Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for: Quadrivalent human papillomavirus (Types 6,11,16 & 18) recombinant vaccine

Proprietary Product Name: Gardasil

Sponsor: Merck Sharp & Dohme

May 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (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:	20 December 2012
Active ingredient(s):	Quadrivalent human papillomavirus (Types 6,11,16 & 18) recombinant vaccine
Product Name(s):	Gardasil
Sponsor's Name and Address:	Merck Sharpe & Dohme (Australia) Pty Limited 66 Waterloo Road, North Ryde NSW 2113
Dose form(s):	Suspension for injection
Strength(s):	Each 0.5 mL dose contains HPV 6 L1 protein 20 µg, HPV 11 L1 protein 40 µg, HPV 16 L1 protein 40 µg, & HPV 18L1 protein 20 µg.
Container(s):	Single dose vial/ Prefilled syringe
Approved Therapeutic use:	Gardasil is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine). Gardasil is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV Types 6, 11, 16, 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.
Route(s) of administration:	Intramuscular (IM)
Dosage:	Three separate 0.5 mL doses.
ARTG Number (s)	124408 and 124410

Product Background

This AusPAR describes the application by the Merck Sharpe & Dohme (Australia) for an extension of indications for Gardasil. The extension is for prevention of anal cancer, precancerous or dysplastic lesions caused by HPV Types 6,11,16 and 18 (which are included in the vaccines) in males and females. The current indications in males 9 through 26 years are for prevention of external genital lesions and infection caused by HPV Types 6,11,16 and 18. Current indications in females aged 9 through 45 years are for prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by HPV Types 6,11,16 and 18.

Regulatory Status

Gardasil is approved for use in more than 130 countries and territories worldwide. The first notable registration was in Mexico in 1 June 2006 and has since been approved in the USA, Australia, Canada, New Zealand and the European Union.

The currently approved therapeutic indication for Gardasil in Australia is as follows:

> *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.*

Anal pre-cancer/cancer indication

The additional indications for Gardasil to include prevention of anal cancer and anal intraepithelial neoplasia (AIN) were approved by the FDA on 22 December 2010 and by Health Canada on 24 May 2011.

Although the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) did not agree to the inclusion of anal pre-cancer in the *Therapeutic Indications* section of the European Union (EU) Summary of Product Characteristics (SmPC), the data from the men who have sex with men (MSM) sub study, was included in the section *Pharmacodynamic Properties: Clinical Studies* to demonstrate the efficacy in men.

The application for anal cancer and AIN will be submitted to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) once the outcome of the Australian application becomes clearer, so that the labels can be aligned.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The current Australian submission consisted of clinical data only. The update is based on men who have sex with men (MSM) substudy within the Protocol 020.

The Protocol 020 study results have been previously reviewed and formed the basis of approval for use of Gardasil in males (9-26 years) for prevention of external genital lesions and infection caused by HPV Types 6, 11, 16 and 18 following consideration by the Advisory Committee on prescription medicines (ACPM) at its June 2010 meeting. For more details please see the Gardasil AUSPAR at http://www.tga.gov.au/pdf/auspar/auspar-gardasil.pdf.

The Protocol 020 and the MSM substudy were stated to have complied with the Good Clinical Practice (GCP) and ethical standards.

Pharmacokinetics

No new data were submitted.

Pharmacodynamics

No new data were submitted.

Efficacy

Protocol 020 and MSM substudy

The primary objective of Protocol 020 was to determine Gardasil vaccine efficacy in preventing External Genital Lesions (EGL)[1] related to HPV Types 6, 11, 16 and/or 18 in men who were naïve to these HPV types at baseline, following completion of 3 dose course of vaccination administered at 0, 2 and 6 months. The design was randomised, double blind, placebo controlled.

The MSM substudy was embedded within the Protocol 020 and its objective was to determine the prophylactic effect of vaccine on incidence of HPV Types 6, 11, 16, and 18 related Anal Intraepithelial Neoplasia (AIN) or Anal Cancer (AC). The 'men who have sex with men' (MSM) population was identified because of perceived higher risk of AIN/AC in this population.

