NEW ZEALAND DATA SHEET

1 PRODUCT NAME

GARDASIL® 9

Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine, Recombinant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human papillomavirus vaccine

Human Papillomavirus 9-valent Vaccine, Recombinant

1 dose (0.5 mL) contains approximately:
Human Papillomavirus[1] 6 L1 Protein[2,3] 30 micrograms
Human Papillomavirus[1] 11 L1 Protein[2,3] 40 micrograms
Human Papillomavirus[1] 16 L1 Protein[2,3] 60 micrograms
Human Papillomavirus[1] 18 L1 Protein[2,3] 40 micrograms
Human Papillomavirus[1] 31 L1 Protein[2,3] 20 micrograms
Human Papillomavirus[1] 33 L1 Protein[2,3] 20 micrograms
Human Papillomavirus[1] 45 L1 Protein[2,3] 20 micrograms
Human Papillomavirus[1] 52 L1 Protein[2,3] 20 micrograms
Human Papillomavirus[1] 58 L1 Protein[2,3] 20 micrograms

[1]Human Papillomavirus = HPV.

[2]L1 protein in the form of virus-like particles produced in yeast cells (Saccharomyces cerevisiae CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.

[3]Adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.5 milligrams Al).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for intramuscular injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GARDASIL 9 is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

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GARDASIL 9 is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

* Evidence of vaccine efficacy is based on core efficacy population of females 16 to 26 years of age. Immunogenicity studies have been conducted to link efficacy to younger populations (females and males 9 to 15 years of age). Currently there are no data from studies of GARDASIL 9 relating to females over 26 years of age (see Section 5.1, Immune Response to GARDASIL 9 at Month 7 Across All Clinical Studies).

4.2 Dose and method of administration

Dosage

GARDASIL 9 should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

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

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. 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 14 years of age, GARDASIL 9 can be administered according to a 2-dose schedule; the second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

The use of GARDASIL 9 should be in accordance with official recommendations.

Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

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

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for GARDASIL 9.

For information regarding administration of GARDASIL 9 after receipt of GARDASIL, see Section 5.1 *Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL*.

Method of administration

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with GARDASIL 9. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9.

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GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL 9 must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

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.

Prior to agitation, GARDASIL 9 may appear as a clear liquid with a white precipitate. After thorough agitation, GARDASIL 9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured.

Prefilled Syringe Use
Inject the entire contents of the syringe.

The prefilled syringe is for single use only and should not be used for more than one individual.

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.

For single-use vials a separate sterile syringe and needle must be used for each individual.
NOTE: When choosing a needle, it should fit securely on the syringe.

4.3 Contraindications

Hypersensitivity to the active substances of GARDASIL 9 or GARDASIL or to any of the inactive ingredients of either vaccine (see Section 5,).

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL 9 or GARDASIL should not receive further doses of GARDASIL 9.

4.4 Special warnings and precautions for use

General

As for any vaccine, vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

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

This vaccine will not protect against diseases that are not caused by HPV or non-vaccine genotypes.

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Routine cervical screening and detection and removal of cervical lesions should be continued in individuals who receive the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9 (see Section 4.8).

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.

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 Section 4.5).

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.

Paediatric Use

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

Use in the Elderly

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

Genotoxicity

GARDASIL 9 has not been evaluated for genotoxic potential.

Carcinogenicity

GARDASIL 9 has not been evaluated for carcinogenic potential.

Use in Immunocompromised Individuals

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals (see Section 4.5, Use with Systemic Immunosuppressive Medications).

4.5 Interaction with other medicines and other forms of interaction

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL 9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel [Tetanus Toxoid, Reduced

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Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax[1] [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (dTap-IPV) (see Section 5.1, *Concomitant Use of GARDASIL 9 With Other Vaccines*).

Use with Hormonal Contraceptives

In 7,269 women (16 through 26 years of age, from Protocols 001 and 002), 60.2% used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL 9.

Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines (see Section 4.4, *Use in Immunocompromised Individuals*).

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Non-clinical studies: Animal Toxicology
GARDASIL 9 administered to female rats at a dose approximately 240 times the human dose (mg/kg basis) had no effects on mating performance, fertility, or embryonic/foetal survival.

GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) had no effects on development, behavior, reproductive performance or fertility of the offspring.

A repeat dose toxicity study has been performed in rats at a dose approximately 250 times the human dose (mg/kg basis) and revealed no special hazards to humans.

Use in Pregnancy (Category B2)

Studies in Female Rats
Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the foetus due to GARDASIL 9 vaccination prior to mating and at gestational day 6.

An evaluation of the effect of GARDASIL 9 on embryo-foetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-foetal or pre- and postweaning development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental signs, behaviour, reproductive performance, or fertility of the offspring. GARDASIL 9 induced a specific antibody response against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 9 HPV types were transferred to the offspring during the period of gestation and lactation.

[1] Not currently registered in New Zealand

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Clinical Studies in Humans
There are 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 9.

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of GARDASIL 9. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL 9 were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

The overall proportion of pregnancies occurring at any time during the studies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late foetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 12.9% (174/1,353) in women who received GARDASIL 9 and 14.4% (187/1,303) in women who received GARDASIL. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL 9 or GARDASIL. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL 9 or GARDASIL. In pregnancies with onset more than 30 days following vaccination, 30 and 23 cases of congenital anomaly were observed in women who have received GARDASIL 9 and GARDASIL, respectively. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in the general population.

Thus, there is no evidence to suggest that administration of GARDASIL 9 adversely affects fertility, pregnancy, or infant outcomes.

Use in Lactation

Studies in Female Rats
GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) vaccination prior to mating and at gestational day 6 had no effects on development, behavior, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during the period of gestation and lactation.

Clinical Studies in Humans

GARDASIL 9 may be administered to lactating women.

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

A total of 92 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9 in women aged 16 to 26 years. In these studies, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period. In addition, vaccine immunogenicity was comparable between nursing women and women who did not nurse.

