Registration No.: 1C 11/55 (NB)

Importer / Manufacturer: MSD (Thailand) Ltd. / Merck Sharp & Dohme Corp., West Point, Pennsylvania 19486, USA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

GARDASIL is a recombinant, quadrivalent vaccine that protects against Human Papillomavirus (HPV).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

N/A

3. PHARMACEUTICAL FORM

Suspension for injection in a single-dose 0.5 mL vial and 10 single-dose 0.5 mL vials.
Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GARDASIL is a vaccine indicated in girls and women 9 through 45 years for the prevention of cervical, vulvar, vaginal, and anal cancer; precancerous or dysplastic lesions; genital warts; and infections caused by Human Papillomavirus (HPV).
GARDASIL is indicated to prevent the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And infections 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
- VIN grade 1 and VaIN grade 1
- Anal intraepithelial neoplasia (AIN) grades 1, 2, 3

The safety and efficacy of GARDASIL in female older than 26 years of age also have been evaluated (See SIDE EFFECTS and CLINICAL PHARMACOLOGY, Clinical Studies).

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of external genital lesions and infection and the following diseases caused by HPV types included in the vaccine:

- Anal 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:

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

Limitation 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 Counselling Information).

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.

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

GARDASIL has not been demonstrated to protect against disease due to HPV types not contained in the vaccine.

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.

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

4.2 Posology and method of administration

Dosage
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.

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 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.

Method of 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.

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.

4.3 Contraindication

Hypersensitivity to the active substances or to any of the excipients of the vaccine.

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

4.4 Special warnings and precautions for use

General

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 SIDE EFFECTS, Post-Marketing Reports).

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

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization (see DRUG INTERACTIONS).

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

4.5 Interaction with other medical products and forms of interaction

Use with Other Vaccines

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

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 PRECAUTIONS, *General*).

4.6 Pregnancy and lactation

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.

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).

During clinical trials, 3,819 women (vaccine N = 1,894 vs. placebo N = 1,925) 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% (446/1,973) in individuals who received GARDASIL and 23.1% (460/1,994) 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.

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

NURSING MOTHERS
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 placebo were given to a total of 1,133 women who were breast feeding at any time 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.

4.7 Effects on the ability to drive and use machines

N/A

4.8 Undesirable effects

Clinical Trials
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. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). 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 (6,995 girls and women 9 through 45 years of age and 3,093 boys and men 9 through 26 years of age at enrollment) who received GARDASIL and 7,995 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 listed according to frequency and system organ class.

The frequency classifications are as follows:
Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000)

Vaccine-Related Clinical Adverse Experiences in 9-Through 45-Year-Old Girls and Women

Nervous system disorders
Very Common: headache
Common: *dizziness*

Gastrointestinal disorders
Common: *nausea*

Musculoskeletal and connective tissue disorders
Common: *pain in extremity*

General disorders and administration site conditions
Very Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common: *erythema, pain, and swelling. Common: pruritus and hematoma.*

Most injection-site reactions were mild to moderate.

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

Vaccine-Related Clinical Adverse Experiences in 9-Through 26-Year-Old Boys and Men

Nervous system disorders
Common: *headache*

General disorders and administration site conditions
Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common: *erythema, pain, and swelling.*

The following injection-site reaction occurred at a greater incidence in the group that received GARDASIL compared with the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing placebo group: Common: *hematoma*.

Most injection-site reactions were mild to moderate.

Concomitant Administration with Other Vaccines
The safety of GARDASIL when administered concomitantly with other vaccines was evaluated in clinical studies.

The frequency of adverse experiences observed with concomitant administration with hepatitis B vaccine (recombinant) was similar to the frequency when GARDASIL was administered alone.

There was an increase in headache and injection-site swelling when GARDASIL was given concomitantly with Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content).

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 these adverse experiences seen with concomitant administration with other vaccines were reported as being mild to moderate in intensity.

Post-Marketing Reports
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: idiopathic thrombocytopenic purpura, lymphadenopathy

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

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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

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

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

USE IN ELDERLY
The safety and efficacy of GARDASIL have not been evaluated in adults above the age of 45 years.

USE IN OTHER SPECIAL POPULATIONS
The safety, immunogenicity, and efficacy of GARDASIL have not been fully evaluated in HIV-infected individuals.

4.9 Overdose
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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
N/A

5.2 Pharmacokinetic properties
N/A

5.3 Preclinical safety data
N/A

CLINICAL PHARMACOLOGY

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.

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.

Clinical Studies

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Girls and Women
GARDASIL was highly efficacious in reducing the incidence of cervical, vulvar, and vaginal cancers; CIN (any grade); AIS; non-invasive cervical cancer (CIN 3 and AIS); and external genital lesions, including condyloma acuminata, VIN (any grade) and VaIN (any grade) caused by HPV types 6, 11, 16, and 18. Based on a pre-specified analysis of lesions evident beginning 30 days Postdose 1, there was evidence that the vaccine was already efficacious during the course of the 3-dose vaccination regimen.