In Protocol 020, the enrolment was regardless of baseline exposure to HPV. A total of 4065 men were randomised to the two groups, including 3463 heterosexual men (HM) aged 16 to 23 and 602 MSM aged 16 to 26 years. All study participants (HM and MSM) contributed to the primary efficacy objective of Protocol 020, that is, prevention of EGL.

The MSM substudy participants only contributed to the evaluation of the MSM efficacy objective, that is, prevention of AIN or AC.

In Protocol 020, the duration of follow up for each participant was 36 months. The study employed a fixed event design. The data submitted formed the final report of the controlled data at 36 months. The median duration of follow up now stands at 35.3, 35.4, and 32.2 months for the overall, HM and MSM groups, respectively. The study is ongoing as single arm with vaccination of placebo recipients.

The EGL primary efficacy analysis in Protocol 020 and the AIN/AC efficacy analysis in the MSM substudy were conducted in randomised subjects who were naïve to the relevant vaccine HPV type(s) at baseline and remained PCR negative to the relevant type(s) through the vaccination period including Month 7, that is, 4 weeks after the last dose (Dose 3). The Per Protocol Efficacy (PPE) Population thus defined comprised of 2877/4065 (71%) randomised participants for the Protocol 020 objective (EGL) and 418/602 (69%) randomised participants for the MSM objective (AIN/AC).

The operation definition of the Protocol 020 primary EGL efficacy outcome was determination of combined incidence of HPV 6, 11, 16, and/or 18 related external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile/perianal/perineal cancer in subjects who were seronegative at baseline and Polymerase Chain Reaction (PCR)[2] negative from Day 1 through Month 7 to the relevant HPV type compared to placebo.

The operation definition of the MSM substudy AIN/AC efficacy outcome was determination of combined incidence of HPV 6, 11, 16 or 18 related AIN or Anal Cancer in

[1] External genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), or penile/perianal/perineal cancer.
[2] PCR=a technique for rapidly producing many copies of a fragment of DNA for diagnostic or research purposes

MSM who were seronegative at baseline and PCR negative from Day 1 through Month 7 to the relevant HPV type compared to placebo.

The results in the modified Intent to Treat (ITT) population (Full Analysis Set (FAS)) have been provided as secondary outcomes.

For details of eligibility criteria and diagnostic procedures in Protocol 020, please see Gardasil AUSPAR noted above. The comparator groups were well balanced. The mean age of participants in the MSM study was 22 years.

Additional procedures for MSM subjects only included intra anal swab specimen collection for HPV PCR and anal cytology at Day 1 and at Months 7, 12, 18, 24, 30, and 36. The substudy subjects also underwent digital rectal examination at these timepoints and if indicated a simple anoscopy (mass detected on digital examination). The subjects were triaged to high resolution anoscopy (HRA) on the basis of a pre specified algorithm as shown in Table 1.

Table 1. Protocol Specified Anal Cytology Result Algorithm

ThinPrep™ Pap Result	Action
Negative for squamous intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.)	Routine visit interval as specified by the protocol
Atypical Squamous Cells of Undetermined Significance (ASC-US)	Referral to High Resolution Anoscopy
Atypical Squamous Cells, cannot rule out HSIL (ASC-H)	Referral to High Resolution Anoscopy
Low-grade Squamous Intraepithelial Lesion (LSIL)	Referral to High Resolution Anoscopy
High-grade Squamous Intraepithelial Lesion (HSIL)	Referral to High Resolution Anoscopy
Atypical Glandular Cells	Referral to High Resolution Anoscopy
Inadequate specimen	Repeat Pap Test as soon as possible
High resolution anoscopy should be performed according to the guidelines in this table.	

All MSM subjects underwent mandatory HRA at the Month 36 final visit regardless of anal Pap smear[3] results. All areas of abnormalities noted on HRA were biopsied.

