Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Gardasil

Proprietary Product Name: Human Papillomavirus Quadrivalent Vaccine

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA..

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	8 October 2010
Active ingredient(s):	Human papilloma virus (HPV) quadrivalent L1 VLP vaccine adjuvanted with amorphous aluminium hydroxyphosphate sulfate (AAHS)
Product Name(s):	Gardasil
Sponsor's Name and Address:	Merck Sharp & Dohme (Australia) Pty Limited 54-68 Ferndell Street, South Granville NSW 2142
Dose form(s):	Suspension for injection, 0.5 mL
Strength(s):	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine 20, 40, 40, 20 micrograms[1]
Container(s):	Vial
Approved Therapeutic use:	Males aged 9 through to 26 years for the prevention of external genital lesions and infection caused by Human Papilloma virus (HPV) types 6, 11, 16 and 18.
Route(s) of administration:	Intramuscular (IM)
Dosage:	0.5 mL
ARTG number(s)	124408 and 124410

Product Background

This application proposes an extension of indication for Quadrivalent Human Papilloma virus (HPV) Recombinant Vaccine to include males aged 9 through 26 years for the prevention of external genital lesions and infection caused by HPV Types, 6, 11, 16 and 18. Gardasil is already registered for the treatment of 9-45 years old females and 9-15 years old males (ARTG no's 124410 and 124408).

HPV causes disease in men, and men play an important role in transmission of the virus to women. Whilst genital warts are a common external genital lesion (EGL), it is important to note that HPV infection is associated with a variety of other conditions, including pre-malignant and malignant conditions.

Penile cancer, although a relatively rare disease, is associated with considerable morbidity and mortality. Approximately 40-50% of penile cancers are related to HPV, with HPV 16 and 18 accounting for greater than 60% of HPV detected. In Australia there were 69 cases of penile cancer reported in 2005. The median age of penile cancer diagnosis ranges between 55-65 years, with patients seeking health care later than patients with other types of cancer. In the US, the fatality rate for penile cancer has been reported as 41%. HPV positivity has been

[1] HPV 6 L1 VLP - 20 mg, HPV11 L1 VLP - 40 mg, HPV 16 L1 VLP - 40 mg, HPV 18 L1 VLP - 20 mg

reported in up to 84% of low grade penile/perianal/perineal intraepithelial neoplasia (PIN) cases and in over 90% of PIN 3[2] cases, with HPV 16 the most common type detected.

The full indications Gardasil now read as:

> Gardasil is indicated in females aged 9 to 45 years* for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by Human Papilloma virus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine).
>
> Gardasil is indicated in males aged 9 through 26 years for the prevention of external genital lesions and infection caused by Human Papilloma virus (HPV) types 6, 11, 16 and 18.
>
> *Immunogenicity studies have been conducted to link efficacy in females and males aged 16 to 26 years to the younger populations.

Regulatory Status

Details of Overseas Regulatory Status

Region/Country	Adult Women Submission Date	Review Milestones
USA	17 December 2008	Approved 16 October 2009
EU	Target Date for submission is 18 June 2010	The introduction and implementation of new regulatory procedures in the EU delayed the filing of the Men's data.
Canada	13 February 2009	Approved 22 February 2010

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

There were no new quality data submitted with the current Australian submission.

III. Nonclinical Findings

Introduction

Overall quality of the nonclinical dossier

In order to support this extension of indication the sponsor has submitted a male fertility study. This study was Good Laboratory Practice (GLP) compliant and well-designed. Sufficient non clinical data are considered to have been submitted to support this application.

Pharmacology and Pharmacokinetics

There were no relevant studies submitted under these headings.

Toxicology

Male fertility

[2] PIN can be subdivided into different stages, based on the level of cell atypia. PIN was formerly classified as PIN 1, 2 or 3, in order of increasing cell irregularities. PIN 1 is referred to as low grade PIN, and PIN 2 and PIN 3 are grouped together as high grade PIN

The current male population registered for vaccination with Gardasil is predominantly sexually inactive. This application is to extend the registration of Gardasil to include the treatment of the sexually active 16-26 year old male population. Therefore the sponsor has conducted a male fertility study in rats. There are no HPV animal disease models but the rats in this study mounted an immune response to all four antigens in the vaccine and are therefore considered to have been a suitable choice of animal. Group size (20) was sufficiently large, the dose was of adequate size and frequency, being the clinical dose administered on one or three occasions.

In this study the histology of the testes and epididymides was examined, as well as sperm number and motility, and fertility. There was no effect of treatment on any of these parameters. Thus, Gardasil did not affect the fertility of male rats in this study.

Nonclinical Summary and Conclusions

- The GLP compliant male fertility study is considered adequate to support the extension of indications.
- Gardasil had no effect on the fertility of male rats.
- There are no nonclinical objections to the proposed extension of indication.

IV. Clinical Findings

Introduction

The submission represents an application to extend the indications for Gardasil to males, aged 16 through 26 years, based on data from a single clinical trial. Study P020V1 was a randomised, placebo controlled efficacy and safety study conducted in 4065 subjects, with 2032 of the subjects exposed to Gardasil.

The Clinical Overview states that all the trials undertaken in the development of Gardasil were conducted according to Good Clinical Practice (GCP) and, therefore by implication, in accordance with the principles of the Declaration of Helsinki.

Pharmacokinetics/ Drug Interactions/ Pharmacodynamics

No additional data were included under these headings in the current Australian submission.

Efficacy

Methodology for Study P020V1

Study P020V1 was a multinational, multicentre, randomised, placebo controlled, double blind, parallel group efficacy, safety and immunogenicity study. The study was sponsored and coordinated by Merck Research Laboratories. It was conducted at 71 study centers in Australia, Brazil, Canada, Costa Rica, Croatia, Finland, Germany, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Taiwan, and the US.

The inclusion criteria included:

- For healthy heterosexual males (HM) between the ages 16 years and 0 days and 23 years and 364 days, subjects had to be a heterosexual male who had exclusively female sexual partners.
- For men having sex with men (MSM): healthy males between the ages 16 years and 0 days and 26 years and 364 days. Subjects had to identify themselves as a man who had sex with men and must have engaged in either insertive or receptive anal intercourse or oral sex with another male sexual partner within the past year.

- There had to be no clinical evidence of gross genital lesion suggesting sexually-transmitted disease and no clinically present anogenital warts.
- Afebrile: no body temperatures≥100°F or ≥37.8°C (oral) within 24 hours prior to vaccinations (vaccinations were to be scheduled at a later date when the temperature was in the normal range).
- Subjects had to agree to refrain from sexual activity (including vaginal and anal penetration and any genital contact) for 2 calendar days prior to any scheduled visit that included sample collection to avoid detection of viral deoxyribonucleic acid (DNA) deposited in the male genital area during sexual intercourse and was not the result of ongoing infection.
- HM who had experienced sexual debut but had no more than five lifetime sexual partners.
- MSM subjects may not have had any lifetime sexual partners but must not have had more than five lifetime sexual partners. MSM subjects who had not had a lifetime sexual partner had to identify themselves as a man who had sex with men and must have engaged in oral sex with another man within the past year.

The exclusion criteria included:

- Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of genital specimens.
- History of known prior vaccination with an HPV vaccine.
- Receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 21 days prior to enrollment.
- Individuals who had a history of anogenital warts, or who had clinically present anogenital warts at Day 1.
- History of severe allergic reaction (for example, swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.
- Individuals allergic to any vaccine component, including aluminum, yeast or Benzonsae (nuclease, Nycomed). Individuals who had received any immune globulin or blood derived products within the 6 months prior to the first injection, or who planned to receive any of these products through Month 7 of the study.
- Individuals with history of splenectomy, known immune disorders (for example, systemic lupus erythematosus, rheumatoid arthritis) or were receiving immunosuppressives (for example, substances or treatments known to diminish the immune response such as radiation therapy, administration of antimetabolites, antilymphocytic sera or systemic corticosteroids).
- Individuals who had received periodic treatments with immunosuppressives, defined as at least three courses of oral corticosteroids each lasting at least 1 week in duration for the year prior to enrollment, were excluded. However, subjects using topical steroids (that is, inhaled, nasal or dermal preparations) were eligible for vaccination.
- Individuals who were immunocompromised or diagnosed to have infection with the Human Immunodeficiency Virus (HIV).
- Individuals with any haemostatic disorder, including thrombocytopenia, which would contraindicate intramuscular injections.
- History of recent (within the last 12 months) or ongoing alcohol or drug abuse
- Any condition, which in the opinion of the investigator, might interfere with the evaluation of the study objectives.
- HM with no or more than five lifetime sexual partners.
- MSM subjects with more than five lifetime sexual partners**.**

The study treatments were:

1. Quadrivalent HPV vaccine, 0.5-mL containing HPV 6 L1 VLP 20 µg, HPV 11 L1 VLP 40 µg, HPV 16 L1 VLP µg, HPV 18 L1 VLP µg, and 225 µg of aluminum as amorphous aluminum hydroxyphosphate sulfate (AAHS)
2. Placebo, 0.5 mL, containing 225 µg of aluminum as AAHS in normal saline.

The treatments were administered as three doses given at Day 1 and in Month 2 and Month 6. Subjects were block randomised by the centre using an Interactive Voice Response System in a 1:1 ratio.

All subjects enrolled underwent an inspection for external genital lesion and swabbing for HPV detection and their medical history updated at Day 1 and in Months 7, 12, 18, 24, 30, and 36. All new genital lesions judged by the investigator to be possibly, probably or definitely HPV related, or any lesion where the etiology was unknown were biopsied. MSM subjects participating in the substudy underwent intra-anal swab specimen collection for HPV polymerase chain reaction (PCR) and anal cytology (ThinPrep) testing at Day 1 and during the Month 7, 12, 18, 24, 30, and 36 visits. Blood samples for anti-HPV antibodies were obtained at Day 1 and in Months 7, 24 and 36.

The primary efficacy outcome measure was: HPV 6, 11, 16, 18 related external genital lesion (EGL), which included external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), and penile, perianal or perineal cancer, from 4 weeks post-Dose 3. The primary efficacy outcome measure for the MSM substudy was HPV 6, 11, 16, 18 related anal intraepithelial neoplasia (AIN) or anal cancer.

The secondary efficacy outcome measures were:

- the incidence of persistent HPV 6, 11, 16, 18 related infection,
- HPV 6, 11, 16, 18 related DNA detected by a PCR assay on an anogenital swab or biopsy sample at one or more visits from 4 weeks post-Dose 3.

