GMT Response to Variation in Dosing Regimen in 18- Through 26-Year-Old Women

Girls and women evaluated in the PPE population of clinical studies received all 3 vaccinations within 1 year of enrollment. 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 impact the immune responses to GARDASIL.

Duration of the Immune Response to GARDASIL

The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. The peak anti-HPV GMTs for HPV types 6, 11, 16, and 18 occurred at Month 7. Anti-HPV GMTs for HPV types 6, 11, 16, and 18 were similar between measurements at Month 24 and Month 60 in Study 2.

14.8 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, double-blind, study of 1871 women aged 16 through 24 years at enrollment. The race distribution of the girls and women in the clinical trial was as follows: 61.6% White; 1.6% Hispanic (Black and White); 23.8% Other; 11.9% Black; 0.8% Asian; and 0.3% American Indian.

Subjects either received GARDASIL and RECOMBIVAX HB (n = 466), GARDASIL and RECOMBIVAX HB-matched placebo (n = 468), RECOMBIVAX HB and GARDASIL-matched placebo (n = 467) or RECOMBIVAX-matched placebo and GARDASIL-matched placebo (n = 470) at Day 1, Month 2 and Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series.

Concomitant administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with RECOMBIVAX HB or separately.

14.9 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 an open-labeled, randomized, controlled study of 1040 boys and girls 11 through 17 years of age at enrollment. The race distribution of the subjects in the clinical trial was as follows: 77.7% White; 6.8% Hispanic (Black and White); 1.4% Multi-racial; 12.3% Black; 1.2% Asian; 0.2% Indian; and 0.4% American Indian.

One group received GARDASIL in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 517). The second group received the first dose of GARDASIL on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 523). Subjects in both vaccination groups received the second dose of GARDASIL at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL).

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)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with Menactra and Adacel or separately.

16 HOW SUPPLIED/STORAGE AND HANDLING

All presentations for GARDASIL contain a suspension of 120 mcg L1 protein from HPV types 6, 11, 16, and 18 in a 0.5-mL dose. GARDASIL is supplied in vials and syringes.

Carton of one 0.5-mL single-dose vial. **NDC** 0006-4045-00.

Carton of ten 0.5-mL single-dose vials. **NDC** 0006-4045-41.

Carton of six 0.5-mL single-dose prefilled Luer Lock syringes, preassembled with UltraSafe Passive®[2] delivery system. One-inch, 25-gauge needles are provided separately in the package. **NDC** 0006-4109-06.

Carton of six 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. **NDC** 0006-4109-09.

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

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

GARDASIL can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling.]

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care.
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
- Since syncope has been reported following vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
- Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
- Information regarding benefits and risks associated with vaccination.
- GARDASIL is not recommended for use in pregnant women.
- Importance of completing the immunization series unless contraindicated.
- Report any adverse reactions to their health care provider.

Manufactured and Distributed by:

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Printed in USA
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[1] Registered trademark of MERCK & CO., Inc. Whitehouse Station, NJ 08889, USA

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[2] UltraSafe Passive® delivery system is a Trademark of Safety Syringes, Inc.