Efficacy Results

MSM substudy

Based on PPE population as defined, the incidence rate of HPV 6/11/16/18 related AIN/AC was 1.3/100 Person Years (PY) in the Gardasil group compared to 5.8/100 PY in the placebo group, representing a Vaccine Efficacy (VE) of 77.5% ($p < 0.001$) and a 95% Confidence Interval (CI) of 39.6% to 93.3% The results are described in Table 2 below. All cases were AIN. There was no occurrence of AC in either group at the 36 Month timepoint.

[3] A test for cancer in which a smear of exfoliated cells is specially stained and examined under a microscope for pathological changes. Also called *Pap test*.

Table 2. MSM Substudy Results. Analysis of Efficacy against HPV 6/11/16/18-related AIN and Anal Cancer† by HPV type and Lesion type (MSM Per Protocol Efficacy Population).

	qHPV Vaccine (N=299)				Placebo (N=299)						
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 (%)	CI‡	P-value§
HPV 6/11/16/18-Related AIN and Anal Cancer	194	5	381.1	1.3	208	24	411.6	5.8	77.5	(39.6, 93.3)	<0.001
By HPV Type											
HPV 6-Related AIN and Anal Cancer	141	3	275.2	1.1	144	10	298.5	3.4	67.5	(-26.4, 94.2)	
HPV 11-Related AIN and Anal Cancer	141	0	279.2	0.0	144	6	298.2	2.0	100	(9.3, 100)	
HPV 16-Related AIN and Anal Cancer	167	2	330.6	0.6	170	6	341.9	1.8	65.5	(-92.8, 96.6)	
HPV 18-Related AIN and Anal Cancer	173	0	345.3	0.0	193	4	387.4	1.0	100	(-70.0, 100)	
By Lesion Type											
AIN 1	194	4	383.1	1.0	208	16	413.8	3.9	73.0	(16.3, 93.4)	
Condyloma Acuminatum	194	0	386.8	0.0	208	6	418.2	1.4	100	(8.2, 100)	
Non-acuminate	194	4	383.1	1.0	208	11	416.7	2.6	60.4	(-33.5, 90.8)	
AIN 2 or worse	194	3	383.9	0.8	208	13	417.2	3.1	74.9	(8.8, 95.4)	
AIN 2	194	2	384.5	0.5	208	9	418.6	2.2	75.8	(-16.9, 97.5)	
AIN 3	194	2	385.4	0.5	208	6	419.7	1.4	68.7	(-103.0, 96.4)	
Anal Cancer	194	0	386.8	0.0	208	0	421.1	0.0	NA	NA	

†Cases found from performing an HRA due to the presence of perianal external lesions are not included in this analysis to eliminate potential ascertainment bias.

‡ A 95.1% CI is reported for the HPV 6/11/16/18-related AIN and anal cancer endpoint. For all analyses by HPV type and lesion type, a 95% CI is reported. The CI reported for the HPV 6/11/16/18-related AIN and anal cancer endpoint differs from the other analyses due to the alpha adjustment applied.

§A p-value≤0.0245 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 0% and supports the conclusion that the vaccine is efficacious against the given endpoint

N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the MSM substudy who have at least one follow-up visit after Month 7.

AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; HRA = High resolution anoscopy; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Using the FAS, the incidence rate was 6.3 and 12.6 per 100 PY in the two groups, respectively, representing a VE of 50.3% with 95% CI of 25.7% to 67.2% (Table 3).