Exploratory endpoints were:

- incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint but regardless of HPV relatedness,
- incidence of procedures for the treatment of external genital warts, PIN, penile, perianal or perineal cancer, regardless of the HPV relatedness of the lesion,
- in MSM subjects, the incidence of AIN or anal cancer as defined in the MSM substudy endpoint, but regardless of HPV-relatedness,
- in MSM subjects, the incidence of procedures for the treatment of AIN or anal cancer regardless of the HPV relatedness of the lesion,
- in MSM subjects, the incidence of anal Papanicolaou (Pap) test abnormalities,
- the duration of persistent infection,
- the incidence of clearance of infection in the sets of subjects who were, (i) PCR positive and seronegative at Day 1, or (ii) PCR positive and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine,
- the recurrence of persistent infection and DNA detection in the set of subjects who were PCR negative and seropositive at Day 1 to assess the potential therapeutic effects of the vaccine,
- the incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint, in the sets of subjects who were, (i) PCR positive and seronegative at Day 1, (ii) PCR positive and seropositive at Day 1, or (iii) PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine,

- in MSM subjects, the incidence of clinically diagnosed AIN or anal cancer, as defined in the MSM substudy endpoint, in the sets of subjects who were, (i) PCR positive and seronegative at Day 1, (ii) PCR positive and seropositive at Day 1, or (iii) PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine.

Statistical analysis plan for Study P020V1

The primary efficacy hypothesis was: Administration of a three-dose regimen of quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine (qHPV) reduces the combined incidence of HPV 6, 11, 16, 18 related external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer in young men who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type compared to placebo recipients. The MSM substudy efficacy hypothesis was: administration of a three-dose regimen of qHPV reduces the combined incidence of HPV 6, 11, 16, and 18 related AIN or anal cancer in MSM subjects who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type compared to placebo recipients. Secondary efficacy hypotheses were:

(1) Administration of a three-dose regimen of qHPV reduces the incidence of persistent HPV 6, 11, 16, or 18 infection in young men who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, compared to placebo recipients.
(2) Administration of a 3-dose regimen of qHPV reduces the incidence of HPV 6, 11, 16, 18 DNA detection at one or more visits in young men who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type compared to placebo recipients.

The primary efficacy outcome measure was examined using the per-protocol efficacy (PPE) population. This population consisted of subjects who:

- received all 3 doses of vaccine or placebo within 1 year,
- had Month 7 PCR results on swab samples collected within 14 to 72 days post-Dose 3,
- were HPV naïve (that is, seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analyzed (HPV naïve to both Types 6 and 11 in analysis of HPV 6 related and HPV 11-related endpoints),
- did not violate the protocol in ways that could interfere with the evaluation of efficacy of the qHPV vaccine.

For the primary efficacy outcome measure, the hypothesis test was based on the lower bound of the 95% confidence interval (CI) for vaccine efficacy, which should not include 20%. Vaccine efficacy (VE) was defined as:

VE = 100%•[1-(incidence rate in vaccine group/incidence rate in the placebo group)]

The hypotheses were tested by constructing a two-sided exact 95% confidence interval for VE. There was no adjustment for multiplicity for the primary efficacy outcome measure.

The sample size calculation for the HM subgroup determined that a total of 23 cases in the HM subgroup would provide at least 90% power to demonstrate that the efficacy of the vaccine in the subgroup is more than 0%. The primary analysis was to be conducted when, (i) at least 32 cases of the primary endpoint had been observed and, (ii) at least 23 cases had been reported from the HM study sites. Assuming that 6500 person-years would be accrued by the end of the follow-up period, the incidence rate for the primary endpoint was 1% per year and the vaccine was highly efficacious, 32 cases would be expected to occur by the end of the follow-up period in the placebo group. For the MSM substudy, the sample size calculations determined that 590 subjects would be required to give 24 cases of the MSM primary efficacy outcome measure. A minimum of 17 cases of HPV 6, 11, 16, or 18 related

AIN or anal cancer would be required in order to achieve at least 90% power, assuming the true efficacy of the vaccine was 85%.

Results for Study P020V1

A total of 4065 subjects were enrolled in the study with 2032 randomised to qHPV and 2033 to placebo. The primary reason for exclusion from a PPE population was prior exposure to the HPV serotype. The treatment groups were similar in demographic characteristics, except for a higher proportion of the qHPV group that were circumcised: 39.1% compared with 36.8% in the placebo group. The treatment groups were similar in sexual history at enrolment. The treatment groups were similar in history for anogenital tract infections or sexually transmitted infections at enrollment. In the MSM substudy population, there was a higher prevalence of rectal Chlamydia in the qHPV group: 11.1% compared with 7.7% in the placebo group. The treatment groups were similar in their use of concomitant therapies during the trial.

For the primary efficacy outcome variable (HPV 6, 11, 16, 18 related EGL), in the PPE population, qHPV was superior to placebo (Table 1). This efficacy appeared to be independent of serotype, sexual orientation or lesion type. Baseline characteristics and sexual history did not influence efficacy.

Table 1. Analysis of Efficacy against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type and Lesion Type (PPE Population).

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI	P-value[†]
HPV 6/11/16/18-Related EGL	1,397	3	2,830.9	0.1	1,408	31	2,812.2	1.1	90.4	(69.2, 98.1)	< 0.001
By Sexual Orientation											
HM Subjects	1,200	2	2,594.1	0.1	1,198	26	2,563.3	1.0	92.4	(69.6, 99.1)	
MSM Subjects	197	1	236.8	0.4	210	5	248.9	2.0	79.0	(-87.9, 99.6)	
By HPV Type											
HPV 6-Related EGL	1,245	3	2,562.3	0.1	1,244	19	2,553.8	0.7	84.3	(46.5, 97.0)	
HPV 11-Related EGL	1,245	1	2,563.7	0.0	1,244	11	2,552.6	0.4	90.9	(37.7, 99.8)	
HPV 16-Related EGL	1,295	0	2,644.0	0.0	1,271	2	2,586.2	0.1	100	(-420.8, 100)	
HPV 18-Related EGL	1,335	0	2,723.3	0.0	1,354	1	2,726.6	0.0	100	(-3804.6, 100)	
By Lesion Type											
Condyloma	1,397	3	2,830.9	0.1	1,408	28	2,813.9	1.0	89.4	(65.5, 97.9)	
PIN 1 or worse	1,397	0	2,833.3	0.0	1,408	3	2,824.5	0.1	100	(-141.2, 100)	
PIN 1	1,397	0	2,833.3	0.0	1,408	2	2,826.0	0.1	100	(-431.1, 100)	
PIN 2/3 or Cancer	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
PIN 2/3	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
Penile/Perianal/Perineal Cancer	1,397	0	2,833.3	0.0	1,408	0	2,826.2	0.0	NA	NA	

[†] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Using the full analysis population (intention to treat), for the primary efficacy outcome variable, qHPV was superior to placebo (Table 2).

Table 2. Analysis of Efficacy against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type and Lesion Type (Full Analysis Set).

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related EGL	1,943	27	4,625.7	0.6	1,937	77	4,556.5	1.7	65.5	(45.8, 78.6)
By Sexual Orientation										
HM Subjects	1,653	21	4,153.9	0.5	1,648	57	4,087.5	1.4	63.7	(39.3, 79.1)
MSM Subjects	290	6	471.8	1.3	289	20	469.0	4.3	70.2	(23.0, 90.2)
By HPV Type										
HPV 6-Related EGL	1,943	21	4,635.8	0.5	1,937	51	4,576.0	1.1	59.4	(31.2, 76.8)
HPV 11-Related EGL	1,943	6	4,663.7	0.1	1,937	25	4,606.6	0.5	76.3	(40.8, 92.0)
HPV 16-Related EGL	1,943	3	4,663.1	0.1	1,937	10	4,621.9	0.2	70.3	(-15.5, 94.7)
HPV 18-Related EGL	1,943	2	4,670.0	0.0	1,937	3	4,627.9	0.1	33.9	(-476.7, 94.5)
By Lesion Type										
Condyloma	1,943	24	4,635.4	0.5	1,937	72	4,558.8	1.6	67.2	(47.3, 80.3)
PIN 1 or worse	1,943	6	4,658.7	0.1	1,937	5	4,628.2	0.1	-19.2	(-393.8, 69.7)
PIN 1	1,943	3	4,666.1	0.1	1,937	4	4,629.7	0.1	25.6	(-339.9, 89.1)
PIN 2/3 or Cancer	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
PIN 2/3	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
Penile/Perianal/Perineal Cancer	1,943	0	4,670.6	0.0	1,937	0	4,630.5	0.0	NA	NA

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

The MSM sub-study is ongoing because insufficient subjects with the primary outcome measure had been recorded at the time of submission. For the secondary efficacy outcome measures qHPV was superior to placebo for:

- The incidence of persistent HPV 6, 11, 16, 18 related infection (Table 3).
- HPV 6, 11, 16, 18 related DNA detected by a PCR assay on an anogenital swab or biopsy sample at one or more visits from 4 weeks post Dose 3 (Table 4).
- Incidence of procedures for the treatment of external genital warts, PIN, penile, perianal or perineal cancer, regardless of the HPV-relatedness of the lesion (Table 5).

Table 3. Analysis of Efficacy against HPV 6/11/16/18-Related Persistent Infection by Sexual Orientation and HPV Type (PPE Population).

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	CI[†]	P-value[‡]
HPV 6/11/16/18-Related Persistent Infection	1,390	15	2,549.4	0.6	1,400	101	2,469.3	4.1	85.6	(73.4, 92.9)	< 0.001
By Sexual Orientation											
HM Subjects	1,196	14	2,356.5	0.6	1,195	83	2,274.0	3.6	83.7	(71.1, 91.5)	
MSM Subjects	194	1	192.9	0.5	205	18	195.3	9.2	94.4	(64.4, 99.9)	
By HPV Type											
HPV 6-Related Persistent Infection	1,239	4	2,320.2	0.2	1,238	33	2,296.6	1.4	88.0	(66.3, 96.9)	
HPV 11-Related Persistent Infection	1,239	1	2,322.6	0.0	1,238	15	2,315.1	0.6	93.4	(56.8, 99.8)	
HPV 16-Related Persistent Infection	1,290	9	2,382.4	0.4	1,264	41	2,312.9	1.8	78.7	(55.5, 90.9)	
HPV 18-Related Persistent Infection	1,327	1	2,461.9	0.0	1,347	25	2,453.5	1.0	96.0	(75.6, 99.9)	

[†] A 97.5% CI is reported for the HPV 6/11/16/18-related persistent infection endpoint. For all analyses by sexual orientation, HPV type, and severity, a 95% CI is reported. The CI reported for the HPV 6/11/16/18-related persistent infection endpoint differs from the other analyses due to the Hochberg multiplicity adjustment applied.
[‡] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint. The Hochberg multiplicity adjustment has been applied to the p-value reported.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 4. Analysis of Efficacy against HPV 6/11/16/18-Related DNA Detection at one or More Visits by Sexual Orientation and HPV Type (PPE Population).