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4.7 Effects on ability to drive and use machines

Gardasil 9 has no or negligible influence on the ability to drive or use machines. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety and tolerability of GARDASIL was assessed in clinical trials in females 9 through 45 years of age and males 9 through 26 years of age. The safety profile of GARDASIL 9 is generally comparable to that of GARDASIL in the groups studied (women 16 through 26 years of age and girls and boys 9 through 15 years of age).

The safety of GARDASIL 9 was evaluated in 7 clinical studies (Protocols 001, 002, 003, 005, 006, 007, 009) that included 15,776 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Protocol 001 and Protocol 009 included 7,378 individuals who received at least one dose of GARDASIL and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 9,102 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age, and 5,280 girls and boys 9 through 15 years of age (3,481 girls and 1,799 boys) at enrollment who received GARDASIL 9 and 7,078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL.

Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

The vaccine-related adverse experiences that were observed among recipients of either GARDASIL 9 or GARDASIL at a frequency of at least 1% are shown in Tables 1 and 2. Few individuals (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL 9 and GARDASIL in women, men, girls and boys.

Table 1: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% in Individuals Who Received GARDASIL 9 from All Clinical Studies*

Adverse Reaction	Subjects 9 Through 26 Years of Age
	GARDASIL 9 (N=15,776) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)	
Pain†	83.2
Swelling†	36.1
Erythema†	30.8
Pruritus	4.0
Bruising	1.6
Systemic Adverse Reactions (1 to 15 Days Postvaccination)	
Headache	13.2
Pyrexia	6.1
Nausea	3.2
Dizziness	2.3
Fatigue	1.9

*Data from Protocols 001,002, 003, 005, 006, 007, 009
†Designates a solicited adverse reaction
N=number of subjects vaccinated with safety follow-up

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

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL 9 (N=7071) %	GARDASIL (N=7078) %	GARDASIL 9 (N=299) %	GARDASIL (N=300) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)				
Pain†	89.9	83.5	89.3	88.3
Swelling†	40.0	28.8	47.8	36.0
Erythema†	34.0	25.6	34.1	29.3
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	‡	‡
Mass	1.3	0.6	‡	‡
Hemorrhage	1.0	0.7	1.0	2.0
Hematoma	0.9	0.6	3.7	4.7
Warmth	0.8	0.5	0.7	1.7
Induration	0.8	0.2	2.0	1.0
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Postvaccination)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0.0	2.7
Diarrhea	1.2	1.0	0.3	0.0
Myalgia	1.0	0.7	0.7	0.7
Oropharyngeal pain	1.0	0.6	2.7	0.7
Abdominal pain upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

*The data for women are from Protocol 001 and data for girls are from Protocol 009.
†Designates a solicited adverse reaction
‡There are no reports of injection-site bruising or mass for girls.
N=number of subjects vaccinated

Solicited Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

Temperature and injection-site pain, swelling, and erythema were solicited using VRC-aided surveillance for 5 days after each injection of GARDASIL 9 during the clinical studies. The incidence and severity of solicited adverse reactions that occurred within 5 days following each dose of GARDASIL 9 are shown in Table 3.

Table 3: Postdose Evaluation of Solicited Systemic and Injection-Site Adverse Reactions by Incidence and Severity from All Clinical Studies* (1 to 5 Days Postvaccination)

Solicited Systemic Adverse Reaction	Severity	Dose 1 N=15,614 %	Dose 2 N=15,243 %	Dose 3 N=15,062 %	Any Dose N=15,676 %
Temperature	< 37.8 °C (100.0 °F)	97.1	97.4	96.9	92.5
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.5	2.3	2.5	6.3
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.3	0.3	0.5	1.1
	≥ 39.9 °C (103.8 °F) < 40.9 °C (105.6 °F)	0.1	0.1	0.1	0.2
	≥ 40.9 °C (105.6 °F)	0.0	0.0	0.0	0.0
Solicited Injection-site Adverse Reaction	**Severity**	**Dose 1 N=15,773**	**Dose 2 N=15,549**	**Dose 3 N=15,378**	**Any Dose N=15,776**
Pain	Mild	52.3	46.7	44.4	51.1

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	Moderate	10.8	15.1	16.7	28.5
	Severe	0.6	1.4	2.1	3.5
Swelling†	Mild	9.6	14.7	17.9	24.8
	Moderate	1.7	3.7	4.6	7.3
	Severe	0.8	1.6	2.5	4.0
Erythema†	Mild	8.7	13.6	16.1	24.7
	Moderate	0.9	2.0	2.5	4.4
	Severe	0.2	0.5	1.1	1.7

*Data from Protocols 001, 002, 003, 005, 006, 007, 009

†Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

N=Number of individuals with safety follow-up

Serious Adverse Events in Clinical Trials of GARDASIL 9

Serious adverse events were collected throughout the entire study period for the seven integrated clinical studies for GARDASIL 9. Out of the 15,778 individuals who were administered GARDASIL 9 and had safety follow-up, 356 reported a serious adverse event; representing 2.3% of the population. Four individuals administered GARDASIL 9 reported at least one serious adverse event that was determined to be vaccine-related. Four vaccine-related serious adverse events that occurred during the study period were pyrexia, allergy to vaccine, asthmatic crisis and headache.

Clinical Trials Experience for GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

A clinical study (Protocol 006) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with 3 doses of GARDASIL. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall, the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination.

