AUSTRALIAN PRODUCT INFORMATION – GARDASIL® 9 (Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine, Recombinant) Suspension for intramuscular administration

1 NAME OF THE MEDICINE

Human Papillomavirus 9-valent Vaccine, Recombinant

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

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 aluminium-containing adjuvant (Amorphous Aluminium 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 aluminium-containing adjuvant formulation and the final purification buffer.

Each 0.5-mL dose contains approximately 30 micrograms of HPV 6 L1 protein, 40 micrograms of HPV 11 L1 protein, 60 micrograms of HPV 16 L1 protein, 40 micrograms of HPV 18 L1 protein, 20 micrograms of HPV 31 L1 protein, 20 micrograms of HPV 33 L1 protein, 20 micrograms of HPV 45 L1 protein, 20 micrograms of HPV 52 L1 protein, and 20 micrograms of HPV 58 L1 protein.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

GARDASIL 9 is indicated in females aged 9 to 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).

GARDASIL 9 is indicated in males aged 9 to 45 years* for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions, and infection caused by Human Papillomavirus (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 the core efficacy population of females aged 16 to 26 years. Immunogenicity studies have been conducted to link efficacy to younger populations (females and males aged 9 to 15 years). Immunogenicity studies of GARDASIL 9 have been

conducted relating to females over 26 years of age (see section 5.1 CLINICAL TRIALS for GARDASIL 9).

4.2 DOSE AND METHOD OF ADMINISTRATION

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 to 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 need for a booster dose has not been established.

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 5.1 CLINICAL TRIALS *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.

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 2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM and 6.1 LIST OF EXCIPIENTS).

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.

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 4.8 ADVERSE EFFECTS).

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 aetiology. 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

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

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

Use in Immunocompromised Individuals
The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, *Use with Steroids*).

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 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 5.1 CLINICAL TRIALS, *Concomitant Use of GARDASIL 9 With Other Vaccines*).

Use with Hormonal Contraceptives
In 7,269 women (16 to 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Use in Immunocompromised Individuals*).

[1] Not currently registered in Australia

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/fetal 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 fetus due to GARDASIL 9 vaccination prior to mating and at gestational day 6.

An evaluation of the effect of GARDASIL 9 vaccination prior to mating, at gestational day 6 and on lactational day 7 on embryo-fetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted. In 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.

Clinical Studies in Humans

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. Data from more than 1,000 pregnancy exposures to GARDASIL 9 in clinical studies in addition to a small number of pregnancy exposures in post-marketing experience do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages. These pregnancies occurred in women who were pregnant at time of vaccination or became pregnant during the follow-up period in clinical studies. However, these data are considered insufficient to recommend use during pregnancy. As a precautionary measure, the administration of GARDASIL 9 during pregnancy should be avoided. Women who become or plan to become pregnant during the vaccination series should be advised to interrupt or postpone the vaccination regimen until completion of pregnancy.

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 fetal 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 24 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.

Post-marketing Experience

A six-year pregnancy registry for GARDASIL 9 prospectively followed 180 women of which there were 69 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 4.3 % of pregnancies (3/69) and 4.5 % of live born infants (3/67), respectively. These frequencies were consistent with estimated background frequencies. These data support similar findings from a five year pregnancy registry for GARDASIL in which 1,640 pregnancies with known outcomes were included.

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 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of this medicine on a person's ability to drive and use machines were performed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience with GARDASIL 9 and GARDASIL
The safety and tolerability of GARDASIL was assessed in clinical trials in females and males 9 to

45 years of age. The safety profile of GARDASIL 9 is generally comparable to that of GARDASIL in the groups studied (females 9 to 45 years of age, and males 9 to 26 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 enrolment 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 to 26 years of age, 1,394 boys and men 16 to 26 years of age and 5,280 girls and boys 9 to 15 years of age (3,481 girls and 1,799 boys) at enrolment who received GARDASIL 9 and 7,078 girls and women 16 to 26 years of age and 300 girls 9 to 15 years of age at enrolment who received GARDASIL.