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI	P-value[†]
HPV 6/11/16/18-Related DNA Detection	1,390	136	2,455.3	5.5	1,400	241	2,404.1	10.0	44.7	(31.5, 55.6)	< 0.001
By Sexual Orientation											
HM Subjects	1,196	115	2,270.7	5.1	1,195	199	2,215.1	9.0	43.6	(28.7, 55.6)	
MSM Subjects	194	21	184.6	11.4	205	42	189.0	22.2	48.8	(11.6, 71.2)	
By HPV Type											
HPV 6-Related DNA Detection	1,239	51	2,292.4	2.2	1,238	99	2,267.7	4.4	49.0	(27.9, 64.4)	
HPV 11-Related DNA Detection	1,239	16	2,311.7	0.7	1,238	37	2,300.5	1.6	57.0	(20.7, 77.6)	
HPV 16-Related DNA Detection	1,290	62	2,337.7	2.7	1,264	103	2,287.8	4.5	41.1	(18.5, 57.7)	
HPV 18-Related DNA Detection	1,327	25	2,441.3	1.0	1,347	66	2,440.6	2.7	62.1	(39.2, 77.1)	

[†] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint. The Hochberg multiplicity adjustment has been applied to the p-value reported.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; DNA = Deoxyribonucleic acid; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 5. Impact of qHPV Vaccine on the Incidence of EGL Procedures. Generally HPV-Naïve Population.

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Incidence Reduction (%)	95% CI
EGL Biopsy	1,275	27	3,149.6	0.9	1,270	61	3,059.6	2.0	57.0	(31.3, 73.7)
EGL Therapy[†]	1,275	31	3,142.0	1.0	1,270	58	3,060.1	1.9	47.9	(18.1, 67.5)
Surgical	1,275	25	3,146.7	0.8	1,270	47	3,067.6	1.5	48.1	(14.0, 69.4)
Nonsurgical	1,275	7	3,172.8	0.2	1,270	14	3,104.0	0.5	51.1	(-29.5, 83.3)

[†] Surgical therapy includes procedures such as surgical excision, laser ablation, cauterization, coagulation, and cryotherapy. Nonsurgical therapy includes topical treatments, including chemical ablation.
Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; EGL = External genital lesion; HPV = Human papillomavirus; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

There was no significant difference between the treatment groups for:

- The incidence of clearance of infection in the sets of subjects, who were, (i) PCR positive and seronegative at Day 1 or, (ii) PCR positive and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine.
- The recurrence of persistent infection and DNA detection in the set of subjects, who were PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine, except in the MSM subgroup where there was marginal statistical significance. At Month 24, the percent seroconversion (95% CI) was 90.8% (88.8 to 92.6%) for HPV 6, 95.6% (94.0 to 96.8%) for HPV 11, 99.3% (98.5 to 99.7%) for HPV 16 and 62.3% (59.2 to 65.4%) for HPV 18.

Data were not provided for the following exploratory efficacy measures that had been defined in the study protocol:

- Incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint but regardless of HPV relatedness.
- In MSM subjects, incidence of AIN or anal cancer as defined in the MSM substudy endpoint but regardless of HPV relatedness.

- In MSM subjects, the incidence of procedures for the treatment of AIN or anal cancer regardless of the HPV-relatedness of the lesion.
- In MSM subjects, incidence of anal Pap abnormalities.
- The duration of persistent infection.
- The incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint, in the sets of subjects who were, (i) PCR positive and seronegative at Day 1, (ii) PCR positive and seropositive at Day 1, or (iii) PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine.
- In MSM subjects, the incidence of clinically diagnosed AIN or anal cancer, as defined in the MSM substudy endpoint, in subjects who were, (i) PCR positive and seronegative at Day 1, (ii) PCR positive and seropositive at Day 1, or (iii) PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine.

These measures were not included in the statistical analysis section of the protocol and it is evident they were not intended to be used to demonstrate efficacy or safety.

Clinical Evaluator's comments: Study P020V1 demonstrates that in males aged 16 to 23 years inclusive, qHPV has superior efficacy compared with placebo for preventing HPV 6, 11, 16, 18 related EGL. In addition, qHPV decreased the incidence of persistent HPV 6, 11, 16, 18 related infection, decreased the detection of HPV 6, 11, 16, 18 related DNA and decreased the incidence of procedures for the treatment of external genital warts, PIN, penile, perianal or perineal cancer. Results were provided for the endpoints specified in the statistical analysis plan but not for some exploratory endpoints. Insufficient data were provided to demonstrate efficacy in the MSM substudy.

Safety

Adverse events for Study P020V1

A total of 1860 subjects received all three doses of qHPV vaccine and 1823 subjects were followed up for 36 months. Adverse events (AEs) were reported by 1346 (69.2%) subjects in the qHPV group and 1252 (64.2%) in the placebo. A total of 1166 (59.9%) subjects in the qHPV group and 1046 (53.6%) in the placebo experienced injection site AEs. The most frequently reported injection site AEs (shown as n (%) in the qHPV group were: pain 1113 (57.2%), erythema 304 (15.6%) and swelling 219 (11.3%). Injection site AEs were predominantly of mild severity but 25 (1.3%) subjects in the qHPV group and 19 (1.0%) in the placebo reported severe injection site AEs. A total of 615 (31.6%) subjects in the qHPV group and 613 (31.4%) in the placebo reported one or more systemic AEs (Table 6). The most common systemic AE was headache, which was reported by 179 (9.2%) subjects in the qHPV group and 207 (10.6%) in the placebo.

Table 6. Number (%) of Subjects with Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit). (All Vaccinated Subjects).

	qHPV (N=2020)				Placebo (N=2029)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2020				2029			
Subjects without follow-up	75				79			
Subjects with follow-up	1945				1950			
Number (%) of Subjects with one or more systemic adverse experiences	615	(31.6)			613	(31.4)		
Number (%) of Subjects with no systemic adverse experience	1330	(68.4)			1337	(68.6)		
Gastrointestinal Disorders	**125**	**(6.4)**	**35**	**(1.8)**	**120**	**(6.2)**	**33**	**(1.7)**
Abdominal pain upper	19	(1.0)	5	(0.3)	23	(1.2)	7	(0.4)
Diarrhoea	40	(2.1)	10	(0.5)	36	(1.8)	13	(0.7)
Nausea	27	(1.4)	16	(0.8)	16	(0.8)	7	(0.4)
General Disorders And Administration Site Conditions	**160**	**(8.2)**	**109**	**(5.6)**	**169**	**(8.7)**	**122**	**(6.3)**
Fatigue	13	(0.7)	6	(0.3)	19	(1.0)	15	(0.8)
Pyrexia	118	(6.1)	91	(4.7)	125	(6.4)	98	(5.0)
Infections And Infestations	**182**	**(9.4)**	**18**	**(0.9)**	**187**	**(9.6)**	**20**	**(1.0)**
Influenza	42	(2.2)	9	(0.5)	44	(2.3)	7	(0.4)
Nasopharyngitis	44	(2.3)	3	(0.2)	50	(2.6)	5	(0.3)
Pharyngitis	22	(1.1)	1	(0.1)	20	(1.0)		
Upper respiratory tract infection	27	(1.4)	3	(0.2)	20	(1.0)	4	(0.2)
Injury, Poisoning And Procedural Complications	**30**	**(1.5)**			**24**	**(1.2)**		
Musculoskeletal And Connective Tissue Disorders	**61**	**(3.1)**	**21**	**(1.1)**	**50**	**(2.6)**	**15**	**(0.8)**
Nervous System Disorders	**207**	**(10.6)**	**121**	**(6.2)**	**231**	**(11.8)**	**138**	**(7.1)**
Dizziness	19	(1.0)	12	(0.6)	18	(0.9)	14	(0.7)
Headache	179	(9.2)	107	(5.5)	207	(10.6)	119	(6.1)
Respiratory, Thoracic And Mediastinal Disorders	**70**	**(3.6)**	**25**	**(1.3)**	**68**	**(3.5)**	**8**	**(0.4)**
Pharyngolaryngeal pain	38	(2.0)	14	(0.7)	37	(1.9)	2	(0.1)
Skin And Subcutaneous Tissue Disorders	**26**	**(1.3)**	**10**	**(0.5)**	**31**	**(1.6)**	**14**	**(0.7)**

VR = Vaccine related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine. Percentages are calculated based on the number of subjects with follow-up.

Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Serious adverse events (SAEs), deaths and discontinuations due to AEs for Study P020V1

SAEs were reported in eight (0.4%) subjects in the qHPV group and 11 (0.6%) in the placebo. The SAEs were predominantly related to accident and trauma. Death was reported for three (0.2%) subjects in the qHPV group and ten (0.5%) in the placebo. The cause of death was predominantly accident and trauma. None of the deaths appeared to be attributable to study treatment. Five (0.3%) subjects in the qHPV group and 14 (0.7%) in the placebo withdrew because of an AE.

Laboratory tests and vital signs for Study P020V1

There was no difference between the treatment groups in body temperature recorded in the five days following dosing. A total of 116 (6.0%) subjects in the qHPV group and 113 (5.8%) in the placebo had a rise in temperature to ≥37.8°C in the five days following treatment administration. Laboratory safety parameters were not recorded during the study.

Clinical Summary of Safety

The sponsor's Clinical Summary of Safety was an integrated analysis of the safety data from Study P020V1 and also prior data from previous clinical studies conducted in males and females. Overall, 3097 male subjects aged 9 to 45 years received at least one dose of qHPV vaccine in study protocols 016, 018 and 020 (Study P020V1). Overall, the profile of adverse events was similar to that reported for Study P020V1. Of the subjects who received at least one dose of qHPV, 2216 (73.8%) reported at least one AE. A total of 1924 (64.1%) subjects reported AEs at the injection site. The most commonly reported systemic AE was headache (Table 7). No subject died within 15 days of vaccine administration.

