

GARDASIL™

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

Fulfills Part A of the WHO Guidelines for Recombinant Human Papillomavirus Virus-like Particle Vaccines

DESCRIPTION

GARDASIL* is a recombinant, quadrivalent vaccine.

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

COMPOSITION

GARDASIL is a sterile preparation 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, and water for injection. The product does not contain a preservative or antibiotics.

ADMINISTRATION

GARDASIL is recommended for females and males aged 9 to 15 years and females aged 16 to 26 years (see Indications).

*Trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, 08889 USA

COPYRIGHT © 2021 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

All rights reserved

GARDASIL™

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

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 vials are for single use in one patient only. 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.

NOTE: When choosing a needle, it should fit securely on the syringe.

IMMUNIZATION SCHEDULE

Individuals 9 to and including 13 years of age

GARDASIL™

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

GARDASIL can be administered according to a 2-dose schedule (0.5 mL at 0, 6 months) (see Clinical Studies, Immunogenicity).

If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered.

Alternatively, GARDASIL can be administered according to a 3-dose (0.5 mL at 0, 2, 6 months) schedule. The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Individuals 14 years of age and older

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. If an alternate vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose (see Clinical Studies, Schedule Flexibility).

Drug Interactions

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site and in separate limbs) with H-B-VAX II™* [hepatitis B vaccine (recombinant)], Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine],

GARDASIL™

[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant 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)]. GARDASIL has not been studied in clinical trials with vaccines other than the ones listed.

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. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives

In clinical studies 57.5% of women (16 to 26 years of age), 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, 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 subjects 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).

INDICATIONS AND USAGE

GARDASIL is indicated in females aged 9 to 26 years* for the prevention of cervical, vulvar, and vaginal cancer, precancerous or dysplastic lesions, genital warts, and persistent infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).

GARDASIL™

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

GARDASIL is indicated in males aged 9 to 15 years for the prevention of infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).

GARDASIL also provides protection in girls and women 9 through 26 years of age against HPV 31-, 33-, 52- and 58-related CIN (grades 1, 2, 3) or AIS.

*Immunogenicity studies have been conducted to link efficacy in females aged 16 to 26 years to the younger populations.

CONTRAINDICATIONS

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.

PRECAUTIONS

General

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, or vaginal cancers; CIN, VIN, or VaIN related to HPV vaccine types or non-vaccine serotypes.

This vaccine will not protect against diseases that are not caused by HPV. Routine cervical screening and detection and removal of cervical lesions should be continued in individuals who receive the vaccine.

GARDASIL™

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

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after 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 Administration, 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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

Carcinogenicity

GARDASIL has not been evaluated for carcinogenic potential.

Genotoxicity

GARDASIL has not been evaluated for genotoxic potential

GARDASIL™

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

Effects on Fertility

Female rats were given the clinical dose of GARDASIL (500 mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Mating performance and fertility of the dams or their offspring were not affected. The effect of GARDASIL administration on male fertility has not been studied.

Use in Pregnancy

Studies in Female Rats

Female rats were given the clinical dose of GARDASIL (500 mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. High titers of HPV-type specific antibodies were detected in maternal blood during gestation, in near-term fetal blood, and in blood of offspring at weaning and at 11 weeks postnatal, indicative of transplacental and lactational transfer of antibodies (see Use in Lactation). The effect of GARDASIL administration of vaccine-treated males on offspring has not been studied.

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 Immunization Schedule).

During clinical trials, 3,315 women (vaccine = 1,657 vs. placebo = 1,658) 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

GARDASIL™

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

number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 23.2% (393/1693) in subjects who received GARDASIL and 23.8% (403/1692) in subjects 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 0 cases of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 32 cases of congenital anomaly were observed in the group that received GARDASIL compared with 27 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 16 through 26 years of age.

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

Use in Lactation

Female rats were given the clinical dose of GARDASIL (500 mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. Offspring of dams receiving the two doses had higher serum titers of HPV-type specific antibodies at weaning than near term fetuses, suggesting transfer of antibodies in milk as well as via the placenta (see Use in Pregnancy). Antibodies were still present in offspring at postnatal week 11 when they were last measured.

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™

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

A total of 995 nursing mothers were given GARDASIL or placebo during the vaccination period of the clinical trials. 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.