Safety was also evaluated in a clinical trial (Protocol 004) that included 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age who received GARDASIL 9. The safety profile of GARDASIL 9 was comparable between the two age groups.

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 To 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

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 To 26 Years of Age		Girls 9 To 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
	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
‡For Temp ≥ 40.9 °C (105.6 °F), the number of cases reported: 3 (Dose 1), 1 (Dose 2), 2 (Dose 3)

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- to 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- To 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
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 reactions 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 reactions with GARDASIL are relevant to GARDASIL 9 since the vaccines are similar in composition and contain HPV L1 proteins 4 of the same HPV types.

GARDASIL 9

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

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

Gastrointestinal disorders: vomiting.

General disorders and administration site conditions: injection-site nodule.

GARDASIL

Additionally, the following post-marketing adverse reactions 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, dizziness, Guillain-Barré syndrome, headache.

Gastrointestinal disorders: nausea.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no reports of administration of higher than recommended doses of GARDASIL 9. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce. GARDASIL 9 contains the 4 HPV types (6, 11, 16, and 18) that are in GARDASIL plus an additional 5 HPV types (31, 33, 45, 52, and 58) absorbed on amorphous aluminium 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 trials

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).

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 to 26 years of age, 4,055 boys and men 16 to 26 years of age, 3,817 women 24 to 45 years of age). The median duration of follow up in these studies ranged from 2.9 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 enrolment without major deviations from the study protocol, were seronegative to the relevant HPV type(s) (types 6, 11, 16 and 18) prior to dose 1, and among subjects 16 years and older at enrolment 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 To 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 To 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 enrolment, did not have

protocol deviations that could potentially interfere with the efficacy evaluation as judged by the study director, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and who remained PCR negative to the relevant HPV type(s) 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 Aluminium Hydroxyphosphate Sulfate

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 To 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

Effectiveness of GARDASIL in men 27 through 45 years of age is inferred from efficacy data in women 24 through 45 years of age as described above and supported by immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age received a 3-dose regimen of GARDASIL (0, 2, 6 months). A cross-study analysis of per-protocol immunogenicity populations compared Month 7 anti-HPV 6, 11, 16, and 18 GMTs of these 27- through 45-year-old men to those of 16- through 26-year-old boys and men in whom efficacy of GARDASIL had been established (see Table 5). GMT ratios (27- through 45-year-old men/16- through 26-year-old boys and men) for HPV 6, 11, 16, and 18 were 0.82 (95%CI: 0.65, 1.03), 0.79 (95%CI: 0.66, 0.93), 0.91 (95%CI: 0.72, 1.13), and 0.74 (95%CI: 0.59, 0.92), respectively.

Long-term follow-up studies

A subset of subjects who received 3 doses were 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.

Persistence of antibody response was observed for 10 years in adolescents who were 9 to 15 years of age at time of vaccination; 14 years in girls and women, 16 to 23 years of age at time of vaccination; 9.5 years in boys and men, 16 to 26 years of age at time of vaccination, and 9.5 years in women, 24 to 45 years of age at time of vaccination.

Clinical protection was observed in all subjects in the PPE population: no cases of HPV diseases were observed after a follow-up of approximately 10.7 years (median duration of follow up of 10.0 years) in girls who were 9 to 15 years of age at time of vaccination; 10.6 years (median duration of follow up of 9.9 years) in boys, 9 to 15 years of age at time of vaccination; 14 years (median duration of follow-up of 11.9 years) in girls and women, 16 to 23 years of age at time of vaccination; 11.5 years (median duration of follow-up of 9.5 years) in boys and men, 16 to 26 years of age at time of vaccination, and 10.1 years (median duration of follow up of 8.7 years) in women, 24 to 45 years of age at time of vaccination. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 2 cases related to HPV 16 in 246 girls who were 9 to 15 years of age at time of vaccination, and 1 case related to HPV 6 and 1 case related to HPV 16 in 168 boys who were 9 to 15 years of age at time of vaccination. This represents an incidence rate of HPV- 6-, 11-, 16-, or 18-related persistent infection of 4 per 1,000-person years in both girls and boys.