Table 7. Number (%) of Male Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) in the Detailed Safety Population (Protocols 016, 018, and 020).

	qHPV Vaccine (N=3092)				Placebo (N=2303)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	3092				2303			
Subjects without follow-up	90				84			
Subjects with follow-up	3002				2219			
Number (%) of Subjects with one or more systemic adverse experiences	1118	(37.2)			723	(32.6)		
Number (%) of Subjects with no systemic adverse experience	1884	(62.8)			1496	(67.4)		
Gastrointestinal Disorders	**249**	**(8.3)**	**76**	**(2.5)**	**159**	**(7.2)**	**48**	**(2.2)**
Abdominal pain upper	43	(1.4)	12	(0.4)	30	(1.4)	9	(0.4)
Diarrhoea	82	(2.7)	23	(0.8)	48	(2.2)	15	(0.7)
Nausea	59	(2.0)	27	(0.9)	23	(1.0)	11	(0.5)
Vomiting	30	(1.0)	9	(0.3)	18	(0.8)	6	(0.3)
General Disorders And Administration Site Conditions	**323**	**(10.8)**	**223**	**(7.4)**	**196**	**(8.8)**	**140**	**(6.3)**
Fatigue	27	(0.9)	15	(0.5)	23	(1.0)	17	(0.8)
Pyrexia	246	(8.2)	186	(6.2)	145	(6.5)	113	(5.1)
Infections And Infestations	**293**	**(9.8)**	**32**	**(1.1)**	**209**	**(9.4)**	**22**	**(1.0)**
Influenza	57	(1.9)	12	(0.4)	46	(2.1)	7	(0.3)
Nasopharyngitis	78	(2.6)	8	(0.3)	58	(2.6)	6	(0.3)
Pharyngitis	25	(0.8)	1	(0.0)	22	(1.0)		
Upper respiratory tract infection	45	(1.5)	4	(0.1)	22	(1.0)	4	(0.2)
Injury, Poisoning And Procedural Complications	**63**	**(2.1)**	**1**	**(0.0)**	**31**	**(1.4)**		
Musculoskeletal And Connective Tissue Disorders	**127**	**(4.2)**	**44**	**(1.5)**	**64**	**(2.9)**	**21**	**(0.9)**
Myalgia	39	(1.3)	18	(0.6)	16	(0.7)	7	(0.3)
Nervous System Disorders	**414**	**(13.8)**	**248**	**(8.3)**	**277**	**(12.5)**	**170**	**(7.7)**
Dizziness	35	(1.2)	23	(0.8)	21	(0.9)	17	(0.8)
Headache	368	(12.3)	225	(7.5)	249	(11.2)	149	(6.7)
Respiratory, Thoracic And Mediastinal Disorders	**153**	**(5.1)**	**36**	**(1.2)**	**93**	**(4.2)**	**12**	**(0.5)**
Cough	30	(1.0)	10	(0.3)	25	(1.1)	4	(0.2)
Pharyngolaryngeal pain	84	(2.8)	20	(0.7)	47	(2.1)	4	(0.2)
Skin And Subcutaneous Tissue Disorders	**50**	**(1.7)**	**15**	**(0.5)**	**38**	**(1.7)**	**14**	**(0.6)**

Percentages are calculated based on the number of subjects with follow-up.

Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Adverse experience terms are from MedDRA Version 11.0

VR = Vaccine related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.

N = Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the give column.

n = Number of subjects specific injection-site adverse experience.

Post-marketing Experience:

A Periodic Safety Update Report was provided for the time period 1st December 2007 to 31st May 2008. The Sponsor did not report any findings that altered the safety profile of qHPV. Data were not presented by gender. Hence the post-marketing data did not provided any further information about the adverse event profile of qHPV in males.

Clinical Summary and Conclusions

Study P020V1 demonstrates that in males aged 16 to 23 years inclusive, qHPV has superior efficacy compared with placebo for preventing HPV 6, 11, 16, 18 related EGL. In addition, qHPV decreased the incidence of persistent HPV 6, 11, 16, 18 related infection, decreased the detection of HPV 6, 11, 16, 18 related DNA and decreased the incidence of procedures for the treatment of external genital warts, PIN, penile, perianal or perineal cancer. Results were provided for the endpoints specified in the statistical analysis plan, but not for some exploratory endpoints. Insufficient data were provided to demonstrate efficacy in the MSM substudy.

Study P020V1 indicates that qHPV has a similar adverse event profile in males and females. AEs at the injection site were predominantly mild in intensity. Systemic AEs occurred at a similar frequency in qHPV treated subjects as for placebo treated subjects. Systemic AEs were uncommon and did not appear to be attributable to qHPV.

The risk benefit profile for Gardasil in males aged 16 to 23 years is favourable. Benefit has clearly been demonstrated with the efficacy data. The adverse event profile indicates few serious AEs.

Deficiencies in the Submission

Data were not presented for some of the exploratory efficacy outcome measures stated in the methods section of Study P020V1. Although these outcome variables were not stated in the statistical analysis plan it is assumed that the data were collected and analysed and should have been presented in the study report.

Recommendations

Gardasil should be approved for the extended indication:

> *"Gardasil is indicated in males aged 9 through 26 years for the prevention of external genital lesions and infection caused by Human Papilloma virus (HPV) Types 6, 11, 16 and 18 (which are included in the vaccine)."*

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission. However, a condition of registration was that a Risk Management Plan, as agreed with the Office of Product Review, be implemented (see **Outcome** below).

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new quality data submitted.

Nonclinical

A single GLP compliant rat fertility study was submitted. The results showed no effect of treatment on the fertility of male rats. There are no non clinical objections to the proposed extension of indications.

Clinical

Clinical evaluation report: Study P020V1 demonstrates efficacy of qHPV in males aged 16 to 23 years in preventing HPV 6, 11, 16, 18 related EGL. In addition, qHPV decreased the incidence of persistent HPV 6,11,16, 18 related infection and decreased the incidence of incident HPV 6, 11, 16, 18 related infection after the third dose.

The clinical evaluation report described immunogenicity results for Study 020. An additional table showing geometric mean titres (GMT) results is shown below (Table 8). At Month 7 seroconversion rates were in the range 97.4% to 99.2% across anti-HPV6, 11, 16 and 18 groups and with narrow 95% CI. In a parallel testing procedure the GMT estimates at Month 7 in 16 to 26 year old males were two to three-fold lower than GMTs in 9 to 15 year old males. Estimated GMTs at Month 7 in 16 to 26 year old males appeared to be in the same order as those reported in previous studies in older female populations.

Table 8. Anti-HPV Geometric Mean Titers by Vaccination Group (PPI Population) Study 020.

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2,025)					Placebo (N=2,030)
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1,093	< 7	(<7, <7)	1,110	< 7	(<7, <7)
Month 7	1,093	447	(422.1, 473.5)	1,110	< 7	(<7, <7)
Month 24	906	80.3	(76.2, 84.6)	904	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,093	< 8	(<8, <8)	1,109	< 8	(<8, <8)
Month 7	1,093	624.2	(594.4, 655.6)	1,109	< 8	(<8, <8)
Month 24	906	94.5	(89.8, 99.5)	902	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,136	< 11	(<11, <11)	1,128	< 11	(<11, <11)
Month 7	1,136	2,402.50	(2,270.6, 2,542.0)	1,128	< 11	(<11, <11)
Month 24	937	347.8	(329.3, 367.4)	904	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,175	< 10	(<10, <10)	1,205	< 10	(<10, <10)
Month 7	1,175	402.2	(380.2, 425.6)	1,205	< 10	(<10, <10)
Month 24	966	38.7	(36.2, 41.3)	952	< 10	(<10, <10)

The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.

N = Number of subjects randomized to the respective vaccination group who received at least at least 1 injection. n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

qHPV had a similar adverse event profile in males and females. AEs at the injection site were predominantly mild. Systemic AEs occurred at a similar frequency in qHPV and placebo groups. Serious AEs were uncommon and did not appear attributable to qHPV. The risk benefit of qHPV in males 16-23 is favourable.

The safety of Gardasil in follow up 12 months post GEP: An Office of Medicines Safety Monitoring (OMSM) report prepared on 31 January 2010 concludes that very few additional

reports of "reactions of interest" have been received since the finalisation of the Gardasil Expert Panel **(**GEP) Report and the overall numbers of the various conditions examined by the GEP remain low. The TGA has now received 13 confirmed reports of central nervous system (CNS) demyelination and a single case of Guillain–Barré syndrome (GBS). The total number of cases of new onset demyelination remains no more than would have been expected to have occurred as part of the background rate for these disease Overall, the adverse drug reaction (ADR) reports received by the TGA, the data generated through the US post licensure study and the analysis of cumulative data presented in the Periodic Safety Update Report (PSUR; #6) do not suggest the safety profile of Gardasil has altered significantly since its first approval.

Risk-Benefit Analysis

Delegate's Comments: The Study 020 results support efficacy of qHPV in prevention of HPV type 6 and 11 related condyloma. There were very few PIN cases, only 2 HPV 16 related EGL and 1 HPV 18 related EGL were observed in Study 020. The indication for males 9 through 26 years proposed by the sponsor refers to prevention of external genital lesions caused by HPV Types 6, 11, 16 and 18. Because the study endpoint, external genital lesions, is composed of PIN/cancer endpoints that differ fundamentally from the condyloma endpoints the Delegate supported an indication limited to prevention of genital warts. That is, "Gardasil is indicated in males aged 9 through 26 years for the prevention of genital warts and infection (incident and persistent) caused by HPV Types 6, 11, 16 and 18 (which are included in the vaccine)".

Although the point estimate of efficacy for the primary endpoint in the MSM subgroup (16-26 years) was lower (with a lower 95% CI bound of -87.9%) than the HM subgroup (16-23 years) , the results for the overall study population support the indication in males 9 through 26 years of age.
The duration of follow-up for efficacy in this report of Study 020 is limited to a median of 2.9 years. The MSM substudy had not observed sufficient cases for analysis. The sponsor has provided a commitment to US FDA to extend the long term evaluation of vaccine efficacy to 10 years in Study 020.

A comparison of immunogenicity data from males 9-15 years and males 16-26 years supports extension of the efficacy results in prevention of genital warts to the younger population. There were few safety signals in the male study populations in which a total of 3092 males have received qHPV and 2303 have received placebo (predominantly amorphous aluminium hydroxyphosphate sulphate, AAHS). The sponsor has provided a commitment to US FDA to conduct a post licensure, observational safety study in a US Managed Care Organization to assess the general short term safety of the vaccine as it is administered to a larger male population 9 through 26 years of age. The study population will consist of up to 44,000 male subjects completing the three dose regimen, or 135,000 males receiving at least one dose of Gardasil. The study will estimate the incidence of medical events resulting in hospitalization or an emergency room visit in the first 60 days after vaccination, relative to a self-comparison reference period. As a secondary objective, subjects will also be followed for 6 months after each vaccination for reporting of several prespecified new onset autoimmune conditions. Incidence of events occurring on the day of vaccination will also be analysed.