Paediatric Use

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

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.

Use in the Elderly

The safety and efficacy of GARDASIL have not been evaluated in the elderly population.

Use in other special populations

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

SIDE EFFECTS

In 5 clinical trials (4 placebo-controlled), subjects 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 subjects (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 subjects who were monitored using VRC-aided surveillance included 6,160 subjects (5,088 females 9 to 26 years of age, 1,072 males 9 to 16 years of age at enrolment) who received GARDASIL and 4,064 subjects who received placebo.

GARDASIL™

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

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

GARDASIL™

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

Table 1
Vaccine-Related Injection-Site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Post-vaccination)	GARDASIL	Aluminum-Containing Placebo	Saline Placebo
	(N = 6,160) %	(N = 3,470) %	(N = 594) %
<i>Injection-Site</i>			
Pain	81.3	75.4	45.4
Swelling	24.2	15.8	7.7
Erythema	23.6	18.4	13.2
Bruising	2.6	3.2	2.2
Pruritus	2.7	2.8	0.9
<hr/>			
Adverse Experience (1 to 15 Days Post-vaccination)	GARDASIL	Placebo	
	(N = 6,160) %	(N = 4,064) %	
<i>Systemic</i>			
Fever	10.1	8.4	

*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.

All-cause Common Systemic Adverse Experiences

All-cause systemic adverse experiences for subjects that were observed at a frequency of greater than or equal to 1% where the incidence in the vaccine group was greater than or equal to the incidence in the placebo group are shown in Table 2.

GARDASIL™

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

Table 2
All-cause Common Systemic Adverse Experiences

Adverse Experience (1 to15 Days Post-vaccination)	GARDASIL (n = 6160) %	Placebo* (n = 4064) %
Pyrexia	12.9	11.0
Diarrhea	3.7	3.6
Vomiting	2.4	2.1
Myalgia	2.0	2.0
Cough	1.9	1.6
Upper respiratory tract infection	1.5	1.5
Toothache	1.3	1.3
Malaise	1.2	1.2
Arthralgia	1.2	1.0
Nasal congestion	1.1	1.0
Insomnia	1.0	0.9

* Aluminum and/or non-aluminum containing placebo

In addition, in a clinical trial of women 24 to 45 years of age (GARDASIL N= 1908, Placebo N=1902), pain in the extremity was reported by 4.7% of GARDASIL recipients and 2.2% of Placebo recipients.

Overall, 94.4% of subjects who received GARDASIL judged their injection-site adverse experience to be mild or moderate in intensity.

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

GARDASIL™

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

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: injection-site cellulitis

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

GARDASIL™

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

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.

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.

Storage

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

Data from stability studies demonstrate that the vaccine components are stable for 72 hours when stored at temperatures from 8°C to 42°C. At the end of this period GARDASIL should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Shelf life