Persistence of antibody response to GARDASIL was also assessed in a clinical trial using a 2-dose regimen. One month after the last dose, antibody responses to the 4 HPV types were non-inferior among girls 9 through 13 years of age who received 2 doses of GARDASIL 6 months apart compared with girls and women 16 through 26 years of age who received 3 doses of the vaccine within 6 months. In post hoc analyses at 3 and 10 years of follow-up, non-inferiority criteria were also met for all 4 HPV types.

Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of the 3 dose regimen of GARDASIL 9 were assessed in nine 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 Titres [GMT]) of GARDASIL 9 compared with GARDASIL (Protocols 001, 009 and 020).

The analysis of efficacy for GARDASIL 9 was evaluated in the PPE population of 16 to 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 to 15-year-old adolescents and to 16- to 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, did not have protocol deviations that could potentially interfere with the immunogenicity evaluation as judged by the study director, met predefined criteria for the interval between the Month 6 and Month 7 visit and were HPV-naive (seronegative and among female subjects 16 to 26 years of age in Protocols 001 and 002, PCR negative) to the relevant HPV type(s) prior to dose 1 and who remained PCR-negative (in girls and women 16 to 26 years of age; Protocols 001 and 002) to the relevant HPV type(s) 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 to 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 to 15 years of age and women 16 to 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 to 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 to 26 years of age and in girls and women 16 to 26 years of age (N=2,515: 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 to 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 to 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 to 26 years of age at enrolment with a mean age of 21.7 years; 3,498 girls 9 to 15 years of age at enrolment with a mean age of 12.0 years; 1,416 boys and men 16 to 26 years of age at enrolment with a mean age of 21.1 years; and 1,809 boys 9 to 15 years of age at enrolment with a mean age of 12.1 years.

Two additional immunological bridging studies were conducted. Protocol 020 evaluated immunogenicity of GARDASIL 9 compared to GARDASIL in boys and men 16 through 26 years of age (N=500: 249 receiving GARDASIL 9 and 251 receiving GARDASIL). Protocol 004 evaluated immunogenicity of GARDASIL 9 in girls and women 16 through 26 years of age compared to women 27 through 45 years of age (N=1,210: 640 women 27 through 45 years and 570 girls and women 16 through 26 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.

One clinical trial (Protocol 010) assessed the 2-dose regimen of GARDASIL 9. Protocol 010 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 to 14 years of age and 3 doses of GARDASIL 9 in girls 9 to 14 years of age and girls and women 16 to 26 years of age; (N=1,516; 751 girls; 451 boys and 314 women). The mean age for the girls and boys 9 to 14 years of age was 11.5 years; the mean age for girls and women 16 to 26 years of age was 21.0 years.

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 (Types 6, 11, 16, 18) vaccine, 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 to 26-year-old women from Protocol 001, 9 to 15-year-old girls from Protocol 009, and 16- to 26-year-old boys and men from Protocol 020. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects who received all 3 vaccinations within pre-defined day ranges, did not have protocol deviations that could potentially interfere with the immunogenicity evaluation as judged by the study director, met predefined criteria for the interval between the Month 6 and Month 7 visit and were HPV-naïve [PCR negative (in girls and women 16 through 26 years of age; Protocol 001) and seronegative (Protocols 001, 009 and 020) 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.