1. **In the Pre-Advisory Committee on Prescription Medicines (ACPM) meeting response the sponsor should commit to providing reports to TGA of the ongoing efficacy study and the post-marketing safety study in males 9 to 26 years of age.**

Sponsor's Pre-ACPM response:

The sponsor agrees to provide the TGA with reports on the ongoing efficacy study and the postmarketing safety study in males 9 to 26 years of age.

2. In the Pre-ACPM response the sponsor should also comment on the follow-up of AEs of special interest recommended in the Gardasil Expert Panel Final Report.

Sponsor's Pre-ACPM response:

The sponsor closely monitors all adverse event reports on a continuous basis and analyses them in the Periodic Safety Update Reports (PSURs). In addition, there is a formal Risk Management Plan which addresses monitoring for conditions of special interest including demyelinating conditions. The action plans presented in the RMP include, in addition to routine pharmacovigilance, additional studies designed to detect safety signals in the postmarketed period. These studies include a postmarketing safety surveillance study and the Nordic Long-term Follow-Up Study.

The post marketing safety surveillance study of Gardasil (V501-031) whose purpose is to detect safety signals with respect to the vaccine is being conducted in a US managed care setting. This study examines the general safety within 60 days after a dose of Gardasil among approximately 44,000 females aged 9-26 years who received 3 doses of Gardasil, and approximately 187,000 subjects who received at least one dose of Gardasil. This study will also look for signals related to selected autoimmune conditions within 6 months after a dose of Gardasil. As indicated in our response to the Gardasil Expert Panel Report dated 15 May 2009, we anticipate providing the final report when available.

The Nordic Long-Term Follow-Up Study (P015-20) will examine long term safety signals in 5400 women in 4 countries (Norway, Sweden, Denmark & Iceland), half of whom were vaccinated in 2004. This study is designed to detect high grade disease due to vaccine types and it will also include surveillance for auto-immune diseases including Guillain-Barre syndrome, acute disseminated encephalomyelitis and multiple sclerosis at time points that are distant from vaccination. The findings in this population will be compared to appropriately stratified national data in the four countries involved. Analyses will be completed every two years. The sponsor provides assurance that these analyses will be forwarded to the agency as they become available.

Delegate's Proposed Action

The Delegate proposed to register an extension of indications:

> "Gardasil is indicated in males aged 9 through 26 years for the prevention of genital warts and infection (incident and persistent) caused by HPV Types 6, 11, 16 and 18. "
>
> * Immunogenicity studies have been conducted to link efficacy in females and in males aged 16 to 26 years to the younger populations."
>
> Gardasil should be administered as 3 separate 0.5 mL doses in a schedule; 0, 2 months and 6 months.

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor' response to these documents, agreed with the Delegate's proposal.
The ACPM recommended approval of the submission from Merck Sharp & Dohme Australia Pty Ltd to extend the indication for quadrivalent human papillomavirus recombinant vaccine (Gardasil) 20, 40, 40, 20 µg / 0.5 mL to include the indication:

> *"Gardasil is indicated in males aged 9 through 26 years for the prevention of external genital lesions and infection caused by Human Papillomavirus (HPV) Types, 6, 11, 16 and 18 (which are included in the vaccine). "*

* Immunogenicity studies have been conducted to link efficacy in females and males aged 16 to 26 years to the younger populations. Gardasil should be administered as 3 separate 0.5 mL doses in a 0, 2 and 6 month schedule.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of *Gardasil* containing *Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine 20,40,40,20 micrograms/0.5mL sterile liquid* for the extended indication:

Males aged 9 through to 26 years for the prevention of external genital lesions and infection caused by Human Papillomavirus (HPV) types 6, 11, 16 and 18**.**

With the special condition that the Risk Management Plan dated 3 December 2009, as agreed with the Office of Product Review, be implemented.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

GARDASIL®

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

DESCRIPTION

GARDASIL® is a recombinant, quadrivalent vaccine.

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

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

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of borax, and water for injection. The product does not contain a preservative or antibiotics.

PHARMACOLOGY

Mechanism of Action

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

Pre-clinical data suggests that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses. Induction of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to the unvaccinated animals.

The induction of a strong anamnestic (immune memory) response has been further demonstrated in clinical trials (See Clinical Studies, *Immune Memory (Anamnestic) Responses).*

CLINICAL STUDIES

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.

CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology). VIN 2/3 and VaIN 2/3 are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.
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. Erythoplasia of Queyrat (EQ), Bowen's disease (BD), and bowenoid papulosis (BP) are clinical presentations of high-grade PIN. BD and EQ have been associated with invasive cancer. BP rarely progresses to malignancy.

The efficacy of GARDASIL or the HPV component of GARDASIL was assessed in 6 placebo-controlled, double-blind, randomized Phase II and III clinical studies. One Phase II study evaluated all four components (i.e., HPV 6, 11, 16, and 18) of GARDASIL (Protocol 007, N = 551 females). An additional phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N=2,391 females). Three Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5,442 (FUTURE I),12,157 (FUTURE II), and 3,817 (FUTURE III) females. A fourth Phase III, Protocol 020, study evaluated GARDASIL in 4055 males.. Together, these studies evaluated 24,358 females 16 through 45 years and 4055 males 16 through 26 years of age at enrolment, the majority of whom had been sexually active.

The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, 2.2 and 2.3 years for Protocol 005, Protocol 007, FUTURE I, FUTURE II, FUTURE III, and Protocol 20, respectively, with a maximum follow-up of 5 years. Subjects received vaccine or placebo on the day of enrolment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies conducted in females combined.

In the clinical studies, HPV status was not assessed before subjects were enrolled. Thus, subjects who had been exposed to a vaccine HPV type prior to enrolment were included in the studies for evaluation. Overall, 73% of 16 through 26 year old females and 67% of 24 through 45 year old females were naïve to all 4 vaccine HPV types at enrolment. Overall, 83% of 16- through 26-year-old males were naïve to all 4 vaccine HPV types at enrollment. The naïve subjects continued to be at risk for infection and disease caused by all 4 vaccine HPV types. Amoung the 24 through 45 year old females, only 0.4% had been exposed to all 4 vaccine HPV types. Among the 16- through 26-year-old males, only 0.2% had been exposed to all 4 vaccine HPV types.

Clinical Studies in 16 Through 26 Year Old Females

Prophylactic Efficacy against HPV Types 6, 11, 16 and 18

The primary analyses of efficacy was conducted in the “per-protocol efficacy (PPE) population”, consisting of subjects who received all 3 vaccinations within 1 year of enrolment, did not have major deviations from the study protocol and were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit. (Table 1). In subjects who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN and VaIN caused by any of the 4 vaccine HPV types were counted as endpoints. Among subjects who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy.

Table 1
Analysis of Efficacy of GARDASIL in the PPE Population of 16 Through 26 Year Old Females

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Protocol 005*	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (<0.0, 100.0)
FUTURE I	2,201	0	2,222	36	100.0 (89.2, 100.0)
FUTURE II	5,306	2**	5,262	63	96.9 (88.2, 99.6)
Combined Protocols***	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2,219	0	2,239	6	100.0 (14.4, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2,219	0	2,239	5	100.0 (<0.0, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	9	100.0 (49.5, 100.0)
HPV 6-, 11-,16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2241	0	2,258	77	100.0 (95.1, 100.0)
FUTURE II	5,388	9†	5,374	145	93.8 (88.0, 97.2)
Combined Protocols***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer)					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,261	0	2,279	74	100.0 (94.9, 100.0)
FUTURE II	5,404	2	5,390	150	98.7 (95.2, 99.8)
Combined Protocols***	7,900	2	7,902	227	99.1 (96.8, 99.9)

*Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL

**There were two cases of CIN 3 that occurred in the group that received GARDASIL. In the first case HPV 16 and HPV 52 were detected. This subject was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This subject was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a Month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

***Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

†Amoung 9 cases of HPV 6, 11,16 or 18 related CIN (any grade) or AIS detected in the PPE population, 6 cases are likely to be due to non vaccine HPV types and not to a vaccine HPV type.

n= Number of subjects with at least one follow-up visit after Month 7

CI = Confidence Interval

Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Note 2: P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001,supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); efficacy against HPV 16/18-related CIN 2/3 is >25% (Combined Protocols); efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I); and efficacy against HPV 6/11/16/18-related external genital lesions (EGL) is >20% (FUTURE I).

GARDASIL was equally efficacious against HPV disease caused by each of the four vaccine HPV types.

Table 2
Analysis of Efficacy of GARDASIL in the PPE Population By HPV Type in the Combined Protocols

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS*	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16-related	7402	2**	7205	93	97.9 (92.3, 99.8)
HPV 18-related	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 6-, 11-,16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-related	6902	0	6828	47	100.0 (92.0, 100.0)
HPV 11-related	6902	0	6828	12	100.0 (64.5, 100.0)
HPV 16-related	6647	8†	6455	137	94.3 (88.5, 97.6)
HPV 18-related	7382	1†	7316	61	98.4 (90.6, 100.0)
HPV 6- or 11-related Genital Warts***	6,932	2	6,856	189	99.0 (96.2, 99.9)
HPV 6-related	6,932	2	6,856	166	98.8 (95.7, 99.9)
HPV 11-related	6,932	0	6,856	32	100.0 (88.0, 100.0)

*Protocols 005, 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria. Subjects in Protocol 005 do not contribute to the endpoints related to Type 18.
**There were two cases of CIN 3 that occurred in the group that received GARDASIL (FUTURE II).In the first case HPV 16 and HPV 52 were detected. This subject was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This subject was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.
***Protocols 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
†Among 9 cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or AIS detected in the PPE population, 6 cases are likely to be due to a non-vaccine HPV type and not to a vaccine HPV type.
n= Number of subjects with at least one follow-up visit after Month 7
CI = Confidence Interval
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Evidence of efficacy was observed during the vaccination period. Among subjects who were naïve to the relevant HPV types prior to vaccination, GARDASIL was 95% efficacious in preventing cases of CIN (any grade) caused by HPV 6, HPV 11, HPV 16, HPV 18, and 97% efficacious in preventing cases of CIN 2 or worse caused by HPV 16 or HPV 18, resulting from infections acquired during the vaccination period (MITT 2 Population).