Table 3. MSM Substudy. Analysis of Efficacy against HPV 6/11/16/18-related AIN and Anal Cancer† by HPV type and Lesion type (MSM Full Analysis Set).

	qHPV Vaccine (N=299)				Placebo (N=299)					
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
HPV 6/11/16/18-Related AIN and Anal Cancer	275	38	607.1	6.3	276	77	611.9	12.6	50.3	(25.7, 67.2)
By HPV Type										
HPV 6-Related AIN and Anal Cancer	275	18	644.8	2.8	276	47	645.3	7.3	61.7	(32.8, 79.1)
HPV 11-Related AIN and Anal Cancer	275	13	651.2	2.0	276	25	660.5	3.8	47.3	(-7.1, 75.2)
HPV 16-Related AIN and Anal Cancer	275	8	668.7	1.2	276	18	678.6	2.7	54.9	(-9.0, 83.0)
HPV 18-Related AIN and Anal Cancer	275	5	671.9	0.7	276	11	684.5	1.6	53.7	(-44.6, 87.4)
By Lesion Type										
AIN 1	275	31	619.3	5.0	276	62	624.1	9.9	49.6	(21.2, 68.4)
Condyloma Acuminatum	275	13	651.3	2.0	276	31	664.2	4.7	57.2	(15.9, 79.5)
Non-acuminate	275	27	636.0	4.2	276	48	641.3	7.5	43.3	(7.3, 66.0)
AIN 2 or worse	275	18	660.1	2.7	276	39	655.2	6.0	54.2	(18.0, 75.3)
AIN 2	275	11	668.0	1.6	276	29	671.5	4.3	61.9	(21.4, 82.8)
AIN 3	275	10	665.9	1.5	276	19	672.8	2.8	46.8	(-20.2, 77.9)
Anal Cancer	275	0	678.4	0.0	276	0	694.8	0.0	NA	NA

N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.

AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; HRA = High resolution anoscopy; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

The VE (6/11/16/18) against AIN (2 or worse) was 74.9% (95% CI 8.8%, 95.4%) when using the PPE population (Table 2) and 54.2% (95% CI 18.0%, 75.3%) when using the FAS population (Table 3).

The VE (any HPV) against AIN (2 or worse) was 24.3% (95% CI -13.8%, 50.0%) when using the FAS population.

The VE in seronegative PCR positive (S-/PCR+) or seropositive (S+)/PCR+ MSM subjects was not confirmed in this trial.

The incidence rate of intra anal persistent infection[4] (HPV Types 6/11/16/18) was 0.5 and 10.2 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 94.9% with 95% CI of 80.4% to 99.4% when using the PPE population.

The incidence rate of HPV 6/11/16/18 persistent infection was 1.3 and 10.8 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 88.0% with 95% CI of 69.5% to 96.3% using the PPE population results. The VE was 52.0% (95% CI 34.2%, 65.3%) when using the FAS population data.

The incidence rate of HPV 6/11/16/18 related DNA detection at one or more visits was 7.9 and 20.9 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 62.1% with 95% CI of 40.7% to 76.4% when using the PPE population data. The VE was 27.2% (95% CI 7.7%, 42.7%) when using the FAS population data.

The results against AIN/AC to any HPV type are provided in Table 4 below.

[4] It is not clear how 'persistent infection' was defined. The sponsor is requested to clarify this measure both in the overall Protocol 020 population and the MSM substudy, in response to this report.

Table 4. MSM Substudy. Analysis of Efficacy against AIN and Anal Cancer due to Any HPV type (MSM Full Analysis Set).