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- To 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men

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 to15-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 to 26-year-	6792	99.8	893.1	6795	99.8	875.2	1.02	(0.99,

old girls and women	(3993)	(99.6, 99.9)	(871.7, 915.1)	(3975)	(99.7, 99.9)	(854.2, 896.8)		1.06)¶
16 to 26-year-old boys and men	249 (228)	98.2 (95.6, 99.5)	758.3 (665.9, 863.4)	251 (226)	98.7 (96.2, 99.7)	618.4 (554.0, 690.3)	1.23	(1.04, 1.45)¶
Anti-HPV 11								
9 to 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 to 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)¶
16 to 26-year-old boys and men	249 (228)	100 (98.4, 100)	681.7 (608.9, 763.4)	251 (226)	100 (98.4, 100)	769.1 (683.5, 865.3)	0.89	(0.76, 1.04)¶
Anti-HPV 16								
9 to 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 to 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)¶
16 to 26-year-old boys and men	249 (234)	100 (98.4, 100)	3924.1 (3513.8, 4382.3)	251 (237)	100 (98.5, 100)	3787.9 (3378.4, 4247.0)	1.04	(0.89, 1.21) ¶
Anti-HPV 18								
9 to 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 to 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)¶
16 to 26-year-old boys and men	249 (234)	99.6 (97.6, 100)	884.3 (766.4, 1020.4)	251 (236)	99.6 (97.7, 100)	790.9 (683.0, 915.7)	1.12	(0.91, 1.37) ¶

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have protocol deviations that could potentially interfere with the immunogenicity evaluation as judged by the study director, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16 to 26-year-old girls and women] and seronegative) to the relevant HPV type(s) prior to dose 1 and among 16 to 26-year-old girls and women, remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7). The data for 16- to 26- year-old girls and women are from Protocol 001, and the data for 9- to 15-year-old girls are from Protocol 009. The data for 16- to 26-year-old boys and men are from Protocol 020.
†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 Titres
cLIA= Competitive Luminex Immunoassay

Prophylactic Efficacy of GARDASIL 9 for HPV Types 31, 33, 45, 52, and 58 in Girls and Women 16 To 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 to 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 to 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 procedures (i.e., biopsies), and cervical definitive therapy procedures (including loop electrosurgical excision procedure [LEEP] or conization). 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 To 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 DiseaseÞ	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 Monthsß	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Monthsà	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Papè Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Biopsy	6013	6	6014	253	97.7 (95.1, 99.0)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Definitive Therapy Procedureð	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 enrolment, did not have protocol deviations that could potentially interfere with the efficacy evaluation as judged by the study director, 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 5.6 years postdose 3 (median 3.5 years)

#No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.

Þincludes VIN1/2/3, VaIN1/2/3, condyloma

ðloop electrosurgical excision procedure (LEEP) or conization

ßPersistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart

àPersistent infection detected in samples from three or more consecutive visits over 6 months (±1 month visit windows) apart

èPapanicolaou 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.

Long-term effectiveness studies

A subset of subjects who received 3 doses is being followed up for 10 to 14 years after GARDASIL 9 vaccination for safety, immunogenicity, and effectiveness against clinical diseases related to the HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Clinical protection has been observed in all subjects in the long-term extension of Protocol 001 registry study in the PPE population. No cases of high-grade CIN were observed through 13.6 years postdose 3 (median duration of follow-up of 10.4 years) in girls and women (n = 1628) who were 16 through 26 years of age at time of vaccination.

In the long-term extension of Protocol 002, in the PPE population no cases of high-grade intraepithelial neoplasia or genital warts were observed through 11 years postdose 3 (median duration of follow-up of 10.0 years) in girls (n = 872) and through 10.6 years postdose 3 (median duration of follow-up of 9.9 years) in boys (n = 262) who were 9 through 15 years of age at time of vaccination with GARDASIL 9. In girls and boys, incidence rates of 6 month persistent infections related to vaccine HPV types observed during the study were 52.4 and 54.6 per 10,000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of GARDASIL 9 and GARDASIL vaccine).