Prophylactic Efficacy against Cancer Endpoints

In a supplemental analysis, the efficacy of GARDASIL was evaluated against HPV 16/18-related FIGO Stage 0 cervical cancer (CIN 3 and AIS) in the per-protocol efficacy (PPE) population and the modified intention to treat-2 (MITT-2) population. The "MITT-2 population" consisted of subjects who were naïve to the relevant HPV types(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes subjects with major protocol violations and also subjects who became infected with a vaccine HPV type during the vaccination period. Cases were counted starting after Day 30.

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

Table 3
Supplemental Analyses of Cancer-Related Endpoints: Efficacy Against HPV 16/18-Related Invasive Cancer Precursors for the Combined Protocols in the PPE* Population of 16 through 26 Year Old Females

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 3					
Per-protocol	8,493	2**	8,464	64	96.9 (88.4, 99.6)
HPV 16- or 18-related AIS					
Per-protocol	8,493	0	8,464	7	100.0 (30.6, 100.0)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrolment, 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).
** There were two cases of CIN 3 that occurred in the group that received GARDASIL (FUTURE II). In the first case HPV 16 and HPV 52 were detected. This subject was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This subject was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.
n = Number of subjects with at least one follow-up visit after Day 1.
CI = Confidence Interval
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Efficacy against HPV 16/18-related disease was 96.7% (95% CI: 90.2%, 99.3%) and 100.0% (95% CI: 60.0%, 100.0%) for CIN 3 and AIS, respectively, in the MITT-2 population.

The supplemental analysis also evaluated efficacy against immediate precursors to vulvar and vaginal cancer (VIN 2/3 or VaIN 2/3). In this analysis the efficacy of GARDASIL against VIN 2/3 or VaIN 2/3 due to HPV 16 and 18 was 100% (95% CI: 78.6%, 100.0%) in the per-protocol population, and 97.0% (95% CI: 82.4%, 99.9%) in the MITT-2 population.

Long-term Prophylactic Efficacy

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related persistent infection or disease through 60 months was 95.8% (95% CI: 83.8%, 99.5%), with efficacy against disease due to these HPV types being 100% (95% CI: 12.4, 100), a function of sustained immunity.

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

Cross Protection Efficacy against HPV Types 31, 33, 45, 52, 56, 58 and 59

The World Health Organization recommends that the evaluation of cross protection focus on the efficacy of the vaccine against CIN (any grade), CIN 2/3, or AIS, demonstrated by the reduction in the incidence of lesions, caused by oncogenic non-vaccine types. Viral persistence (at least 12 months) can also be used to demonstrate cross protection.

The cross-protective efficacy of GARDASIL was evaluated in the combined database of the FUTURE I and FUTURE II trials (N = 17,599). The primary endpoint of this analysis was the combined incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) or AIS. The secondary endpoint of this analysis was the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS. Analyses were also conducted to evaluate efficacy with respect to CIN (grades 1, 2, 3) or AIS caused by non-vaccine HPV types individually. In subjects who were naïve to the relevant vaccine HPV types at Day 1 (MITT-2 population, n = 16,895 for the 31/45 composite endpoint and n=16,969 for the 31,33,45,52,58 composite endpoint), a trend towards a reduction in the incidence of HPV 31- and 45-related and HPV 31,33,45,52,58 related CIN (grades 1, 2, 3) or AIS was

observed. Administration of GARDASIL reduced the incidence of HPV 31 and HPV 45 related CIN (grades 1,2,3) by 37.3% (95% CI: 17.0%, 52.8%) compared with placebo. Administration of GARDASIL reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS by 26.4% (95% CI: 12.9%, 37.8%), compared with placebo. Efficacy was driven by reductions in HPV 31-, 33-, 52-, and 58-related endpoints. There was no clear evidence of efficacy for HPV 45. In a post-hoc analysis, prophylactic administration of GARDASIL also reduced the incidence of HPV 56-related and HPV 59-related CIN (grades 1, 2, 3) or AIS, compared with placebo in this population.

Further post-hoc analyses considered efficacy in a generally HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve subjects plus subjects prior to or shortly after sexual debut. When GARDASIL was administered to the generally HPV naïve subjects, there were statistically significant reductions in the incidences of CIN (grades 1,2,3) or AIS caused by HPV 31, 33, 52 , and 58 (Table 4). Although there was a trend of reduction in the incidence of CIN (grades 1, 2, 3) or AIS caused by HPV 56 or 59, statistically significant reduction has not been demonstrated.

Table 4

Impact of GARDASIL on the Rates of CIN (any Grade) or AIS for the Combined FUTURE I and FUTURE II Disease Cross Protection Data Set in 16 Through 26 Year old Females

HPV Types	Population	% Reduction	95% CI
HPV 31/45-related**	Generally HPV-naïve* (n = 9,296)	43.6	12.9, 64.1
HPV 31/33/45/52/58-related***	Generally HPV-naïve	29.2	8.3, 45.5
HPV 31/33/52/58-related	Generally HPV-naïve	33.8	13.4, 49.6
HPV 56-related	Generally HPV-naïve	27.6	<0.0, 49.3
HPV 59-related	Generally HPV-naïve	22.3	<0.0, 58.9

*Generally HPV-naïve population included subjects who, at Day 1, had a negative for SIL Pap test and were negative to all of the following HPV types: HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; and had follow-up after Day 30 of the study. Case counting started at Day 30.

**Primary pre-specified endpoint of the analysis.

***Secondary pre-specified endpoint of the analysis.

CI = Confidence Interval

Population Impact

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

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

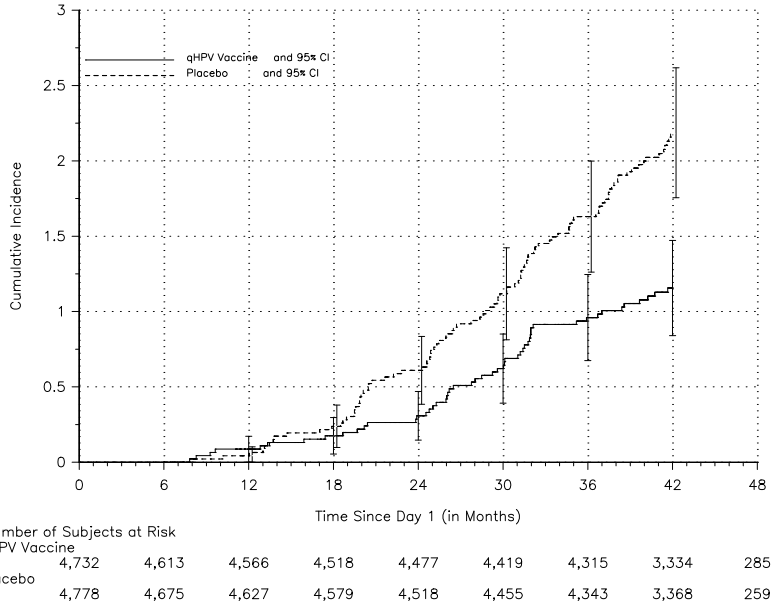
Subjects with evidence of prior infection that had resolved by vaccination onset were protected from reacquisition or recurrence of infection leading to clinical disease.

GARDASIL has not been shown to protect against the diseases caused by every HPV type, and will not treat existing disease. The overall efficacy of GARDASIL in each population will

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

The benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time (Figure 1). GARDASIL does not impact the course of infections or disease present at vaccination onset. Over a longer duration of follow-up, the proportion of disease in unvaccinated subjects due to new infection will increase, and the estimated efficacy against disease due to any HPV-type will become more apparent.

Figure 1
Cumulative Incidence of CIN 2/3 or AIS Lesions (Caused by Any HPV Type) Among a Generally HPV-naïve Population of Subjects in the Phase III Clinical Trials (FUTURE I and FUTURE II) in 16 Through 26 Year Old Females



Clinical Studies in 24 Through 45 Year Old Females

Prophylactic Efficacy Analysis in the Per-Protocol Population

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 subjects compared to younger subjects. 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 subjects up to and including age 45 years, an efficacy study (FUTURE III) was conducted.

GARDASIL was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL was also highly efficacious in reducing the incidence of a HPV 16/18-related Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit (Table 5).

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 subjects up to and including age 45 years can be inferred.

Table 5
Analysis of Efficacy of GARDASIL in the PPE Population of 24- Through 45-Year-Old Females

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	1,615	4*	1,607	41	90.5 (73.7, 97.5)
HPV 16- or 18-related CIN (any grade), Persistent Infection, or EGL	1,601	4*	1,579	23	83.1 (50.6, 95.8)
HPV 6- or 11-related CIN (any grade), Persistent Infection, or EGL	1,329	0	1,323	19	100.0 (79.0, 100.0)
HPV 16/18-related Pap Diagnosis of ASC-US Positive for High-risk HPV	1,579	1	1,565	17	94.2 (63.2, 99.9)

*There were 3 cases of HPV 16 infection and 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. All 4 cases occurred early in the follow-up period. Two of the 3 cases of persistent infection had antibody levels to HPV 16 at Month 7 that were very high and suggestive of an anamnestic response to a previous infection. The third persistent infection case had anti-HPV 16 levels that were higher than the anti - HPV 16 GMT amoung subjects who received HPV vaccine within the Per-Protocol Immunogenicity population of Protocol 019. HPV 16 infection was detected in Month 18 and Month 24 swabs. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy.
CI = Confidence interval
ASC-US = Atypical Squamous Cells of Undetermined Significance

Clinical Studies in 16 Through 26 Year Old Males

Prophylactic Efficacy Analysis in the Per-Protocol Population

In clinical studies in males, efficacy was evaluated using the following endpoints: external genital warts; penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer; and persistent infection. High grade PIN is associated with certain types of penile/perineal/perianal cancers. Persistent infection is a predictor of clinical disease.

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population. This population consisted of subjects who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of external genital lesions (Condyloma and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 6).