Table 4: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥ 1% and Greater Than Saline Placebo for GARDASIL 9 in 12- through 26-year-old Girls and Women Who Have Been Previously Vaccinated with GARDASIL*

Adverse Reaction	GARDASIL 9 (N=608) %	SALINE PLACEBO (N=305) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain†	90.3	38.0
Swelling†	49.0	5.9
Erythema†	42.3	8.5
Pruritus	7.7	1.3
Hematoma	4.8	2.3
Reaction	1.3	0.3
Mass	1.2	0.7
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0

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Dizziness	3.0	1.6
Abdominal pain upper	1.5	0.7
Influenza	1.2	1.0

*The data for GARDASIL 9 and Placebo are from Protocol 006.
†Designates a solicited adverse reaction
N=number of subjects vaccinated

Clinical Trials Experience for Concomitant Administration of GARDASIL 9 with Other Vaccines

The safety of GARDASIL 9 when administered concomitantly with other vaccines was evaluated in clinical studies.

There was an increase in injection-site swelling reported at the injection site for GARDASIL 9 when GARDASIL 9 was administered concomitantly with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV)] or Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] and Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] as compared to non-concomitant vaccination. The majority of injection-site swelling seen with concomitant administration with other vaccines was reported as being mild to moderate in intensity.

Post-marketing Reports

The post-marketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

The safety profile of GARDASIL 9 and GARDASIL are similar. The post-marketing adverse experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are similar in composition and contain L1 HPV proteins 4 of the same HPV types.

GARDASIL 9

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

Nervous system disorders: syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: vomiting.

GARDASIL

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL:

Infections and infestations: cellulitis

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy

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

Nervous system disorders: acute disseminated encephalomyelitis, Guillain-Barré syndrome,

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Musculoskeletal and connective tissue disorders: arthralgia, myalgia

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

There have been no reports of administration of higher than recommended doses of GARDASIL 9. For advice on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766.

5 PHARMACOLOGICAL PROPERTIES

DESCRIPTION

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The L1 proteins are produced by separate fermentations using recombinant yeast *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on pre-formed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant formulation and the final purification buffer.

GARDASIL 9 is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 60 mcg of HPV 16 L1 protein, 40 mcg of HPV 18 L1 protein, 20 mcg of HPV 31 L1 protein, 20 mcg of HPV 33 L1 protein, 20 mcg of HPV 45 L1 protein, 20 mcg of HPV 52 L1 protein, and 20 mcg of HPV 58 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 500 mcg of aluminium (as amorphous aluminium 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, residual traces of yeast protein (estimated at <0.7 mcg/dose using a specific ELISA test) and water for injection. The product does not contain a preservative or antibiotics.

PHARMACOLOGY

GARDASIL 9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV). Each virus-like particle (VLP) is composed of a unique recombinant L1 major capsid protein for the respective HPV type. The VLPs do not contain DNA fragments in a form that could allow them to infect cells or reproduce. GARDASIL 9 contains the 4 HPV

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VLP types (6, 11, 16, and 18) that are in GARDASIL plus an additional 5 HPV VLP types (31, 33, 45, 52, and 58) absorbed on amorphous aluminum hydroxyphosphate adjuvant (AAHS).

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

CLINICAL STUDIES

HPV infection is very common; in the absence of vaccination, the majority of sexually active individuals will become infected with HPV during their lifetime.

Most HPV infections clear without sequelae but some progress to HPV-related diseases including cervical cancers and their precursors (Cervical Intraepithelial Neoplasia or CIN grades 1, 2, and 3), anal, vulvar, vaginal, and penile cancers and their precursors (Anal Intraepithelial Neoplasia or AIN, Vulvar Intraepithelial Neoplasia or VIN, Vaginal Intraepithelial Neoplasia or VaIN and Penile Intraepithelial Neoplasia or PIN), genital warts, and lesions in the aerodigestive tract including oropharyngeal cancers and recurrent respiratory papillomatosis.

In female subjects, 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.

In male subjects, penile/perineal/perianal intraepithelial neoplasia (PIN) 1 (low grade) and PIN 3 (high grade) has been associated with HPV. HPV 16 is the most common type detected.

GARDASIL 9 is a recombinant vaccine with L1 proteins resembling 9 HPV types. GARDASIL 9 includes the same four HPV types contained in GARDASIL (HPV 6, 11, 16, 18) and five additional HPV types (31, 33, 45, 52, and 58).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Papillomavirus vaccines, ATC code: J07BM03

Efficacy Data for GARDASIL

GARDASIL was first licensed in 2006. Efficacy was assessed in 6 AAHS-controlled, double-blind, randomized Phase II and III clinical studies evaluating 28,413 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age, 3,817 women 24 through 45 years of age). The median duration of follow up in these studies ranged from 2.9 through to 4.0 years, with a maximum follow up of 5 years. The efficacy and long-term effectiveness of GARDASIL against HPV 6-, 11-, 16-, and 18-related disease endpoints have been demonstrated in clinical studies in the PPE (Per Protocol Efficacy) population. The PPE population consisted of individuals who received all 3 vaccinations with GARDASIL in the base study within 1 year of enrollment without major deviations from the study protocol, were seronegative to the relevant HPV type(s) (types 6, 11, 16 and 18) prior

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to dose 1, and among subjects 16 years and older at enrollment in the base study, PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

GARDASIL was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in girls and women in the PPE population (Table 5). In addition, girls and women who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types. Individuals who had prior infection that had been resolved before vaccination (PCR negative and seropositive at baseline) were protected from reinfection or recurrence of infection leading to clinical disease with the same HPV type.

GARDASIL was efficacious in reducing the incidence of external genital lesions (Genital Warts and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16, or 18 in boys and men in the PPE population (Table 5). GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men in the PPE population (Table 5).

Table 5: Analysis of Efficacy of GARDASIL in the Per Protocol Efficacy (PPE)* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- Through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	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)	7900	2	7902	227	99.1 (96.8, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- Through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Genital Warts	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (<0.0, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).
†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N=Number of individuals with at least 1 follow-up visit after Month 7
CI=Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 5 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

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A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals compared to younger individuals. Therefore, to confirm the utility of GARDASIL to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study was conducted.

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 per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit (Table 6).