Immunogenicity of GARDASIL 9

Assays to Measure Immune Response

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

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL 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 Across All 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 to 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 to 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 Titre (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 99.2% to 100% who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GMTs were higher in girls and boys than in women 16 through 26 years of age, and higher in boys than in girls and women. As expected for women 27 through 45 years of age (Protocol 004), the observed GMTs were lower than those seen in girls and women 16 through 26 years of age.

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

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9 to 15-year-old girls	2805	2349	99.7 (99.4, 99.9)	1744.6 (1684.7, 1806.7)
9 to 15-year-old boys	1239	1055	99.9 (99.5, 100)	2085.3 (1984.2, 2191.6)
16 to 26-year-old women	7260	4321	99.8 (99.6, 99.9)	893.7 (873.5, 914.3)
Anti-HPV 11				
9 to 15-year-old girls	2805	2350	99.9 (99.7, 100)	1289.7 (1244.3, 1336.8)
9 to 15-year-old boys	1239	1055	100 (99.7, 100)	1469.2 (1397.7, 1544.4)
16 to 26-year-old women	7260	4327	100 (99.9, 100)	669.3 (653.6, 685.4)
Anti-HPV 16				
9 to 15-year-old girls	2805	2405	99.9 (99.7, 100)	7159.9 (6919.7, 7408.5)
9 to 15-year-old boys	1239	1076	100 (99.7, 100)	8444.9 (8054.2, 8854.5)
16 to 26-year-old women	7260	4361	100 (99.9, 100)	3159.0 (3088.6, 3231.1)
Anti-HPV 18				
9 to 15-year-old girls	2805	2420	99.9 (99.6, 100)	2085.5 (2002.2, 2172.3)
9 to 15-year-old boys	1239	1074	100 (99.7, 100)	2620.4 (2474.3, 2775.2)
16 to 26-year-old women	7260	4884	99.8 (99.7, 99.9)	809.9 (789.2, 831.1)
Anti-HPV 31				
9 to 15-year-old girls	2805	2397	100 (99.8, 100)	1883.3 (1811.3, 1958.1)
9 to 15-year-old boys	1239	1069	100 (99.7, 100)	2173.5 (2057.0, 2296.6)
16 to 26-year-old women	7260	4806	99.8 (99.6, 99.9)	664.8 (647.4, 682.6)
Anti-HPV 33				
9 to 15-year-old girls	2805	2418	99.9 (99.7, 100)	960.6 (927.5, 994.9)
9 to 15-year-old boys	1239	1076	100 (99.7, 100)	1178.6 (1120.9, 1239.4)
16 to 26-year-old women	7260	5056	99.7 (99.5, 99.8)	419.2 (409.6, 429.1)
Anti-HPV 45				
9 to 15-year-old girls	2805	2430	99.8 (99.6, 100)	728.7 (697.6, 761.2)
9 to 15-year-old boys	1239	1079	100 (99.7, 100)	841.7 (790.0, 896.7)
16 to 26-year-old women	7260	5160	99.6 (99.4, 99.7)	254.1 (247.0, 261.5)
Anti-HPV 52				
9 to 15-year-old girls	2805	2426	99.9 (99.7, 100)	978.2 (942.8, 1015.0)

9 to 15-year-old boys	1239	1077	100 (99.7, 100)	1062.2 (1007.2, 1120.2)
16 to 26-year-old women	7260	4792	99.8 (99.6, 99.9)	382.4 (373.0, 392.0)
Anti-HPV 58				
9 to 15-year-old girls	2805	2397	99.9 (99.7, 100)	1306.0 (1259.8, 1354.0)
9 to 15-year-old boys	1239	1072	100 (99.7, 100)	1545.8 (1470.6, 1624.8)
16 to 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 protocol deviations that could potentially interfere with the immunogenicity evaluation as judged by the study director, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative [among 16 to 26-year-old girls and women] and seronegative) to the relevant HPV type(s) prior to dose 1 and among 16 to 26-year-old girls and women, remained 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 Titres

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

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

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 16- to 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- to 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- to 26-year-old boys and men (HM) were non-inferior to anti-HPV GMTs among 16- to 26-year-old girls and women (Table 10). Anti-HPV GMTs at Month 7 among 16- to 26-year-old MSM (HIV-negative) were lower than in 16- to 26-year-old HM. The GMT fold difference in 16- to 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.