3 years

GARDASIL™

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

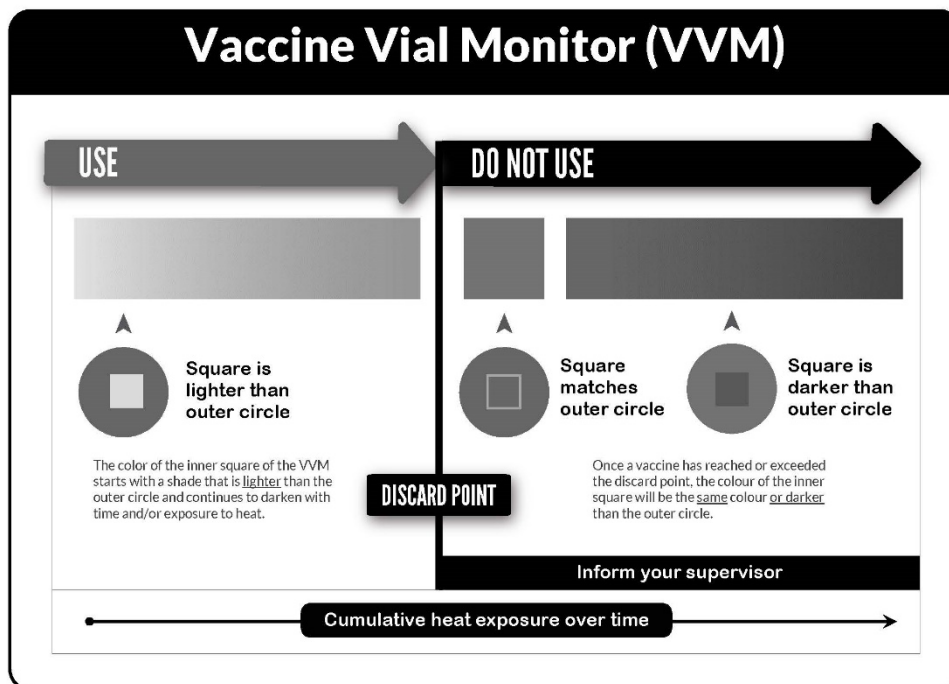
PRESENTATION

Vials

GARDASIL is supplied as a carton of one 0.5-mL single-dose vial.

GARDASIL is supplied as a carton of ten 0.5-mL single-dose vials.

Figure 1 The Vaccine Vial Monitor



The Vaccine Vial Monitors (VVMs) are incorporated into the vial label of GARDASIL manufactured by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The color dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the

GARDASIL™

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

cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its color will change progressively. As long as the color of this square is lighter than the color of the ring, then the vaccine can be used. As soon as the color of the central square is the same color as the ring or of a darker color than the ring, then the vial should be discarded.

PHARMACOLOGY

Mechanism of Action

GARDASIL contains HPV 6, 11, 16, and 18 L1 VLPs. Each VLP is composed of a unique recombinant L1 major capsid protein for the respective HPV type. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

Pre-clinical data suggests that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses. 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.

CLINICAL STUDIES

In female individuals, CIN 2/3 and AIS are the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, their primary prevention through vaccination will prevent invasive cancer.

Invasive cervical cancer cannot be used as an endpoint for efficacy studies of HPV vaccines because of the importance of employing secondary prevention measures. Therefore, the immediate precursors, CIN 2 (moderate-grade cervical dysplasia), CIN 3 (high-grade cervical dysplasia including carcinoma *in situ*), and AIS are the most appropriate endpoints for the demonstration of the prevention of cervical cancer by HPV vaccines.

CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology). VIN 2/3 and VaIN 2/3 are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.

GARDASIL™

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

The efficacy of GARDASIL or the HPV component of GARDASIL was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies. One Phase II study evaluated all four components (i.e., HPV 6, 11, 16, and 18) of GARDASIL (Protocol 007, N = 551 girls and women). An additional phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N=2,391 girls and women). The Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5,442 (FUTURE I) and 12,157 (FUTURE II) girls and women. Together, these studies evaluated 20,541 girls and women 16 to 26 years of age at enrolment, the majority of whom had been sexually active. The median duration of follow-up was 4.0, 3.0, 3.0, and 3.0 years for Protocol 005, Protocol 007, FUTURE I, and FUTURE II, base studies respectively. Individuals received vaccine or placebo on the day of enrolment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies conducted in girls and women combined.

In the clinical studies, HPV status was not assessed before individuals were enrolled. Thus, individuals who had been exposed to a vaccine HPV type prior to enrolment were included in the studies for evaluation. Overall, 73% of individuals were naïve to all 4 vaccine HPV types at enrollment. These individuals were at risk for infection and disease caused by all 4 vaccine HPV types.

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

The primary analyses of efficacy 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 3).

GARDASIL™

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

Table 3

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-, 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)

GARDASIL™

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

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, 2,536 women 16-23 years old during vaccination with GARDASIL in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related high-grade CIN) were observed up to approximately 14 years (median follow-up of 11.9 years). In this study, a durable protection was statistically demonstrated to approximately 12 years.

Supplemental Analysis of Efficacy for Cancer Endpoints in 16- Through 26-Year-Old Girls and Women

In a supplemental analysis, the efficacy of GARDASIL was evaluated against HPV 16/18-related FIGO Stage 0 cervical cancer (CIN 3 and AIS) and for the immediate precursors to vulvar and vaginal cancer

GARDASIL™

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

(VIN 2/3 or VaIN 2/3) in the per-protocol efficacy (PPE) population and a modified intention to treat-2 (MITT-2) population. The MITT-2 population consisted of individuals who were naïve to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and who became infected with a vaccine HPV type during the vaccination period. Efficacy was measured starting 30 days Postdose 1 for the MITT-2 population.