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 6: 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

Long-term follow-up studies

A subset of subjects is currently being followed up for 10 to 14 years after GARDASIL vaccination for safety, immunogenicity and protection against clinical diseases related to HPV types 6/11/16/18.

Currently, persistence of antibody response has been observed for 8 years in adolescents who were 9through 15 years of age at time of vaccination; 9 years in girls and women, 16 through 23 years of age at time of vaccination; 6 years in boys and men, 16 through 26 years of age at time of vaccination, and women, 24 through 45 years of age at time of vaccination.

Clinical protection has been observed in all subjects (including those who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18): no cases of HPV diseases were observed after a follow-up of approximately 6.9 years in girls who were 9 through 15 years of age at time of vaccination; 6.5 years in boys, 9 through 15 years of age at time of vaccination; 8 years in girls and women, 16 through 23 years of age at time of vaccination; 6 years in boys and men, 16 through 26 years of age at time of vaccination, and women, 24 through 45 years of age at time of vaccination.

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Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of the three dose regimen of GARDASIL 9 were assessed in seven clinical studies. Clinical studies evaluating the efficacy of GARDASIL 9 against placebo were not acceptable because HPV vaccination represents the standard of care for protection against HPV infection and disease in many countries. Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

Efficacy against HPV Types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrates comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of GARDASIL 9 compared with GARDASIL (Protocols 001, 002, and 009).

The analysis of efficacy for GARDASIL 9 was evaluated in the PPE population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma in situ (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar, and vaginal disease of any grade; persistent infection; cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types in GARDASIL 9 (31, 33, 45, 52, and 58) was evaluated compared to GARDASIL.

The efficacy is further extended to 9- through 15-year-old adolescents and to 16- through 26-year-old boys and men, for all endpoints studied, using immunological bridging. The immunogenicity bridging analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocols 001 and 002) and seronegative (Protocols 001, 002, 003, 005, 007 and 009)] to the relevant HPV type(s) prior to dose 1 and through Month 7.

Protocol 001 evaluated efficacy and immunogenicity of GARDASIL 9 to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women (N = 14,204: 7,099 receiving GARDASIL 9; 7,105 receiving GARDASIL). Two immunological bridging studies evaluated HPV types 6, 11, 16 and 18 (Protocols 002 and 009) and HPV types 31, 33, 45, 52, and 58 (Protocol 002). Protocol 002 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age (N=3,066: 1,932 girls; 666 boys; and 468 women receiving GARDASIL 9). Protocol 009 evaluated immunogenicity in girls 9 through 15 years of age (N=600; 300 receiving GARDASIL 9 and 300 receiving GARDASIL). Protocol 003 evaluated immunogenicity of GARDASIL 9 in boys and men 16 through 26 years of age and in girls and women 16 through 26 years of age (N=2515:1,103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1,099 women receiving GARDASIL 9).

Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL (N=921; 615 receiving GARDASIL 9 and 306 receiving placebo). Protocols 005 and 007 evaluated GARDASIL 9 concomitantly administered with vaccines recommended routinely in girls and boys 11 through 15 years of age (N=2,295). Together, these seven studies evaluated 15,875 individuals who received GARDASIL 9 (9,152 girls and women 16 through 26 years of age at enrollment with a mean

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age of 21.7 years; 3,498 girls 9 through 15 years of age at enrollment with a mean age of 12.0 years; 1,416 boys and men 16 through 26 years of age at enrollment with a mean age of 21.1 years; and 1,809 boys 9 through 15 years of age at enrollment with a mean age of 12.1 years.

One clinical trial (Protocol 010) assessed the two dose regimen of GARDASIL 9. Protocol 010 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and women 16 through 26 years of age; (N=1,518; 753 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years.

The totality of results from the clinical studies support that GARDASIL 9 was efficacious against HPV disease and persistent infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Therefore the efficacy for cervical, vulvar, vaginal, and anal diseases, genital warts and persistent infection that was demonstrated in the original clinical studies for GARDASIL can be extended to GARDASIL 9. In clinical studies, protective efficacy has been shown to last up to 5.6 years postdose 3 in duration for GARDASIL 9.

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

Comparison of Immune Responses Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the Clinical Studies for GARDASIL 9

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

Because of the high efficacy of GARDASIL, there is no known immune correlate of protection. The minimal anti-HPV response associated with protection against HPV 6-, 11-, 16-, and 18-related infection and disease has not been established. In addition, the existence of HPV Types 6, 11, 16, and 18 antigens in both the formulations for GARDASIL 9 and the active comparator vaccine (GARDASIL) should result in no or few infection and disease endpoints associated with these HPV types. A low number of efficacy endpoints in both vaccination groups preclude a direct measurement of efficacy using disease endpoints associated with these HPV types.

GARDASIL 9 efficacy against HPV 6-, 11-, 16-, and 18-related infection and disease was inferred from comparative studies to the quadrivalent HPV vaccine (Types 6, 11, 16, 18), GARDASIL, in which GARDASIL 9 elicited immune responses as measured by GMT. These studies were designed to evaluate immunologic non-inferiority of GARDASIL 9 to GARDASIL. Therefore, the efficacy findings from the pivotal clinical studies for GARDASIL against HPV Type 6-, 11-, 16-, and 18-related disease were extended to GARDASIL 9 by demonstrating that the immune responses elicited by GARDASIL 9 were non-inferior to the immune responses elicited by GARDASIL.

Comparison of GARDASIL 9 with GARDASIL immunogenicity with respect to HPV types 6, 11, 16, and 18 were conducted in a population of 16- through 26-year-old women from Protocol 001 and 9- through 15-year-old girls from Protocol 009. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocol 001) and seronegative (Protocols 001 and 009) prior to dose one] to the relevant HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age; Protocol 001) to the relevant HPV type(s) through Month 7.

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A statistical analysis of non-inferiority was performed based on Month 7 cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs between individuals administered GARDASIL 9 and individuals administered GARDASIL. Immune responses, measured by GMT, for GARDASIL 9 were non-inferior to immune responses for GARDASIL (Table 7). Therefore, efficacy for GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of GARDASIL.