Endpoint	qHPV Vaccine (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) n	Number Of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
AIN and Anal Cancer Due to Any HPV Type	275	74	569.0	13.0	276	103	588.4	17.5	25.7	(-1.1, 45.6)
HPV 6/11/16/18-Related AIN and Anal Cancer	275	38	607.1	6.3	276	77	611.9	12.6	50.3	(25.7, 67.2)
HPV 6-Related AIN and Anal Cancer	275	18	644.8	2.8	276	47	645.3	7.3	61.7	(32.8, 79.1)
HPV 11-Related AIN and Anal Cancer	275	13	651.2	2.0	276	25	660.5	3.8	47.3	(-7.1, 75.2)
HPV 16-Related AIN and Anal Cancer	275	8	668.7	1.2	276	18	678.6	2.7	54.9	(-9.0, 83.0)
HPV 18-Related AIN and Anal Cancer	275	5	671.9	0.7	276	11	684.5	1.6	53.7	(-44.6, 87.4)
AIN and Anal Cancer Related to any of 10 Assay-identified HPV Types	275	38	635.4	6.0	276	44	648.8	6.8	11.8	(-39.3, 44.4)
HPV 31-Related AIN and Anal Cancer	275	7	675.1	1.0	276	8	687.1	1.2	11.0	(-181.0, 72.5)
HPV 33-Related AIN and Anal Cancer	275	1	677.8	0.1	276	2	690.9	0.3	49.0	(-879.0, 99.1)
HPV 35-Related AIN and Anal Cancer	275	3	675.2	0.4	276	5	687.6	0.7	38.9	(-214.1, 90.5)
HPV 39-Related AIN and Anal Cancer	275	6	670.8	0.9	276	8	689.3	1.2	22.9	(-153.3, 78.0)
HPV 45-Related AIN and Anal Cancer	275	5	671.2	0.7	276	7	686.4	1.0	27.0	(-167.3, 81.7)
HPV 51-Related AIN and Anal Cancer	275	9	674.0	1.3	276	9	683.7	1.3	-1.4	(-188.4, 64.3)
HPV 52-Related AIN and Anal Cancer	275	2	677.1	0.3	276	7	688.1	1.0	71.0	(-52.5, 97.1)
HPV 56-Related AIN and Anal Cancer	275	9	666.4	1.4	276	5	689.2	0.7	-86.1	(-607.0, 44.0)
HPV 58-Related AIN and Anal Cancer	275	5	672.4	0.7	276	6	686.1	0.9	15.0	(-234.4, 79.5)
HPV 59-Related AIN and Anal Cancer	275	11	667.9	1.6	276	9	687.8	1.3	-25.9	(-243.6, 52.6)
AIN and Anal Cancer Not Related to any of 14 Assay-identified HPV Types	275	15	558.7	2.7	276	16	566.0	2.8	5.0	(-105.1, 56.3)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.

AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Protocol 020

Based on the PPE population as defined, the incidence rate for HPV 6/11/16/18 related EGL was 0.1 and 1.0 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 90.6% with 95% CI of 70.1% to 98.2% (Table 5). The VE was 66.7% (95% CI 48.0%, 79.3%) in the FAS population (Table 6).

The incidence rate for AIN Grades 2/3, using FAS, was 0.1/100 PY in both groups, representing a VE of 0.4% (Table 6). The results were similar using the PPE set data (Table 5).

Based on the PPE population, the incidence rate of HPV 6/11/16/18 persistent infection was 0.7 and 4.8 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 85.5% with 95% CI of 77.0% to 91.3%. The VE was 52.2% (95% CI 42.0%, 60.7%) in the FAS population.

Based on the PPE population, the incidence rate of HPV 6/11/16/18 related DNA detection at one or more visits was 5.3 and 10.7 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 51.0% with 95% CI of 40.3% to 59.9%. The VE was 32.1% (95% CI 22.8%, 40.3%) in the FAS population.