GARDASIL was equally efficacious against HPV 16/18-related CIN 3, AIS, VIN 2/3, and VaIN 2/3 in both the PPE and MITT-2 populations (Table 4).

GARDASIL™

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

Table 4

Supplemental Analyses of Cancer-Related Endpoints: Efficacy Against HPV 16/18-Related Invasive Cancer Precursors for the Combined Protocols in the PPE* and MITT2 Populations of 16- Through 26-Year-Old Girls and Women**

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 3					
Per-protocol	8,493	2	8,464	64	96.9 (88.4, 99.6)
MITT-2	9,346	3	9,407	92	96.7 (90.2, 99.3)
HPV 16- or 18-related AIS					
Per-protocol	8,493	0	8,464	7	100.0 (30.6, 100.0)
MITT-2	9,346	0	9,407	11	100.0 (60.0, 100.0)
HPV 16- or 18-related VIN 2/3 or VaIN 2/3					
Per-protocol	7,772	0	7,744	19	100.0 (78.6, 100.0)
MITT-2	8,642	1	8,673	34	97.0 (82.4, 99.9)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

**The MITT-2 consisted of individuals who were naïve to the relevant HPV types(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine/placebo, and had at least one follow-up visit post-Day 30 (case counting on Day 31).

n = Number of individuals with at least one follow-up visit after Day 1

CI = Confidence Interval

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

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

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

GARDASIL™

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

Efficacy in 16- Through 26-Year-Old Girls and Women with Current or Prior Infection with HPV Types 6, 11, 16, or 18

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

Individuals with evidence of a prior infection that had resolved by vaccination onset were protected from reacquisition or recurrence of infection leading to clinical disease.

Individuals, who had early HPV infection at the time of enrollment and who received GARDASIL did not show a statistically significant reduction of CIN (CIN 1 or CIN 2/3) or AIS compared to placebo. Estimated vaccine efficacy was 21.6% (95% CI: <0.0%, 42.1%). Early infection was defined as infection with a vaccine HPV type at enrollment, but no evidence of immune response to it.

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.

GARDASIL™

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

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 (Table 5).

GARDASIL™

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

Table 5
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

Protection Against the Overall Burden of Cervical, Vulvar, and Vaginal HPV Disease in 16- Through 26-Year-Old Girls and Women

The impact of GARDASIL against the overall risk for cervical, vulvar, and vaginal HPV disease (i.e., disease caused by any HPV type) was evaluated in a pre-specified analysis of 17,599 individuals enrolled in FUTURE I and FUTURE II. Among individuals who were naïve to at least one of 14 common HPV types and/or had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 (MITT-2 population), administration of GARDASIL reduced the incidence of CIN 2/3 or AIS caused by vaccine- or non-vaccine HPV types by 33.8% (95% CI: 20.7%, 44.8%).

GARDASIL™

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

Further efficacy analyses were conducted 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.

Among HPV-naïve individuals and among the general study population (including individuals with HPV infection at vaccination onset), 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. Among HPV-naïve individuals (Figure 2) and the general study population (Figure 3), the benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time. This is because GARDASIL does not impact the course of infections that are present at vaccination onset. Such infected individuals may already have CIN 2/3 or AIS at vaccination onset and some will develop CIN 2/3 or AIS during follow-up. GARDASIL reduces the incidence of CIN 2/3 or AIS caused by infections with HPV types 6, 11, 16, 18, 31, 33, 52, 56, 58 and 59 that occur after vaccination onset.