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 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 (Table 1).

Table 1
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 (<0.0, 100.0)
FUTURE I	2,201	0	2,222	36	100.0 (89.2, 100.0)
FUTURE II	5,306	2**	5,262	63	96.9 (88.2, 99.6)
Combined Protocols***	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16-related CIN 2/3 or AIS					
Combined Protocols***	7,402	2	7,205	93	97.9 (92.3, 99.8)
HPV 18-related CIN 2/3 or AIS					
Combined Protocols***	7,382	0	7,316	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	2,219	0	2,239	6	100.0 (14.4, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	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	2,219	0	2,239	5	100.0 (<0.0, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	9	100.0 (49.5, 100.0)
HPV 6-, 11-,16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,241	0	2,258	77	100.0 (95.1,

					100.0)
FUTURE II	5,388	9	5,374	145	93.8 (88.0, 97.2)
Combined Protocols***	7,864	9	7,865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer)					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,261	0	2,279	74	100.0 (94.9, 100.0)
FUTURE II	5,404	2	5,390	150	98.7 (95.2, 99.8)
Combined Protocols***	7,900	2	7,902	227	99.1 (96.8, 99.9)
HPV 6- or 11-related Genital Warts					
Combined Protocols***	6,932	2	6,856	189	99.0 (96.2, 99.9)

*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. 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. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.
***Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria
n = Number of individuals with at least one 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: 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); efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I); and efficacy against HPV 6/11/16/18-related external genital lesions (EGL) is >20% (FUTURE I)

In the long-term extension study of FUTURE II, for 16- to 23-year old women in the PPE population vaccinated with GARDASIL in the base study and followed in the extension, no cases of HPV diseases caused by HPV types 6/11/16/18 related CIN any grade were observed for up to approximately 8 years. In this study, durable protection was statistically demonstrated to approximately 6 years. In this extension study, women will be followed up to 14 years.

Prophylactic Efficacy – 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 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 external genital lesions (Condyloma and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 2).

Table 2
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)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (<0.0, 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	93.3 (76.3, 99.3)

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, cases of AIN 2/3 were the efficacy endpoints used to assess prevention of HPV-related anal cancer. The primary analyses of efficacy were conducted in the PPE population of Protocol 020.

GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline (Table 3).

Table 3
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)

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

The duration of protection against anal cancer is currently unknown. In the long-term extension study of Protocol 020 for 16-26 year old men in the PPE population of men vaccinated with GARDASIL in the base study and followed in the extension, no cases of HPV diseases (HPV types 6/11 related genital warts, HPV 6/11/16/18 external genital lesions and HPV 6/11/16/18 AIN any grade in MSM) were observed up to approximately 6 years. In this extension study, men will be followed up to 10 years.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 24- Through 45-Year-Old Women
A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals compared to younger individuals. Therefore, to confirm the utility of GARDASIL to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study (FUTURE III) was conducted.

GARDASIL was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL was also highly efficacious in reducing the incidence of a HPV 16/18-related Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the PPE population. Efficacy was measured starting after the Month 7 visit (Table 4).

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

Table 4
Analysis of Efficacy of GARDASIL in the PPE Population of 24- Through 45-Year-Old Women

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

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

In the long-term extension study of FUTURE III, for 24- to 45-year-old women in the PPE population vaccinated with GARDASIL in the base study and followed in the extension, no cases of HPV diseases, (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were

observed up to approximately 6 years. In this extension study, women will be followed up to 10 years.

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 5. 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 5
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-,	Prophylactic Efficacy*	8630	16	8680	309	94.8 (91.5, 97.1)

16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	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 5 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 6). 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 6
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	8688	132	8701	350	62.5 (54.0, 69.5)***

	Vaccine or Non-Vaccine HPV Types**					

*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

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

The clinical studies in boys and men 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 7. 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 7
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	460	14	453	25	**--****
	Boys and Men Regardless of Current or Prior Exposure to	1943	27	1937	77	65.5 (45.8, 78.6)†

	Vaccine or Non-Vaccine HPV Types***					
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	460	14	453	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	460	2	453	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 the clinical study in boys and men 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 the study (including boys and men with HPV infection at Day 1), GARDASIL reduced the overall incidence of genital disease (Table 8). 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 8
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