Table 7: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the Per Protocol Immunogenicity (PPI)* Population of 9- through 26-Year-Old Girls and Women

POPULATION	GARDASIL 9			GARDASIL			GARDASIL 9/ GARDASIL	
	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio	(95% CI)#
Anti-HPV 6								
9- through15-year-old girls	300 (273)	100 (98.7, 100)	1679.4 (1518.9, 1856.9)	300 (261)	100 (98.6, 100)	1565.9 (1412.2, 1736.3)	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	99.8 (99.6, 99.9)	893.1 (871.7, 915.1)	6795 (3975)	99.8 (99.7, 99.9)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06)¶
Anti-HPV 11								
9- through 15-year-old girls	300 (273)	100 (98.7, 100)	1315.6 (1183.8, 1462.0)	300 (261)	100 (98.6, 100)	1417.3 (1274.2, 1576.5)	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	100 (99.9, 100)	666.3 (649.6, 683.4)	6795 (3982)	99.9 (99.8, 100)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83)¶
Anti-HPV 16								
9- through 15-year-old girls	300 (276)	100 (98.7, 100)	6739.5 (6134.5, 7404.1)	300 (270)	100 (98.6, 100)	6887.4 (6220.8, 7625.5)	0.97	(0.85, 1.11)¶
16- through 26-year-old girls and women	6792 (4032)	100 (99.9, 100)	3131.1 (3057.1, 3206.9)	6795 (4062)	100 (99.8, 100)	3156.6 (3082.3, 3232.7)	0.99	(0.96, 1.03)¶
Anti-HPV 18								
9- through 15-year-old girls	300 (276)	100 (98.7, 100)	1956.6 (1737.3, 2203.7)	300 (269)	100 (98.6, 100)	1795.6 (1567.2, 2057.3)	1.08	(0.91, 1.29)¶
16- through 26-year-old girls and women	6792 (4539)	99.8 (99.7, 99.9)	804.6 (782.7, 827.1)	6795 (4541)	99.7 (99.5, 99.8)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23)¶

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data for 16- through 26- year-old girls and women are from Protocol 001, and the data for 9- through 15-year-old girls are from Protocol 009.

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

‡Number of individuals contributing to the analysis

§mMU=milli-Merck units

¶p-value <0.001

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

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA= Competitive Luminex Immunoassay

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Prophylactic Efficacy of GARDASIL 9 for HPV Types 31, 33, 45, 52, and 58 in Girls and Women 16 Through 26 Years of Age

Studies Supporting Efficacy of GARDASIL 9 Against HPV Types 31, 33, 45, 52, and 58

The efficacy of GARDASIL 9 in 16- through 26- year-old women was assessed in an active comparator-controlled, double-blind, randomized clinical study (Protocol 001) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105), who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up to 67 months postdose 3, with a median duration of 43 months.

The primary efficacy is based on evaluation of a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58- related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. The efficacy is further supported by evaluation of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58- related abnormal Pap tests, cervical and external genital procedures (i.e., biopsies) and cervical definitive therapy procedures.

Efficacy was evaluated in the PPE population of 16- through 26-year-old women, who were naïve to the relevant HPV type(s) prior to dose one and through Month 7. Efficacy was measured starting after the Month 7 visit. GARDASIL 9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58- related persistent infection and disease (Table 8). GARDASIL 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58- related Pap test abnormalities, cervical and external genital procedures (i.e., biopsies), and cervical definitive therapy procedures (including loop electrosurgical excision procedure [LEEP] or conisation. See Table 8.

Table 8: Analysis of Efficacy of GARDASIL 9 Against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population 16- through 26-Year-old Women

Disease Endpoint	GARDASIL 9 N†=7099		GARDASIL N†=7105		%Efficacy (95% CI)¶
	n‡	Number of cases§	n‡	Number of cases§	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5949	1	5943	87	98.9 (94.1, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS#	5949	1	5943	35	97.1 (83.5, 99.9)
CIN2	5949	1	5943	32	96.9 (81.5, 99.8)
CIN3	5949	0	5943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease▷	6009	1	6012	18	94.4 (67.7, 99.7)
VIN2/3# and VaIN2/3	6009	0	6012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months§	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months▵	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap◊ Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related	6013	6	6014	253	97.7

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Cervical Biopsy					(95.1, 99.0)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Definitive Therapy Procedure[ò]	6013	4	6014	41	90.2 (75.0, 96.8)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7). The data are from Protocol 001.
[†]N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
[‡]n=Number of individuals contributing to the analysis
[§]Number of cases= number of individuals with at least one follow-up visit after Month 7
[¶]Subjects were followed for up to 67 months postdose 3 (median 43 months postdose 3)
[#]No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.
[Þ]includes VIN1/2/3, VaIN1/2/3,condyloma
[ò]loop electrosurgical excision procedure (LEEP) or conization
[ß]Persistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart
[à]Persistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart
[è]Papanicolaou test
CI=Confidence Interval
ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk

Additional Efficacy Evaluation of GARDASIL 9 Against HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58

Since the efficacy of GARDASIL 9 could not be evaluated against placebo, the following exploratory analyses were conducted.