Table 6

Impact of GARDASIL on Overall Burden of HPV Disease in HPV-Naïve and HPV Non-Naïve Girls and Women 16 Through 26 Years of Age

Endpoints Caused by Vaccine or Non-vaccine HPV Types	Analysis	GARDASIL		Placebo		% Reduction (95% CI)
		n	Cases	n	Cases	
CIN 2/3 or AIS	Prophylactic Efficacy*	4,616	77	4,680	136	42.7 (23.7, 57.3)
	Infected With HPV at Day 1	--	344	--	380	--
	General Population Impact**	8,559	421	8,592	516	18.4 (7.0, 28.4)***
VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	4,688	7	4,735	31	77.1 (47.1, 91.5)
	Infected With HPV at Day 1	--	23	--	30	--
	General Population Impact**	8,688	30	8,701	61	50.7 (22.5, 69.3)***
CIN (Any Grade) or AIS	Prophylactic Efficacy*	4,616	272	4,680	390	29.7 (17.7, 40.0)
	Infected With HPV at Day 1	--	695	--	799	--

GARDASIL™

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

	General Population Impact**	8,559	967	8,592	1189	19.1 (11.9, 25.8)***
Genital Warts	Prophylactic Efficacy*	4,688	29	4,735	169	82.8 (74.3, 88.8)
	Infected With HPV at Day 1	--	103	--	181	--
	General Population Impact**	8,688	132	8,701	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

GARDASIL™

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

Figure 2
Cumulative Incidence of CIN 2/3 or AIS Lesions (Caused by Any HPV Type) Among a Generally HPV-Naïve Population in the Phase III Clinical Trials (FUTURE I and FUTURE II) in 16- Through 26-Year-Old Girls and Women

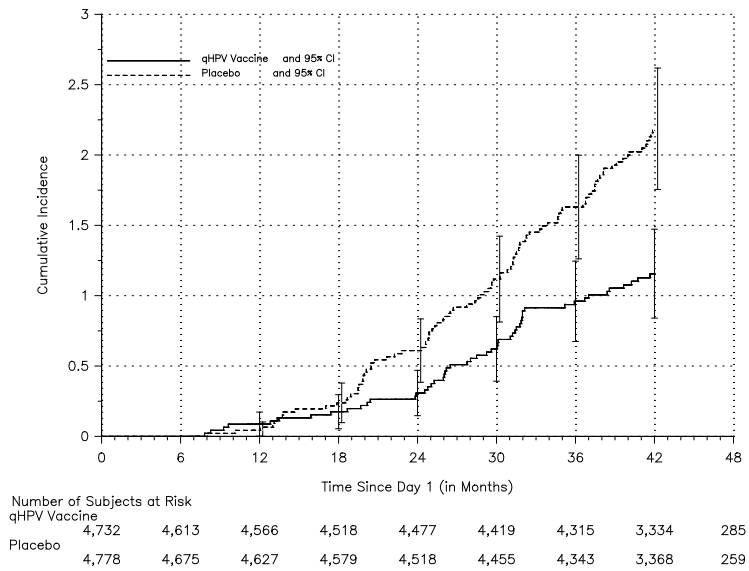
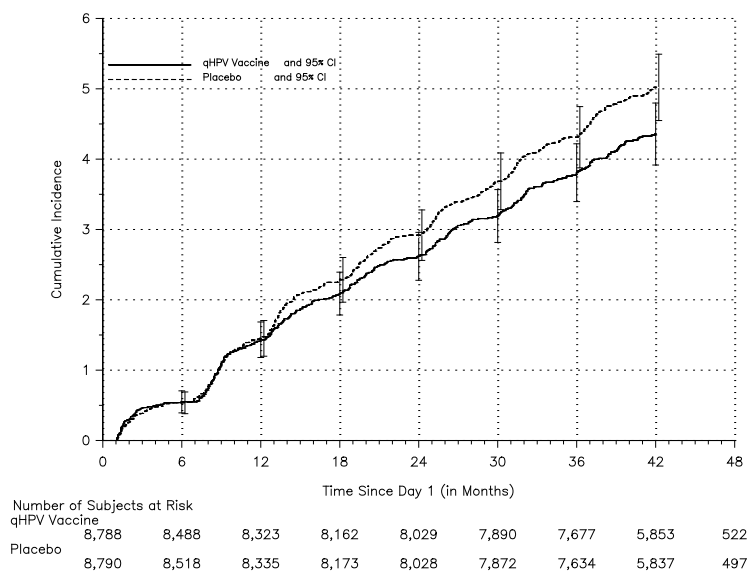


Figure 3
Cumulative Incidence of CIN 2/3 or AIS Lesions (Caused by Any HPV Type) Among the General Study Population Including Those with HPV Infection and CIN 2/3 at Vaccination Onset in the Phase III Clinical Trials (FUTURE I and FUTURE II) in 16- Through 26-Year-Old Girls and Women

GARDASIL™

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



GARDASIL has not been shown to protect against the diseases caused by every HPV type, and will not treat existing disease. 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.