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

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

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

Women 27 Years of Age and Older

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 27- through 45-year-old women was inferred based on non-inferiority of GMTs following vaccination with GARDASIL 9 in 27- through 45-year-old women compared to 16- through 26-year-old girls and women and demonstration of efficacy of GARDASIL in girls and women 16 through 45 years of age. In Protocol 004, GARDASIL 9 elicited seroconversion rates for all nine vaccine HPV types greater than 99% in girls and women 16 through 45 years of age. Anti-HPV antibody GMTs at Month 7 among women 27 through 45 years of age were non-inferior to anti-HPV antibody GMTs among girls and women 16 through 26 years of age for HPV 16, 18, 31, 33, 45, 52, and 58, with GMT ratios between 0.66 and 0.73 (See Table 11). These results support the efficacy of GARDASIL 9 in women 27 through 45 years of age.

Table 11: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 27- through 45-Year-Old Women and 16- through 26-Year-Old Girls and Women for 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				
27- through 45-year-old women	640	448	638.4	ND
16- through 26-year-old girls and women	570	421	787.8	ND
Anti-HPV 11				
27- through 45-year-old women	640	448	453.5	ND
16- through 26-year-old girls and women	570	421	598.7	ND
Anti-HPV 16				
27- through 45-year-old women	640	448	2147.5	0.70 (0.63, 0.77) ¶
16- through 26-year-old girls and women	570	436	3075.8	1
Anti-HPV 18				
27- through 45-year-old women	640	471	532.1	0.71 (0.64, 0.80)¶
16- through 26-year-old girls and women	570	421	744.5	1
Anti-HPV 31				
27- through 45-year-old women	640	488	395.7	0.66 (0.60, 0.74) ¶
16- through 26-year-old girls and women	570	447	596.1	1
Anti-HPV 33				
27- through 45-year-old women	640	493	259.0	0.73 (0.67, 0.80) ¶
16- through 26-year-old girls and women	570	457	354.5	1
Anti-HPV 45				
27- through 45-year-old women	640	515	145.6	0.68 (0.60, 0.76) ¶
16- through 26-year-old girls and women	570	470	214.9	1
Anti-HPV 52				
27- through 45-year-old women	640	496	244.7	0.71 (0.64, 0.78) ¶
16- through 26-year-old girls and women	570	456	346.5	1
Anti-HPV 58				
27- through 45-year-old women	640	478	296.4	0.69 (0.63, 0.76) ¶
16- through 26-year-old girls and women	570	451	428.0	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 004.
†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 0.50
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titres
ND=Not Determined

Men 27 Years of Age and Older

GARDASIL 9 has not been studied in men 27 years of age and older. In men 27 years of age and older, efficacy of GARDASIL 9 is inferred based on (1) high efficacy of GARDASIL in girls and women 16 through 45 years of age and (2) comparable efficacy and immunogenicity of GARDASIL and GARDASIL 9 in individuals less than 27 years of age and (3) robust immunogenicity of GARDASIL in boys and men 16 through 45 years of age.

Immune Responses to GARDASIL 9 Using a 2-dose Schedule in Individuals 9 to 14 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 to 14 years of age receiving 2 doses at a 6 month or 12-month interval (+/- 1 month); girls 9 to 14 years of age receiving 3 doses (at 0, 2, 6 months); and women 16 to 26 years of age 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 to 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 to 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 12).