Table 6
Analysis of Efficacy of GARDASIL in the PPE Population of 16- Through 26-Year-Old Males for Vaccine HPV Types

Endpoint	GARDASIL		AAHS Control		% Efficacy (95% CI*)
	N	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1397	3	1408	31	90.4 (69.2, 98.1)
Condyloma	1397	3	1408	28	89.4 (65.5, 97.9)
PIN 1/2/3	1397	0	1408	3	100 (<0.0, 100.0)
Persistent Infection**					
HPV 6, 11, 16, or 18- related	1390	15	1400	101	85.6 (73.4, 92.9)
HPV 6-related	1239	4	1238	33	88.0 (66.3, 96.9)
HPV 11-related	1239	1	1238	15	93.4 (56.8, 99.8)
HPV 16-related	1290	9	1264	41	78.7 (55.5, 90.9)
HPV 18 -related	1327	1	1347	25	96.0 (75.6, 99.9)

*A 97.5% CI is reported for the HPV 6/11/16/18-related persistent infection endpoint due to the multiplicity adjustment applied.
**persistent infection detected in samples from two or more consecutive visits 6 months apart (±1 month) or longer
N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Immunogenicity

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45- year old females (GARDASIL N = 12,634; placebo N = 11,317) and 5,417 males aged 9 through 26 years (GARDASIL N=3,109; placebo N=2,308). Because of the very high efficacy of GARDASIL in clinical trials, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical HPV disease.

Type-specific assays 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, rather than the total antibodies directed at the VLPs in the vaccine. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not meaningful. The assays used to measure the immune responses to GARDASIL were demonstrated to correlate with the capacity to neutralize live HPV virions.

There was no interference in the immune response to vaccine HPV types induced by GARDASIL. Seropositivity at Day 1 for one vaccine HPV type did not have a negative impact on Postdose 3 anti-HPV responses to other vaccine HPV types.

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of subjects who were seronegative and Polymerase Chain Reaction (PCR) negative to the relevant HPV type(s) at enrolment, remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immune Response to GARDASIL at Month 7 in 9 Through 45-Year-Old Females (Time Point Approximating Peak Immunogenicity)
In the per-protocol immunogenicity population of 9- through 45-year-olds, seropositivity at Month 7 ranged from 96.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age (Table 7). This finding is expected, as the immune responses to vaccines generally decrease was observed age-related decrease in anti-HPV GMTs.

Table 7
Summary of Percent Seroconversion and Anti-HPV cLIA GMTs at Month 7 in the PPI* Population of 9- Through 45-Year-Old Girls and Women

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 17-year-old girls and women	2,349	1,126	99.9 (99.5, 100.0)	866.3 (820.7, 914.4)
18- through 26-year-old women	8,635	3,124	99.8 (99.6, 99.9)	539.6 (524.3, 555.3)
27- through 34-year-old women	667	441	98.4 (96.8, 99.4)	435.5 (393.7, 481.8)
35- through 45-year-old women	957	651	98.2 (96.8, 99.0)	398.4 (366.2, 433.3)
Anti-HPV 11				
9- through 17-year-old girls and women	2,349	1,127	99.9 (99.5, 100.0)	1209.5 (1142.3, 1280.6)
18- through 26-year-old women	8,635	3,147	99.7 (99.5, 99.9)	741.7 (718.3, 765.8)
27- through 34-year-old women	667	441	98.2 (96.5, 99.2)	578.8 (526.6, 636.3)
35- through 45-year-old women	957	651	97.7 (96.2, 98.7)	513.5 (473.0, 557.5)
Anti-HPV 16				
9- through 17-year-old girls and women	2,349	1,118	99.9 (99.5, 100.0)	4391.0 (4089.7, 4714.5)
18- through 26-year-old women	8,635	3,050	99.8 (99.6, 99.9)	2397.2 (2294.4, 2504.7)
27- through 34-year-old women	667	437	99.3 (98.0, 99.9)	2345.1 (2141.5, 2568.0)
35- through 45-year-old women	957	661	98.2 (96.9, 99.1)	2134.2 (1958.7, 2325.5)
Anti-HPV 18				
9- through 17-year-old girls and women	2,349	1,141	99.6 (99.1, 99.9)	909.4 (849.3, 973.6)
18- through 26-year-old women	8,635	3,352	99.5 (99.2, 99.7)	473.4 (456.6, 490.8)
27- through 34-year-old women	667	503	98.0 (96.4, 99.0)	386.0 (349.2, 426.7)
35- through 45-year-old women	957	729	96.4 (94.8, 97.7)	325.8 (298.2, 356.0)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**Number of individuals randomized to the respective vaccination group who received at least 1 injection
***Number of individuals contributing to the analysis
†mMU = milli-Merck units
CI = Confidence Interval

Immune Response to GARDASIL at Month 7 in 9 Through 26-Year-Old Males (Time Point Approximating Peak Immunogenicity)

In the per-protocol immunogenicity population of 9- through 26-year-olds, seropositivity at Month 7 ranged from 97.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age (Table 8). This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination. The efficacy of GARDASIL remained high despite the observed age-related decrease in anti-HPV GMTs.

Table 8
Summary of Percent Seroconversion and Anti-HPV cLIA GMTs at Month 7 in the PPI* Population of 9- Through 26-Year-Old Boys and Men

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year old boys	1,073	885	99.9 (99.4, 100.0)	1,036.9 (962.9, 1,116.6)
16- through 26-year old boys and men	2,025	1093	98.9 (98.1, 99.4)	447.0 (418.2, 477.8)
Anti-HPV 11				
9- through 15-year old boys	1,073	886	99.9 (99.4, 100.0)	1,386.3 (1,298.1, 1,480.4)
16- through 26-year old boys and men	2,025	1,093	99.2 (98.4, 99.6)	624.2 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year old boys	1,073	883	99.8 (99.2, 100.0)	6,047.1 (5,592.8, 6,538.3)
16- through 26-year old boys and men	2,025	1,136	98.8 (97.9, 99.3)	2,402.5 (2,242.6, 2,573.7)
Anti-HPV 18				
9- through 15-year old boys	1,073	888	99.8 (99.2, 100)	1,356.9 (1,249.0, 1,474.2)
16- through 26-year old boys and men	2,025	1,175	97.4 (96.3, 98.2)	402.2 (374.3, 432.3)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**Number of individuals randomized to the respective vaccination group who received at least 1 injection
***Number of individuals contributing to the analysis
†mMU = milli-Merck units
CI = Confidence Interval

Bridging the Efficacy of GARDASIL from Adults to Adolescents

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

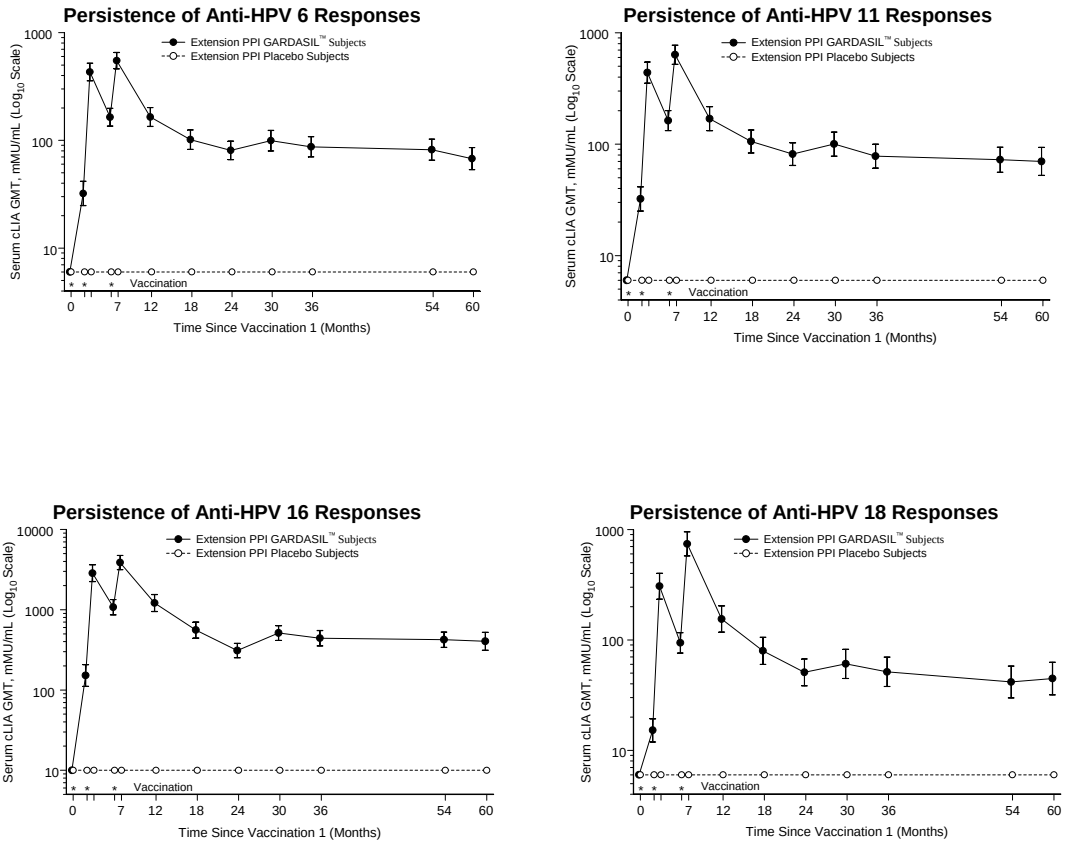
Similar outcomes were observed in a comparison of the anti-HPV responses 1 month Postdose 3 among 9 through 15 year old females with anti-HPV responses in 16 through 26 year old females in the combined database of immunogenicity studies for GARDASIL.

Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses (GMTs) were compared between 9- through 15-year-old males and 16- through 26-year-old males. Among males who received GARDASIL, 97.4% to 99.9% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month postdose 3. Anti-HPV responses in 9- through 15-year-old males were significantly superior to those observed in 16- through 26-year-old males.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9 through 15 year old females is comparable to the efficacy of GARDASIL observed in 16 through 26 year old females. Additionally, the efficacy of GARDASIL in 9- through 15-year-old males is comparable to the efficacy of GARDASIL observed in studies in 16- through 26-year-old males.

Persistence of Immune Response of GARDASIL
In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then stabilized until at least Month 60 (see Figure 2).

Figure 2
Persistence of Anti-HPV Responses Following a 3-dose Regimen of GARDASIL



Immune Memory (Anamnestic) Responses
GARDASIL boosts immunologically primed subjects (i.e., subjects with evidence of a previous natural infection). For each HPV type, anti-HPV GMTs measured 1 month Postdose 3 were approximately 1.4- to 2.4-fold higher in subjects with detectable antibodies for that type at Day 1 compared with subjects who were seronegative for that type at Day 1.

To simulate the potential impact of natural exposure, a study to evaluate immune memory was conducted. Subjects who received a 3-dose primary series of vaccine were given a challenge dose of GARDASIL 5 years after the onset of vaccination.