Table 5. Protocol 020. Analysis of Efficacy against HPV 6/11/16/18-related EGL by Sexual orientation, HPV type and Lesion type (Per Protocol Efficacy 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
HPV 6/11/16/18-Related EGL	1,394	3	3,109.2	0.1	1,404	32	3,106.0	1.0	90.6	(70.1, 98.2)
By Sexual Orientation										
HM Subjects	1,200	2	2,722.4	0.1	1,196	26	2,689.7	1.0	92.4	(69.6, 99.1)
MSM Subjects	194	1	386.9	0.3	208	6	416.3	1.4	82.1	(-47.8, 99.6)
By HPV Type										
HPV 6-Related EGL	1,242	3	2,779.8	0.1	1,243	19	2,790.3	0.7	84.2	(46.2, 97.0)
HPV 11-Related EGL	1,242	1	2,781.2	0.0	1,243	11	2,790.7	0.4	90.9	(37.2, 99.8)
HPV 16-Related EGL	1,292	0	2,883.5	0.0	1,270	3	2,841.1	0.1	100	(-138.4, 100)
HPV 18-Related EGL	1,331	0	2,978.0	0.0	1,352	1	3,013.4	0.0	100	(-3846.4, 100)
By Lesion Type										
Condyloma	1,394	3	3,109.2	0.1	1,404	28	3,108.0	0.9	89.3	(65.3, 97.9)
PIN 1 or worse	1,394	0	3,112.2	0.0	1,404	4	3,124.9	0.1	100	(-52.1, 100)
PIN 1	1,394	0	3,112.2	0.0	1,404	2	3,126.6	0.1	100	(-434.9, 100)
PIN 2/3 or Cancer	1,394	0	3,112.2	0.0	1,404	2	3,125.1	0.1	100	(-434.7, 100)
PIN 2/3	1,394	0	3,112.2	0.0	1,404	2	3,125.1	0.1	100	(-434.7, 100)
Penile/Perianal/Perineal Cancer	1,394	0	3,112.2	0.0	1,404	0	3,126.8	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 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.

Table 6. Protocol 020. Analysis of Efficacy against HPV 6/11/16/18-related EGL by Sexual orientation, HPV type and Lesion type (Full Analysis Set).

	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
HPV 6/11/16/18-Related EGL	1,943	27	4,987.0	0.5	1,937	80	4,914.2	1.6	66.7	(48.0, 79.3)
By Sexual Orientation										
HM Subjects	1,653	21	4,314.4	0.5	1,648	57	4,244.9	1.3	63.8	(39.3, 79.1)
MSM Subjects	290	6	672.6	0.9	289	23	669.4	3.4	74.0	(34.4, 91.4)
By HPV Type										
HPV 6-Related EGL	1,943	21	4,998.3	0.4	1,937	52	4,943.2	1.1	60.1	(32.5, 77.1)
HPV 11-Related EGL	1,943	6	5,029.2	0.1	1,937	26	4,978.9	0.5	77.2	(43.2, 92.3)
HPV 16-Related EGL	1,943	3	5,029.6	0.1	1,937	11	4,998.9	0.2	72.9	(-2.6, 95.1)
HPV 18-Related EGL	1,943	2	5,035.7	0.0	1,937	3	5,008.5	0.1	33.7	(-478.8, 94.5)
By Lesion Type										
Condyloma	1,943	24	4,997.5	0.5	1,937	74	4,918.9	1.5	68.1	(48.8, 80.7)
PIN 1 or worse	1,943	6	5,023.2	0.1	1,937	6	5,006.4	0.1	0.3	(-272.8, 73.4)
PIN 1	1,943	3	5,031.4	0.1	1,937	4	5,008.1	0.1	25.3	(-341.3, 89.1)
PIN 2/3 or Cancer	1,943	3	5,029.6	0.1	1,937	3	5,008.1	0.1	0.4	(-643.4, 86.7)
PIN 2/3	1,943	3	5,029.6	0.1	1,937	3	5,008.1	0.1	0.4	(-643.4, 86.7)
Penile/Perianal/Perineal Cancer	1,943	0	5,037.8	0.0	1,937	0	5,011.1	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 results for EGL to any HPV type are provided Table 7.

Table 7. Protocol 020. Analysis of Efficacy against EGL due to Any HPV type (Full Analysis Set).