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

The impact of GARDASIL on rates of abnormal Pap tests and cervical procedures (colposcopic biopsy, definitive therapy) regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, FUTURE I and FUTURE II. The impact of GARDASIL on rates of genital excisional procedures to treat lesions caused by any HPV type was evaluated in 5,442 individuals enrolled in FUTURE I. Two populations were considered: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

In both populations, GARDASIL reduced the proportions of individuals who experienced a Pap test abnormality suggestive of CIN, a colposcopic biopsy, a definitive cervical therapy procedure

GARDASIL™

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

(Loop Electro-Excision Procedure or Cold-Knife Conization), a vulvar or vaginal biopsy, or a definitive excisional procedure of the vagina or vulva.

In addition, administration of GARDASIL to a generally HPV naïve population of 16- through 26-year-old individuals reduced the incidence of HPV 16-related and HPV 18-related Pap abnormalities (ASC-US HR positive, LSIL, or worse) by 92.4% (95% CI: 83.7%, 97.0%) and 96.9% (95% CI: 81.6%, 99.9%) in the FUTURE I study.

Immunogenicity

Assays to measure Immune response

Type-specific assays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. This multiplexed competitive Luminex immunoassay (cLIA) measured antibodies against neutralizing epitopes for each HPV type, rather than the total antibodies directed at the VLPs in the vaccine. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not meaningful. The assays used to measure the immune responses to GARDASIL were demonstrated to correlate with the capacity to neutralize live HPV virions.

Because of the very high efficacy of GARDASIL in clinical trials, 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 HPV disease.

The immunogenicity of GARDASIL was assessed in 20,132 9- through 26-year-old girls and women (GARDASIL N = 10,723; placebo N = 9409) and 1,346 boys (GARDASIL N=1,071; placebo N=275) 9 through 15 years of age.

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and Polymerase Chain Reaction (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).

GARDASIL™

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

Immune Response to GARDASIL at Month 7 (Time Point Approximating Peak Immunogenicity)

In all age groups tested GARDASIL induced anti-HPV Geometric Mean Titers (GMTs) 1 month Postdose 3 which were substantially higher than those measured in women with evidence of a previous infection. Overall, 99.8%, 99.8%, 99.8%, and 99.5% of individuals 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. Anti-HPV levels induced by the vaccine were substantially higher than those measured in women with evidence of having had an infection who then mounted an immune response that led to clearance of infection prior to enrollment.

In a study that measured immune responses to a 3-dose regimen of GARDASIL during the course of the vaccination regimen, Postdose 2 anti-HPV levels were higher than those observed during long term follow-up of the Phase III studies. Overall, 97.6 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 2. These results support the observation that the protective efficacy of GARDASIL begins during the course of the 3-dose vaccination regimen.

Immunogenicity in Young Adolescents

Bridging the Efficacy of GARDASIL from Adults to Adolescents

A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in 10 through 15 year old boys and girls with responses in 16 through 23 year old adolescents and young adult women. Among subjects who received GARDASIL, 99.1 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3. Anti-HPV responses in both 10 through 15 year old girls and 10 through 15 year old boys were significantly superior to those observed in 16 through 23 year olds.

Similar outcomes were observed in a comparison of the anti-HPV responses 1 month Postdose 3 among 9 through 15 year old girls with anti-HPV responses in 16 through 26 year old adolescents and young adult women in the combined database of immunogenicity studies for GARDASIL.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9 through 15 year old girls is comparable to the efficacy of GARDASIL observed in the Phase III studies in 16 through 26 year old adolescents and young adult women.

Protocol 018 assessed immunogenicity in girls and boys 9-15 years of age. The study was extended to assess the long-term immunogenicity and effectiveness. In the long-term extension of Protocol 018, 369 girls and 326 boys 9-15 years old during vaccination with GARDASIL in the base study were followed. In the PPE population:

- in girls, no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed through 10.7 years (median follow-up of 10.0 years).