These subjects exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3 (Month 7) (Table 9).

Table 9
Comparison of HPV Antibody Responses At Month 7, Month 60, 1 Week Post-Challenge Dose, and 1 Month Post-Challenge Dose for GARDASIL in The Extension Per-Protocol Population*

Time Postdose	n	GMT (mMU/mL)	95% Confidence Interval	Fold Change from Month 7	Fold Change Pre-challenge vs. Post-challenge
HPV 6					
Month 7	80	549.2	(460.6, 654.7)	-	
Month 60 (Pre-challenge)	79	67.7	(53.5, 85.7)	-	
Month 60 + 1 Week Post-challenge	79	503.3	(344.2, 736.1)	0.9	
Month 61 (Post-challenge)	80	693.2	(451.9, 1063.3)	1.3	10.2
HPV 11					
Month 7	80	635.5	(521.3, 774.9)	-	
Month 60 (Pre-challenge)	79	70.1	(52.5, 93.7)	-	
Month 60 + 1 Week Post-challenge	79	1417.5	(1009.0, 1991.4)	2.2	
Month 61 (Post-challenge)	80	2652.4	(1956.7, 3595.3)	4.2	37.8
HPV 16					
Month 7	82	3870.0	(3157.0, 4744.0)	-	
Month 60 (Pre-challenge)	82	404.2	(312.9, 522.1)	-	
Month 60 + 1 Week Post-challenge	81	4466.4	(3095.2, 6445.0)	1.2	
Month 61 (Post-challenge)	81	5714.0	(3829.7, 8525.4)	1.5	14.1
HPV 18					
Month 7	86	741.2	(576.8, 952.4)	-	
Month 60 (Pre-challenge)	85	44.7	(31.8, 62.8)	-	
Month 60 + 1 Week Post-challenge	84	1033.2	(753.9, 1415.8)	1.4	
Month 61 (Post-challenge)	86	1230.0	(904.5, 1672.5)	1.7	27.5

*The extension per-protocol population includes all extension subjects who received 3 primary injections of GARDASIL and antigen challenge of GARDASIL at month 60, were seronegative and Polymerase Chain Reaction (PCR) negative at Day 1 to the respective vaccine HPV types, PCR negative through Month 60 to the respective vaccine HPV types, and had valid serology data 4 weeks post-challenge.
Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Schedule flexibility

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

Studies with Other Vaccines

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

INDICATIONS

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

GARDASIL is indicated in males 9 through 26 years of age for the prevention of external genital lesions and infection caused by HPV types 6, 11, 16, and 18.

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

CONTRAINDICATIONS

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

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

PRECAUTIONS

General

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

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

This vaccine will not protect against diseases that are not caused by HPV. Oncogenic HPV types other than HPV 16 and 18 may cause cervical cancer. Vaccination may therefore not prevent HPV infection and disease due to these other oncogenic types (see Clinical Studies). 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 vaccination with GARDASIL. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL (see ADVERSE REACTIONS, Post Marketing Reports).

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 DRUG INTERACTIONS).

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

Carcinogenicity

GARDASIL has not been evaluated for carcinogenic potential.

Genotoxicity

GARDASIL has not been evaluated for genotoxic potential

Effects on Fertility

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

GARDASIL administered to male rats at a dose of 120 mcg total protein, which corresponds to approximately 200-fold excess relative to the projected human dose, had no effects on reproductive performance including fertility, sperm count, and sperm motility, and there were no vaccine-related gross or histomorphologic changes on the testes and no effects on testes weights.

Use in Pregnancy (Category B2)

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

Clinical Studies in Humans
GARDASIL is not recommended for use in pregnant women.

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2, and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

During clinical trials, 3,620 women (vaccine N = 1,796 vs. placebo N = 1,824) reported at least one pregnancy. The overall proportions of pregnancies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death, congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 23.3% (423/1, 812) in subjects who received GARDASIL and 24.1% (438/1, 820) in subjects who received placebo.

Further sub-analyses were done to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 35 cases of congenital anomaly were observed in the group that received GARDASIL compared with 29 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women 16 through 45 years of age.

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

Use in Lactation

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

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

GARDASIL may be administered to lactating women.

GARDASIL or placebo were given to a total of 1,132 women who were breast feeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

Paediatric Use

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

Use in the Elderly

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

Use in other special populations

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

Drug Interactions

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant). GARDASIL has not been studied in clinical trials with other vaccines.

Use with Common Medications

In clinical studies in females aged 16 to 26 years, 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations respectively. In a clinical study in females aged 24 to 45 years, 30.6%, 20.2%, 11.6%, and 7.5% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. In a clinical study in males aged 16 to 26 years, 10.3%, 7.8%, 6.8%, 3.4% and 2.6% of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives

In clinical studies 50.2% of females (16 to 45 years of age), who received GARDASIL, used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

Use with Steroids

In clinical studies in females aged 16 to 26 years, 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively. In a clinical study in females aged 24 to 45 years, 1.4% (n = 27) used corticosteroids for systemic use. In a clinical study in males aged 16 to 26 years, 1.0% (n = 21) used corticosteroids for systemic use. The corticosteroids for all subjects were administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few subjects in the clinical studies were taking steroids and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications
There are no data on the concomitant use of potent immunosuppressants with GARDASIL. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization (see PRECAUTIONS, General).

ADVERSE REACTIONS

In 7 clinical trials (6 placebo-controlled), subjects were administered GARDASIL or placebo on the day of enrolment, and approximately 2 and 6 months thereafter. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). Few subjects (0.2%) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The subjects who were monitored using VRC-aided surveillance included 10,088 subjects (6,995 females 9 through 45 years of age, 3,093 males 9 through 26 years of age at enrolment) who received GARDASIL and 7,995 subjects who received placebo.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are shown in Tables 10 and 11.

Table 10
Vaccine-related Injection-site and Systemic Adverse Experiences: 9- Through 45-Year-Old Females*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 6,995) %	AAHS** Adjuvant – containing Placebo (N = 5,372) %	Saline Placebo (N = 320) %
Injection Site			
Pain	81.5	70.6	48.6
Swelling	23.5	14.2	7.3
Erythema	21.9	15.6	12.1
Pruritus	2.7	2.3	0.6
Bruising	2.2	2.8	1.6

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 6,995) %	Placebo (N = 5,692) %
Systemic		
Headache	20.5	20.3
Fever	10.1	8.7
Nausea	3.7	3.4
Dizziness	2.9	2.7
Pain in extremity	1.5	1.0

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.
** amorphous aluminium hydroxyphosphate sulfate

Of those females who reported an injection site reaction, 94.2% judged their injection-site adverse experience to be mild or moderate in intensity.

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

Table 11
Vaccine-Related Injection-Site and Systemic Adverse Experiences: 9- Through 26-Year-Old Males*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 3,093) %	AAHS** Adjuvant-containing Placebo (N = 2,029) %	Saline Placebo (N = 274) %
Injection Site			
Pain	61.4	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2
Bruising	1.0	0.3	3.3

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 3,093) %	Placebo (N = 2,303) %
Systemic		
Headache	7.5	6.7
Fever	6.3	5.1

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.
**amorphous aluminum hydroxyphosphate sulfate

Of those males who reported an injection site reaction, 96.4% judged their injection-site adverse reaction to be mild or moderate in intensity.

All-cause Common Systemic Adverse Experiences
All-cause systemic adverse experiences for subjects that were observed at a frequency of

greater than or equal to 1% where the incidence in the vaccine group was greater than or equal to the incidence in the placebo group are shown in Table 12 and 13.

Table 12
All-cause Common Systemic Adverse Experiences in Females

Adverse Experience (1 to15 Days Postvaccination)	**GARDASIL** (n = 6995) %	**Placebo*** (n = 5692) %
Headache	28.1	28.1
Pyrexia	12.7	11.6
Nausea	5.9	5.5
Nasopharyngitis	5.8	5.8
Dizziness	4.0	3.9
Diarrhea	3.4	3.3
Pain in extremity	2.7	2.4
Abdominal Pain, upper	2.6	2.5
Vomiting	2.0	1.7
Myalgia	1.8	1.6
Cough	1.7	1.5
Upper respiratory tract infection	1.6	1.5
Toothache	1.5	1.4
Malaise	1.3	1.3
Arthralgia	1.1	0.9
Migraine	1.0	1.0

*Aluminum and/or non-aluminum containing placebo

Table 13
All-cause Common Systemic Adverse Experiences in Males

Adverse Experience (1 to15 Days Postvaccination)	**GARDASIL** (n = 3093) %	**Placebo*** (n = 2303) %
Headache	12.3	11.2
Pyrexia	8.3	6.5
Oropharyngeal pain	2.8	2.1
Diarrhea	2.7	2.2
Nasopharyngitis	2.6	2.6
Nausea	2.0	1.0
Upper respiratory tract infection	1.5	1.0
Abdominal pain upper	1.4	1.4
Myalgia	1.3	0.7
Dizziness	1.2	0.9
Vomiting	1.0	0.8

*Aluminum and/or non-aluminum containing placebo

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. The frequency of adverse experiences observed with concomitant administration was similar to the frequency when GARDASIL was administered alone.

Post-marketing Reports

The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy

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

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

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

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

DOSAGE AND ADMINISTRATION

Dosage

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

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

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. If an alternate vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose. (see CLINICAL STUDIES, Schedule Flexibility).

Method of Administration

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

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

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

The prefilled syringe is for single use only and should not be used for more than one individual. The vials are for single use in one patient only. For single-use vials a separate sterile syringe and needle must be used for each individual.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discoloured.

Prefilled Syringe Use
Inject the entire contents of the syringe.

Single-dose Vial Use
Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

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

PRESENTATION & STORAGE CONDITIONS

Presentation

GARDASIL is a sterile cloudy white liquid.

Storage

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

GARDASIL should be administered as soon as possible after being removed from refrigeration. GARDASIL can be out of refrigeration at temperatures, at or below 25°C, for a total time of not more than 72 hours.

OVERDOSAGE

There have been reports of administration of higher than recommended doses of GARDASIL.
In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL.

NAME AND ADDRESS OF SPONSOR in Australia

Merck Sharp & Dohme (Australia) Pty Limited
54-58 Ferndell St
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DISTRIBUTOR in Australia

CSL Biotherapies Pty Ltd
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Auckland

DISTRIBUTOR in New Zealand

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POISONS SCHEDULE

Schedule 4 – Prescription Medicine

This product information was approved by the Therapeutic Goods Administration on 12 October 2010.

Therapeutic Goods Administration

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