	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
EGL Due to Any HPV Type	1,943	38	4,971.1	0.8	1,937	92	4,894.5	1.9	59.3	(40.0, 72.9)
HPV 6/11/16/18-Related EGL	1,943	27	4,987.0	0.5	1,937	80	4,914.2	1.6	66.7	(48.0, 79.3)
HPV 6-Related EGL	1,943	21	4,998.3	0.4	1,937	52	4,943.2	1.1	60.1	(32.5, 77.1)
HPV 11-Related EGL	1,943	6	5,029.2	0.1	1,937	26	4,978.9	0.5	77.2	(43.2, 92.3)
HPV 16-Related EGL	1,943	3	5,029.6	0.1	1,937	11	4,998.9	0.2	72.9	(-2.6, 95.1)
HPV 18-Related EGL	1,943	2	5,035.7	0.0	1,937	3	5,008.5	0.1	33.7	(-478.8, 94.5)
EGL Related to any of 10 Assay-identified HPV Types	1,943	9	5,020.4	0.2	1,937	18	4,989.5	0.4	50.3	(-16.5, 80.3)
HPV 31-Related EGL	1,943	0	5,037.8	0.0	1,937	5	5,004.1	0.1	100	(-8.4, 100)
HPV 33-Related EGL	1,943	1	5,037.8	0.0	1,937	3	5,007.6	0.1	66.9	(-312.7, 99.4)
HPV 35-Related EGL	1,943	1	5,036.2	0.0	1,937	0	5,011.1	0.0	NA	NA
HPV 39-Related EGL	1,943	0	5,037.8	0.0	1,937	1	5,010.6	0.0	100	(-3778.9, 100)
HPV 45-Related EGL	1,943	0	5,037.8	0.0	1,937	1	5,009.4	0.0	100	(-3778.0, 100)
HPV 51-Related EGL	1,943	1	5,035.7	0.0	1,937	4	5,008.3	0.1	75.1	(-151.3, 99.5)
HPV 52-Related EGL	1,943	3	5,031.3	0.1	1,937	4	5,003.0	0.1	25.4	(-340.8, 89.1)
HPV 56-Related EGL	1,943	2	5,033.0	0.0	1,937	1	5,010.7	0.0	-99.1	(-11647.1, 89.6)
HPV 58-Related EGL	1,943	0	5,037.8	0.0	1,937	3	5,005.4	0.1	100	(-140.4, 100)
HPV 59-Related EGL	1,943	2	5,035.2	0.0	1,937	1	5,009.5	0.0	-99.0	(-11639.4, 89.6)
EGL Not Related to any of 14 Assay-identified HPV Types	1,943	8	4,875.4	0.2	1,937	12	4,792.0	0.3	34.5	(-74.3, 76.8)

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 lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

The analysis of the clearance of HPV DNA among subjects who were PCR positive at baseline (therapeutic efficacy) did not confirm such effect.

The EGL, persistent infection and detection of HPV DNA at one or more visits stratified by baseline serostatus and PCR status analysis did not confirm efficacy in non S-/PCR- populations.

Immunogenicity Results

Protocol 020

The GMTs of anti HPV antibodies against each vaccine type HPV (6/11/16/18) peaked at Month 7, that is, one month after the third and final dose of the vaccine. This was followed by a decline to levels which were still some folds over the baseline values and these were then maintained to Month 36 (Figure 1).

At 36 months, the seroconversion rates (anti HPV 6/11/16/18 cLIA[5] antibody at the specified cut offs) were 88.9%, 94.0%, 97.9% and 57.0% for HPV 6, 11, 16 and 18, respectively. The GMTs, stratified by baseline serostatus/PCR status, are provided in Tables 8, 9 and 10.

[5] cLIA=competitive Luminex-based Immunoassay

Figure 1. Protocol 020. Longitudinal plots of anti-HPV geometric mean titers in vaccinated subjects (Per Protocol Immunogenicity Population).