In the same study, in girls and boys 9 to 14 years of age, 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 to 14 years of age 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 12). The clinical relevance of these findings is unknown.

Persistence of antibody response to GARDASIL 9 was observed for 3 years in girls and boys who were 9 through 14 years of age at time of vaccination receiving 2 doses at 6-month or 12-month interval. At Month 36, non-inferiority criteria were also met for GMTs in girls and boys 9 through 14 years of age receiving 2 doses at a 6-month interval (+/-1 month) compared to GMTs in women 16 through 26 years of age receiving 3 doses of GARDASIL 9.

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

Table 12. Summary of Anti-HPV cLIA Geometric Mean Titres 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 to 14-year-old girls (0, 6)†	301	258	1657.9 (1479.6, 1857.6)
9 to 14-year-old boys (0, 6)†	301	263	1557.4 (1391.5, 1743.1)
9 to 14-year-old girls (0, 12)†	150	123	2685.7 (2274.6, 3171.2)
9 to 14-year-old boys (0, 12)†	150	134	2672.4 (2279.1, 3133.5)
9 to 14-year-old girls (0, 2, 6)†	300	254	1496.1 (1334.1, 1677.8)
16 to 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)
Anti-HPV 11			
9 to 14-year-old girls (0, 6)†	301	258	1388.9 (1240.4, 1555.3)
9 to 14-year-old boys (0, 6)†	301	264	1423.9 (1273.2, 1592.3)
9 to 14-year-old girls (0, 12)†	150	123	2915.9 (2475.1, 3435.1)
9 to 14-year-old boys (0, 12)†	150	134	2965.9 (2534.9, 3470.1)
9 to 14-year-old girls (0, 2, 6)†	300	254	1306.3 (1165.5, 1464.0)
16 to 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)
Anti-HPV 16			
9 to 14-year-old girls (0, 6)†	301	272	8004.9 (7160.5, 8948.8)
9 to 14-year-old boys (0, 6)†	301	273	8474.8 (7582.4, 9472.3)
9 to 14-year-old girls (0, 12)†	150	129	13828.1 (11780.6, 16231.5)

9 to 14-year-old boys (0, 12)†	150	135	14825.2 (12675.7, 17339.3)
9 to 14-year-old girls (0, 2, 6)†	300	269	6996.0 (6254.1, 7825.8)
16 to 26-year-old women (0, 2, 6)†	314	249	3154.0 (2807.1, 3543.7)
Anti-HPV 18			
9 to 14-year-old girls (0, 6)†	301	272	1872.8 (1651.6, 2123.6)
9 to 14-year-old boys (0, 6)†	301	272	1860.9 (1641.1, 2110.2)
9 to 14-year-old girls (0, 12)†	150	129	2696.0 (2252.4, 3227.0)
9 to 14-year-old boys (0, 12)†	150	137	2922.5 (2454.7, 3479.5)
9 to 14-year-old girls (0, 2, 6)†	300	270	2049.3 (1806.4, 2324.8)
16 to 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)
Anti-HPV 31			
9 to 14-year-old girls (0, 6)†	301	272	1436.3 (1272.1, 1621.8)
9 to 14-year-old boys (0, 6)†	301	271	1498.2 (1326.5, 1692.0)
9 to 14-year-old girls (0, 12)†	150	132	2086.4 (1761.7, 2471.1)
9 to 14-year-old boys (0, 12)†	150	136	2148.1 (1818.3, 2537.7)
9 to 14-year-old girls (0, 2, 6)†	300	271	1748.3 (1548.1, 1974.5)
16 to 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)
Anti-HPV 33			
9 to 14-year-old girls (0, 6)†	301	273	1030.0 (920.4, 1152.7)
9 to 14-year-old boys (0, 6)†	301	271	1040.0 (928.9, 1164.3)
9 to 14-year-old girls (0, 12)†	150	132	2037.4 (1737.6, 2389.0)
9 to 14-year-old boys (0, 12)†	150	137	2363.6 (2021.6, 2763.3)
9 to 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)
16 to 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)
Anti-HPV 45			
9 to 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)
9 to 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)
9 to 14-year-old girls (0, 12)†	150	132	439.6 (366.0, 528.0)
9 to 14-year-old boys (0, 12)†	150	136	397.6 (331.9, 476.2)
9 to 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)
16 to 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)
Anti-HPV 52			
9 to 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)
9 to 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)
9 to 14-year-old girls (0, 12)†	150	131	1028.2 (885.0, 1194.7)
9 to 14-year-old boys (0, 12)†	150	137	1222.7 (1055.9, 1415.9)
9 to 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)
16 to 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)
Anti-HPV 58			
9 to 14-year-old girls (0, 6)†	301	270	1251.2 (1119.6, 1398.4)
9 to 14-year-old boys (0, 6)†	301	270	1325.7 (1186.2, 1481.6)
9 to 14-year-old girls (0, 12)†	150	129	2244.7 (1919.2, 2625.3)
9 to 14-year-old boys (0, 12)†	150	136	2650.7 (2275.6, 3087.6)
9 to 14-year-old girls (0, 2, 6)†	300	273	1229.3 (1100.7, 1373.0)
16 to 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 ranges, did not have protocol deviations that could potentially interfere with the immunogenicity evaluation as judged by the study director, 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) 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 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 Titre