Efficacy Evaluation of GARDASIL 9 Against Cervical High Grade Diseases Caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE

The efficacy of GARDASIL 9 against CIN 2 and worse related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to GARDASIL was 94.4% (95% CI 78.8; 99.0) with 2/5,952 versus 36/5,947 cases. The efficacy of GARDASIL 9 against CIN 3 related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to GARDASIL was 100% (95% CI 46.3; 100.0) with 0/5,952 versus 8/5,947 cases. These results reflect efficacy of GARDASIL 9 versus GARDASIL against disease caused by HPV types 31, 33, 45, 52, and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Impact of GARDASIL 9 Against Cervical Biopsy and Definite Therapy Related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE

The efficacy of GARDASIL 9 against cervical biopsy related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to GARDASIL was 95.9% (95% CI 92.7; 97.9) with 11/6,016 versus 262/6,018 cases. The efficacy of GARDASIL 9 against cervical definitive therapy (including loop electrosurgical excision procedure [LEEP] or conization) related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 compared to GARDASIL was 90.7% (95% CI 76.3; 97.0) with 4/6,016 versus 43/6,018 cases. These results reflect efficacy of GARDASIL 9 versus GARDASIL against procedures associated with HPV types 31, 33, 45, 52, and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Immunogenicity of GARDASIL 9

Assays to Measure Immune Response

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

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Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL 9 it has not been possible to establish minimum antibody levels that protect against clinical disease caused by vaccine HPV types.

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

Immune Response to GARDASIL 9 at Month 7 In Clinical Studies

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age) and seronegative prior to dose one] to the relevant HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age) to the relevant HPV type(s) through Month 7.

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 9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses measured at Month 7 (Table 9). In clinical studies 99.6% to 100% who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested.

Table 9: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9- through 15-year-old girls	2805	2349	99.7 (99.4, 99.9)	1744.6 (1684.7, 1806.7)
9- through 15-year-old boys	1239	1055	99.9 (99.5, 100)	2085.3 (1984.2, 2191.6)
16- through 26-year-old women	7260	4321	99.8 (99.6, 99.9)	893.7 (873.5, 914.3)
Anti-HPV 11				
9- through 15-year-old girls	2805	2350	99.9 (99.7, 100)	1289.7 (1244.3, 1336.8)
9- through 15-year-old boys	1239	1055	100 (99.7, 100)	1469.2 (1397.7, 1544.4)
16- through 26-year-old women	7260	4327	100 (99.9, 100)	669.3 (653.6, 685.4)
Anti-HPV 16				
9- through 15-year-old girls	2805	2405	99.9 (99.7, 100)	7159.9 (6919.7, 7408.5)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	8444.9 (8054.2, 8854.5)
16- through 26-year-old women	7260	4361	100 (99.9, 100)	3159.0 (3088.6, 3231.1)
Anti-HPV 18				
9- through 15-year-old girls	2805	2420	99.9 (99.6, 100)	2085.5 (2002.2, 2172.3)
9- through 15-year-old boys	1239	1074	100 (99.7, 100)	2620.4 (2474.3, 2775.2)
16- through 26-year-old women	7260	4884	99.8 (99.7, 99.9)	809.9 (789.2, 831.1)
Anti-HPV 31				
9- through 15-year-old girls	2805	2397	100 (99.8, 100)	1883.3 (1811.3, 1958.1)
9- through 15-year-old boys	1239	1069	100 (99.7, 100)	2173.5 (2057.0, 2296.6)
16- through 26-year-old women	7260	4806	99.8 (99.6, 99.9)	664.8 (647.4, 682.6)
Anti-HPV 33				
9- through 15-year-old girls	2805	2418	99.9 (99.7, 100)	960.6 (927.5, 994.9)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	1178.6 (1120.9, 1239.4)

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16- through 26-year-old women	7260	5056	99.7 (99.5, 99.8)	419.2 (409.6, 429.1)
Anti-HPV 45				
9- through 15-year-old girls	2805	2430	99.8 (99.6, 100)	728.7 (697.6, 761.2)
9- through 15-year-old boys	1239	1079	100 (99.7, 100)	841.7 (790.0, 896.7)
16- through 26-year-old women	7260	5160	99.6 (99.4, 99.7)	254.1 (247.0, 261.5)
Anti-HPV 52				
9- through 15-year-old girls	2805	2426	99.9 (99.7, 100)	978.2 (942.8, 1015.0)
9- through 15-year-old boys	1239	1077	100 (99.7, 100)	1062.2 (1007.2, 1120.2)
16- through 26-year-old women	7260	4792	99.8 (99.6, 99.9)	382.4 (373.0, 392.0)
Anti-HPV 58				
9- through 15-year-old girls	2805	2397	99.9 (99.7, 100)	1306.0 (1259.8, 1354.0)
9- through 15-year-old boys	1239	1072	100 (99.7, 100)	1545.8 (1470.6, 1624.8)
16- through 26-year-old women	7260	4818	99.8 (99.6, 99.9)	489.2 (477.5, 501.2)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) prior to dose 1, and among 16-through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data are from Protocols 001, 002, 005, 007 and 009.
†Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck Units
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titers

Table 9 displays the Month 7 immunogenicity data for girls and women and boys. Anti-HPV responses at Month 7 among 9- through 15-year-old girls were comparable to anti-HPV responses in 16- through 26-year-old women in the combined database of immunogenicity studies for GARDASIL 9. Anti-HPV responses at Month 7 among 9- through 15-year-old boys were comparable to anti-HPV responses in both 16- through 26-year-women and 9- through 15-year-old girls.

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

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 16- through 26-Year-Old Boys and Men

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority comparison in Protocol 003 of GMTs following vaccination with GARDASIL 9 among 16- to 26-year-old boys and men with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population, which included subjects who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were seronegative to the relevant HPV type(s) prior to dose 1. Anti-HPV GMTs at Month 7 among 16- through 26-year-old boys and men (HM) were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 10). Anti-HPV GMTs at Month 7 among 16- through 26-year-old MSM (HIV-negative) were lower than in 16- through 26-year-old HM. The GMT fold difference in 16- through 26-year-old MSM relative to the HM was 0.6 to 0.8; anti-HPV GMTs for the MSM subjects ranged between 157.5 and 2294.0 mMU/mL. The fold differences observed with GARDASIL 9 for MSM compared to HM were generally similar to those previously observed with GARDASIL. In Protocol 003, 99.6% to 100% in the HM population and 99.4 to 100% in the MSM population who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7.