GARDASIL™

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

- in boys, no cases of HPV diseases (HPV types 6/11/16/18 related External Genital Lesions) were observed through 10.6 years (median follow-up of 9.9 years).

Persistence of The Immune Response to GARDASIL

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

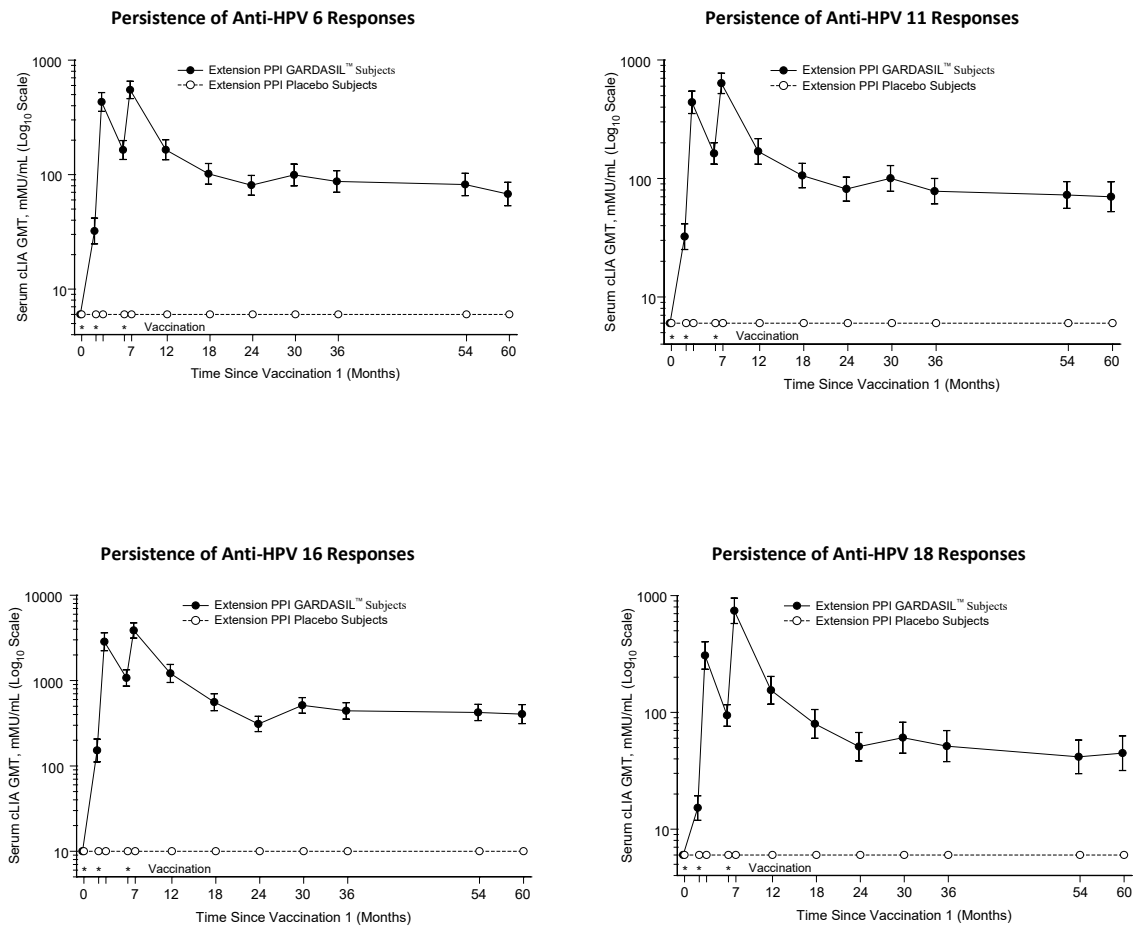
In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then stabilized until at least Month 60 (see Figure 4).

GARDASIL™

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

Figure 4

Persistence of Anti-HPV Responses Following a 3-Dose Regimen of GARDASIL



Subsets of individuals enrolled in Protocol 018 and FUTURE II were followed for long-term safety, immunogenicity and effectiveness. Total IgG Luminex Immunoassay (IgG LIA) was used to assess the persistence of immune response in addition to cLIA.