Prophylactic Efficacy in a Generally HPV-naïve Population and the General Study Population – HPV Types 31, 33, 45, 52, 56, 58 and 59 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). The primary endpoint of this analysis was the combined incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) or AIS. The secondary endpoint of this analysis was the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS. Analyses were also conducted to evaluate efficacy with respect to CIN (grades 1, 2, 3) or AIS caused by non-vaccine HPV types individually. In

individuals who were naïve to the relevant vaccine HPV types at Day 1 (MITT-2 population, n = 16,895 for the 31/45 composite endpoint and n = 16,969 for the 31/33/45/52/58 composite endpoint), a trend towards a reduction in the incidence of HPV 31- and 45-related and HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS was observed. Administration of GARDASIL reduced the incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) by 37.3% (95% CI: 17.0%, 52.8%) compared with placebo. Administration of GARDASIL reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS by 26.4% (95% CI: 12.9%, 37.8%), compared with placebo. Efficacy was driven by reductions in HPV 31-, 33-, 52-, and 58-related endpoints. There was no clear evidence of efficacy for HPV 45. In a post-hoc analysis, prophylactic administration of GARDASIL also reduced the incidence of HPV 56-related and HPV 59-related CIN (grades 1, 2, 3) or AIS, compared with placebo in this population.

Further post-hoc analyses considered efficacy in 2 clinically relevant populations: (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. Administration of GARDASIL to HPV-naïve individuals reduced the incidences of HPV 31-, 33-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS, HPV 56-related CIN (grades 1, 2, 3) or AIS, and HPV 59-related CIN (grades 1, 2, 3) or AIS. Reductions in the rates of these diseases were also observed in the general study population (which included HPV-naïve and HPV-infected individuals).

Cross-protection efficacy analyses demonstrate that prophylactic administration of GARDASIL to individuals reduces the risk of acquiring CIN 1, CIN 2/3, and AIS caused by HPV types 31, 33, 52, 56, 58, and 59 (Tables 9 and 10).

Table 9
Impact of GARDASIL on the Rates of CIN (any Grade) 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**	HPV-naïve* (n = 9,296)	43.6	12.9, 64.1
	General Population (Including HPV-infected*** Individuals) (n = 17,151)	23.2	5.6, 37.7
HPV 31/33/45/52/58-related†	HPV-naïve	29.2	8.3, 45.5
	General Population (Including HPV-infected Individuals)	19.6	8.2, 29.6
HPV 31/33/52/58-related	HPV-naïve	33.8	13.4, 49.6
	General Population (Including HPV-infected Individuals)	21.2	9.6, 31.3
HPV 56-related	HPV-naïve	27.6	<0.0, 49.3
	General Population (Including HPV infected Individuals)	16.8	<0.0, 32.8
HPV 59-related	HPV-naïve	22.3	<0.0, 58.9
	General Population (Including HPV-infected Individuals)	39.2	8.1, 60.3

*HPV-naïve population included individuals who, at Day 1, had a Pap test that was negative for SIL

[Squamous Intraepithelial Lesion] and were negative to all of the following HPV types: HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; and had follow-up after Day 30 of the study. Case counting started at Day 30.
***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

Table10
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

Composite Endpoint	GARDASIL cases	Placebo cases	%Efficacy	95%CI
(HPV 31/45)‡	11	27	58.7%	14.1, 81.5
(HPV 31/33/45/52/58)§	44	66	32.5%	-0.3, 55.0
10 non-vaccine HPV Types‖	62	93	32.5%	6.0, 51.9
HPV-16 related types (A9 species)	44	69	35.4%	4.4, 56.8
HPV 31	8	27	70.0%	32.1, 88.2†
HPV 33	12	16	24.0%	<0, 67.2†
HPV 35	4	4	0.0%	<0, 81.1†
HPV 52	17	23	25.2%	<0, 62.5†
HPV 58	16	20	18.9%	<0, 60.7†
HPV-18 related types (A7 species)	11	21	47.0%	<0, 76.9
HPV 39	4	10	59.6%	<0, 90.7†
HPV 45	3	2	0.0%	<0, 82.6†
HPV 59	5	9	43.8%	<0, 85.2†
A5 species (HPV 51)	16	15	0.0%	<0, 50.0†
A 6 species (HPV 56)	12	16	24.1%	<0, 67.2†

†The studies were not powered to assess efficacy against disease caused by individual HPV types.
‡Efficacy was based on reductions in HPV 31-related CIN 2/3 or AIS
§Efficacy was based on reductions in HPV 31-, 33-, 52-, and 58-related CIN 2/3 or AIS
‖Includes assay-identified non-vaccine HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N/A

6.2 Incompatibilities

N/A

6.3 Shelf life

36 months

6.4 Special precautions for storage

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.

6.5 Nature and content of container

GARDASIL is available in a single-dose 0.5 mL vial and 10 single-dose 0.5 mL vials.
GARDASIL is available in a single-dose 0.5 ml and 10 single-dose 0.5 ml pre-filled syringe with needle size 1 inch.

6.6 Special precautions for disposal and other handling

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.

PATIENT COUNSELLING INFORMATION

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.

7. MARKETING AUTHORISATION HOLDER

MSD (Thailand) Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 11/55 (NB)

9. DATE OF FIRST AUTHORAISATION/RENEWAL OF THE AUTHORISATION

22-May-2012

10. DATE OF REVISION OF THE TEXT

Feb-2015