Variation in Dosing Regimen in 16 To 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 4.2 DOSE AND METHOD OF 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 to 15 year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 10 years; depending on HPV type, 81 to 98 % of subjects were seropositive.

In 16 to 26 year-old girls and women (Protocol 001), persistence of antibody response has been demonstrated for at least 5 years; depending on HPV type, 78 to 100% 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.

Evidence of Anamnestic (Immune Memory) Response
Evidence of an anamnestic response was seen in vaccinated women who were seropositive to relevant HPV type(s) prior to vaccination. In addition, women (n = 150) who received 3 doses of GARDASIL 9 in Protocol 001 and a challenge dose 5 years later, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month postdose 3.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL
Protocol 006 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 to 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrolment 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.

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 to 15 years of age at enrolment.

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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, *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 to 15 years of age at enrolment.

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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, *Use with Other Vaccines*).

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Not applicable

Distribution
Not applicable

Metabolism
Not applicable

Excretion
Not applicable

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
GARDASIL 9 has not been evaluated for genotoxic potential.

Carcinogenicity
GARDASIL 9 has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 0.5-mL dose of the vaccine contains approximately 500 micrograms of aluminium (as amorphous aluminium hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of histidine, 50 micrograms of polysorbate 80, 35 micrograms of borax, residual traces (<7 micrograms/dose) of yeast protein and water for injection.

The product does not contain a preservative or antibiotics.

6.2 INCOMPATIBILITIES

Not applicable. Please refer to 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for further information.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store refrigerated at 2°C to 8°C (36 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 discolored.

6.5 NATURE AND CONTENTS OF CONTAINER

GARDASIL 9 may be supplied as

- a single-dose pre-filled (glass) syringe of vaccine
- a box of ten single-dose pre-filled (glass) syringes of vaccine
- a single-dose (glass) vial of vaccine[#]
- a box of ten single-dose (glass) vials of vaccine[#]

[#]*not currently available in Australia*

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

The tip cap and plunger stopper of the pre-filled syringe are not made with natural rubber latex. The vial stopper is not made with natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Not applicable.

CAS number
Not applicable.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A,
26 Talavera Road
Macquarie Park NSW 2113
http://www.msd-australia.com.au
Tel: 02 8988 8000

9 DATE OF FIRST APPROVAL

29 June 2015

10 DATE OF REVISION

23 October 2025

Summary table of changes

Section changed	Summary of new information
8	Removal of distributor details

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