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Table 10: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men for All GARDASIL 9 Vaccine HPV Types

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16-through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
16- through 26-year-old HM	1103	847	782.0	1.11 (1.02, 1.21)
16- through 26-year-old girls and women	1099	708	703.9	1
Anti-HPV 11				
16- through 26-year-old HM	1103	851	616.7	1.09 (1.00, 1.19)
16- through 26-year-old girls and women	1099	712	564.9	1
Anti-HPV 16				
16- through 26-year-old HM	1103	899	3346.0	1.20 (1.10, 1.30)
16- through 26-year-old girls and women	1099	781	2788.3	1
Anti-HPV 18				
16- through 26-year-old HM	1103	906	808.2	1.19 (1.08, 1.31)
16- through 26-year-old girls and women	1099	831	679.8	1
Anti-HPV 31				
16- through 26-year-old HM	1103	908	708.5	1.24 (1.13, 1.37)
16- through 26-year-old girls and women	1099	826	570.1	1
Anti-HPV 33				
16- through 26-year-old HM	1103	901	384.8	1.19 (1.10, 1.30)
16- through 26-year-old girls and women	1099	853	322.0	1
Anti-HPV 45				
16- through 26-year-old HM	1103	909	235.6	1.27 (1.14, 1.41)
16- through 26-year-old girls and women	1099	871	185.7	1
Anti-HPV 52				
16- through 26-year-old HM	1103	907	386.8	1.15 (1.05, 1.26)
16- through 26-year-old girls and women	1099	849	335.2	1
Anti-HPV 58				
16- through 26-year-old HM	1103	897	509.8	1.25 (1.14, 1.36)
16- through 26-year-old girls and women	1099	839	409.3	1

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Protocol 003.
†Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck Units
¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titers

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

Women 27 Years of Age and Older

No studies have been conducted in women older than 26 years of age. In women 27-through 45 years of age, efficacy of GARDASIL 9 for the 4 original types is expected based on (1) high efficacy of GARDASIL in women 16-through 45 years of age and (2) comparable immunogenicity of GARDASIL 9 and GARDASIL in girls and women 9-through 26 years of age.

Immune Responses to GARDASIL 9 Using a 2-dose Schedule in Individuals 9- through14 Years of Age

Protocol 010 measured HPV antibody responses to the 9 HPV types after GARDASIL 9 vaccination in the following cohorts: girls and boys 9- through 14 years old receiving 2 doses

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at a 6 month or 12-month interval (+/- 1 month); girls 9- through 14 years old receiving 3 doses (at 0, 2, 6 months); and women 16- through 26 years old receiving 3 doses (at 0, 2, 6 months).

GMTs were non-inferior in girls and boys who received 2 doses of GARDASIL 9 (at either 0, 6 months or 0, 12 months) to GMTs in 16 through 26 year old girls and women who received 3 doses of GARDASIL 9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2-dose regimen of GARDASIL 9 in 9 through 14 year old girls and boys is inferred. One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types (Table 11).

In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 11). The clinical relevance of these findings is unknown.

Duration of protection of a 2-dose schedule of GARDASIL 9 has not been established.

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Table 11. Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population at One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses† or 3 Doses† of GARDASIL 9

Population (Regimen)	N	n	GMT (95% CI) mMU§/mL
Anti-HPV 6			
9- through 14-year-old girls (0, 6)†	301	258	1657.9 (1479.6, 1857.6)
9- through 14-year-old boys (0, 6)†	301	263	1557.4 (1391.5, 1743.1)
9- through 14-year-old girls (0, 12)†	150	123	2685.7 (2274.6, 3171.2)
9- through 14-year-old boys (0, 12)†	150	134	2672.4 (2279.1, 3133.5)
9- through 14-year-old girls (0, 2, 6)†	300	254	1496.1 (1334.1, 1677.8)
16- through 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)
Anti-HPV 11			
9- through 14-year-old girls (0, 6)†	301	258	1388.9 (1240.4, 1,555.3)
9- through 14-year-old boys (0, 6)†	301	264	1423.9 (1273.2, 1592.3)
9- through 14-year-old girls (0, 12)†	150	123	2915.9 (2475.1, 3435.1)
9- through 14-year-old boys (0, 12)†	150	134	2965.9 (2534.9, 3470.1)
9- through 14-year-old girls (0, 2, 6)†	300	254	1306.3 (1165.5, 1464.0)
16- through 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)
Anti-HPV 16			
9- through 14-year-old girls (0, 6)†	301	272	8004.9 (7160.5, 8948.8)
9- through 14-year-old boys (0, 6)†	301	273	8474.8 (7582.4, 9472.3)
9- through 14-year-old girls (0, 12)†	150	129	13828.1 (11780.6, 16231.5)
9- through 14-year-old boys (0, 12)†	150	135	14825.2 (12675.7, 17339.3)
9- through 4-year-old girls (0, 2, 6)†	300	269	6996.0 (6254.1, 7825.8)
16- through 26-year-old women (0, 2, 6)†	314	249	3154.0 (2807.1, 3,543.7)
Anti-HPV 18			
9- through 14-year-old girls (0, 6)†	301	272	1872.8 (1651.6, 2123.6)
9- through 14-year-old boys (0, 6)†	301	272	1860.9 (1641.1, 2110.2)
9- through 14-year-old girls (0, 12)†	150	129	2696.0 (2252.4, 3227.0)
9- through 14-year-old boys (0, 12)†	150	137	2922.5 (2454.7, 3479.5)
9- through 14-year-old girls (0, 2, 6)†	300	270	2049.3 (1806.4, 2324.8)
16- through 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)
Anti-HPV 31			
9- through 14-year-old girls (0, 6)†	301	272	1436.3 (1272.1, 1621.8)
9- through 14-year-old boys (0, 6)†	301	271	1498.2 (1326.5, 1692.0)
9- through 14-year-old girls (0, 12)†	150	132	2086.4 (1761.7, 2471.1)
9- through 14-year-old boys (0, 12)†	150	136	2148.1 (1818.3, 2537.7)
9- through 14-year-old girls (0, 2, 6)†	300	271	1748.3 (1548.1, 1974.5)
16- through 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)
Anti-HPV 33			
9- through 14-year-old girls (0, 6)†	301	273	1030.0 (920.4, 1152.7)
9- through 14-year-old boys (0, 6)†	301	271	1040.0 (928.9, 1164.3)
9- through 14-year-old girls (0, 12)†	150	132	2037.4 (1737.6, 2389.0)
9- through 14-year-old boys (0, 12)†	150	137	2363.6 (2021.6, 2763.3)
9- through 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)
16- through 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)
Anti-HPV 45			
9- through 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)
9- through 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)
9- through 14-year-old girls (0, 12)†	150	132	439.6 (366.0, 528.0)
9- through 14-year-old boys (0, 12)†	150	136	397.6 (331.9, 476.2)
9- through 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)
16- through 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)
Anti-HPV 52			
9- through 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)
9- through 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)
9- through 14-year-old girls (0, 12)†	150	131	1028.2 (885.0, 1194.7)
9- through 14-year-old boys (0, 12)†	150	137	1222.7 (1055.9, 1415.9)
9- through 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)
16- through 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)
Anti-HPV 58			
9- through 14-year-old girls (0, 6)†	301	270	1251.2 (1119.6, 1398.4)
9- through 14-year-old boys (0, 6)†	301	270	1325.7 (1186.2, 1481.6)
9- through 14-year-old girls (0, 12)†	150	129	2244.7 (1919.2, 2625.3)
9- through 14-year-old boys (0, 12)†	150	136	2650.7 (2275.6, 3087.6)
9- through 14-year-old girls (0, 2, 6)†	300	273	1229.3 (1100.7, 1,373.0)
16- through 26-year-old women (0, 2, 6)†	314	261	491.1 (438.6, 549.8)