In all populations (girls and women 9–23 years, boys 9–15 years), peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs cLIA were observed at Month 7. Afterwards, the GMTs declined through

GARDASIL™

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

Month 24 - 48 and then generally stabilized. The duration of immunity following a 3-dose series has been observed for up to 14 years post-vaccination.

Girls and boys vaccinated with GARDASIL at 9-15 years of age in the Protocol 018 base study were followed up in an extension study. Depending on HPV type, 60-96% and 78-98% of subjects were seropositive by cLIA and IgG LIA respectively 10 years after vaccination.

Women vaccinated with GARDASIL at 16-23 years of age in the FUTURE II base study were followed up in an extension study. Fourteen years after vaccination, 91%, 91%, 98% and 52% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 98%, 98%, 100% and 94% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

In these studies, individuals who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 in the cLIA were still protected against clinical disease after a follow-up of 14 years for 16-23 year-old women.

Evidence of Anamnestic (Immune Memory) Response

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

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

In addition, a subset of individuals that received a 3-dose primary series of vaccine became nominally anti-HPV 18 seronegative by Month 60. Although these individuals were nominally anti-HPV 18 seronegative, no cases of HPV 18-related disease were detected among these individuals. They also

GARDASIL™

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

showed immune memory: when these individuals were given a challenge dose of GARDASIL (at Month 60), 93% and 97% became anti-HPV 18 seropositive by 1 week and 1 month post-challenge, respectively; 73% had anti-HPV 18 levels at 1 month post-challenge that were higher than their Month 7 (1 month Postdose 3) anti-HPV 18 level.

Persistence of Immune Response in Phase III Studies of 9- Through 26-Year-Old Girls and Women for GARDASIL

Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositivity was highest at Month 7, and then declined at persistence time points.

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

Immune Responses to GARDASIL Using a 2-dose Schedule in Individuals 9-13 Years of Age

A clinical trial showed that among girls who received 2 doses of HPV vaccine 6 months apart, antibody responses to the 4 HPV types, one month after the last dose were non-inferior to those among young women who received 3 doses of the vaccine within 6 months.

At Month 7, in the Per Protocol population, the immune response in girls aged 9-13 years (n=241) who received 2 doses of GARDASIL (at 0, 6 months) was non-inferior and numerically higher to the immune response in women aged 16-26 years (n=246) who received 3 doses of GARDASIL (at 0, 2, 6 months).

At 36 month follow-up, the GMT in girls (2 doses, n=86) remained non-inferior to the GMT in women (3 doses, n=86) for all 4 HPV types.

The duration of immunity following a 2-dose schedule has been observed for up to 10 years post-vaccination. At 120 month follow-up, the GMT in girls (2 doses, n=35) remained non-inferior to the

GARDASIL™

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

GMT in women (3 doses, n=30) for all 4 HPV types. Among the girls receiving 2 doses of the vaccine, seropositivity rates were >95% for HPV 6, 11, and 16, and >80% for HPV 18, in the cLIA.

In the same study, in girls aged 9-13 years, the immune response after a 2-dose schedule was generally numerically lower than after a 3-dose schedule (n=248 at Month 7; n=82 at Month 36; n=51 at Month 60). The clinical relevance of these findings is unknown.

Schedule Flexibility

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

Studies with Other Vaccines

H-B-VAX II [hepatitis B vaccine (recombinant)]

The safety and immunogenicity of co-administration of GARDASIL with H-B-VAX II [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites and in separate limbs) were evaluated in a randomized study of 1,871 women aged 16 through 24 years at enrollment. Immune response and safety profile to both H-B-VAX II [hepatitis B vaccine (recombinant)] and GARDASIL were similar whether they were administered at the same visit or at a different visit.

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

The safety and immunogenicity of co-administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (same visit, injections at separate sites) were evaluated in a randomized study of 843 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] does not interfere with the antibody response to any of the components of either vaccine. In addition, the safety profile was generally similar (see Side Effects, *Concomitant Administration with Other Vaccines*).

GARDASIL™

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

Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]

The safety and immunogenicity of co-administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in a randomized study of 1040 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] does not interfere with the antibody response to any of the components of any of the vaccines. In addition, the safety profile was generally similar (see Side Effects, *Concomitant Administration with Other Vaccines*).

REVISED April 2021

WHO-PI-V501-I-042021-sub