*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day

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ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.
†2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).
§mMU=milli-Merck Units.
N = Number of individuals randomized to the respective vaccination group who received at least 1 injection.
n = Number of individuals contributing to the analysis.
CI=confidence interval
cLIA=competitive Luminex immunoassay
GMT=Geometric Mean Titer

Variation in Dosing Regimen in 16-through 26-Year-Old Women

All individuals evaluated for efficacy in the PPE population of Protocol 001 received all 3 vaccinations 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 9 (see DOSAGE AND ADMINISTRATION*, Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL).*

Persistence of Immune Response to GARDASIL 9

The persistence of antibody response following a complete schedule of vaccination with GARDASIL 9 is being studied in a subset of individuals who will be followed up for at least 10 years after vaccination for safety, immunogenicity and effectiveness.

In 9- through 15 year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 3 years; depending on HPV type, 93 to 99 % of subjects were seropositive.

In 16- through 26 year-old girls and women (Protocol 001), persistence of antibody response has been demonstrated for at least 3.5 years; depending on HPV type, 78-98% of subjects were seropositive. Efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months postdose 3; median follow-up duration of 43 months).

GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received GARDASIL or GARDASIL 9 for at least 3.5 years.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Protocol 006 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrollment in the study, over 99% of subjects had received 3 injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The GMTs to HPV Types 31, 33, 45, 52, and 58 were lower than in the population who had not previously received GARDASIL in Protocols 001, 002, 005, 007 and 009. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

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Concomitant Use of GARDASIL 9 with Other Vaccines

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

In Protocol 005, the safety and immunogenicity of co-administration of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in a study of 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL 9).

Concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody response to any of the vaccine antigens when GARDASIL 9 was given concomitantly with Menactra and Adacel or separately (see Section 4.5, *Use with Other Vaccines*).

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

In Protocol 007, 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) (dTap-IPV)] (same visit, injections at separate sites) were evaluated in a study of 1,053 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and Repevax in the opposite limb concomitantly on Day 1 (n = 525). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Repevax at Month 1 in the opposite limb (n = 528). Subjects in both vaccination groups received the second dose of Gardasil 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Repevax and 3 doses for GARDASIL 9).

Concomitant administration of GARDASIL 9 with Repevax did not interfere with the antibody response to any of the vaccine antigens when GARDASIL 9 was given concomitantly with Repevax or separately (see Section 4.5, Use with Other Vaccines).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
L-histidine
Polysorbate 80
Sodium borate
Water for injections
For adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided total cumulative time out of refrigeration (at temperatures between 0°C and 25°C) does not exceed 72 hours. These are not, however, recommendations for storage.

Discard the product if it is frozen, particulates are present, or if it appears discoloured.

6.5 Nature and contents of container

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. GARDASIL 9 is a sterile cloudy white liquid.

GARDASIL 9 may be supplied as

- a single-dose pre-filled syringe of vaccine
- a box of ten single-dose pre-filled syringes of vaccine
- a single-dose vial of vaccine*
- a box of ten single-dose vials of vaccine*

**not currently available in New Zealand*

The prefilled syringe is not supplied with a needle; the single-use vial is not supplied with a needle or syringe.

6.6 Special precautions for disposal

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

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7 MEDICINE SCHEDULE

Schedule 4 – Prescription Medicine

8 SPONSOR

NAME AND ADDRESS OF SPONSOR in New Zealand

Merck Sharp & Dohme (NZ) Limited
123 Carlton Gore Road
Newmarket
Auckland
Tel: 0800 500 673

DISTRIBUTOR in New Zealand

Seqirus (NZ) Ltd
PO Box 62 590
Greenlane
Auckland 1546

9 DATE OF FIRST APPROVAL

18 February 2016

10 DATE OF REVISION OF THE TEXT

4 March 2020

CCDS-V503-I-082019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of Changes
Section 4.8, 5.1	Editorial revisions for clarity

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