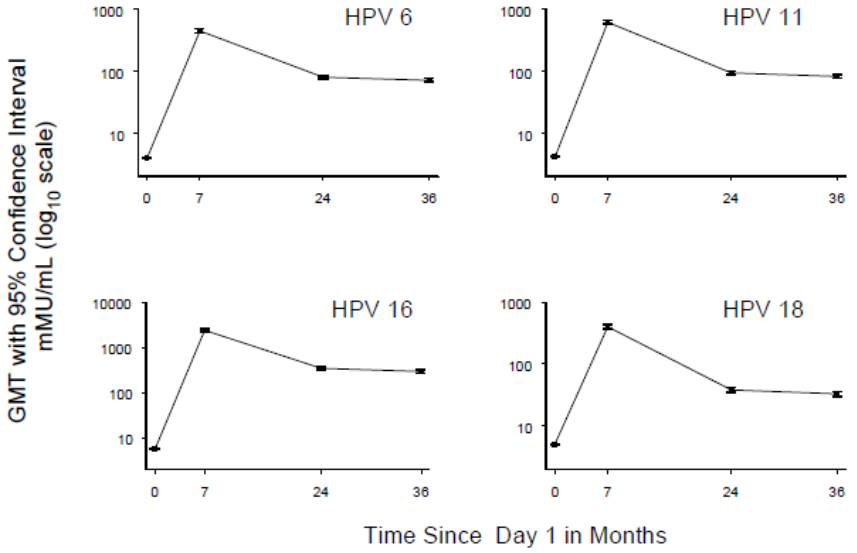


Table 8. Protocol 020. Summary of anti-HPV geometric mean titers by Vaccination group (Seropositive/PCR negative population).

Assay (cLIA) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	59	55.6	(45.5, 67.9)	65	56.9	(47.0, 68.8)
Month 7	45	557.4	(355.9, 872.9)	49	43.1	(28.0, 66.2)
Month 24	42	284.0	(208.2, 387.4)	46	39.1	(29.0, 52.6)
Month 36	32	209.9	(148.7, 296.3)	33	40.5	(28.9, 56.9)
Anti-HPV 11						
Day 1	18	53.4	(33.3, 85.8)	23	49.2	(32.4, 74.9)
Month 7	15	1,895.2	(1,005.7, 3,571.4)	18	34.3	(19.2, 61.1)
Month 24	13	544.3	(292.6, 1,012.4)	16	26.7	(15.3, 46.8)
Month 36	8	638.5	(268.5, 1,518.5)	13	24.6	(12.5, 48.6)
Anti-HPV 16						
Day 1	26	46.3	(30.5, 70.3)	33	69.1	(47.7, 100.1)
Month 7	19	1,207.9	(512.2, 2,848.4)	29	48.9	(24.4, 97.9)
Month 24	17	631.7	(281.9, 1,415.2)	26	66.2	(34.5, 127.2)
Month 36	12	281.9	(104.0, 764.0)	19	66.8	(30.3, 147.6)
Anti-HPV 18						
Day 1	21	74.6	(47.9, 116.1)	14	66.9	(38.9, 115.0)
Month 7	16	550.8	(299.0, 1,014.5)	12	36.8	(18.2, 74.5)
Month 24	16	132.9	(67.7, 261.1)	11	33.8	(15.0, 76.4)
Month 36	12	83.9	(41.1, 171.4)	7	15.1	(<10, 38.6)

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 1 injection.

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; 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.

Table 9. Protocol 020. Summary of anti-HPV geometric mean titers by Vaccination group (Seropositive/PCR positive population).

Assay (cLIA) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	19	83.3	(54.1, 128.2)	26	75.1	(51.9, 108.5)
Month 7	15	352.5	(152.8, 813.1)	17	60.9	(27.8, 133.5)
Month 24	13	298.9	(144.2, 619.4)	15	56.7	(28.7, 111.6)
Month 36	8	159.6	(60.9, 418.0)	8	71.0	(27.1, 185.9)
Anti-HPV 11						
Day 1	6	113.5	(37.7, 341.6)	6	58.3	(19.4, 175.5)
Month 7	1	1,103.0	(23.9, 50,886.6)	4	18.4	(<8, 125.2)
Month 24	4	260.9	(76.0, 895.6)	2	148.1	(25.9, 847.4)
Month 36	2	450.3	(63.4, 3,199.5)	3	85.7	(17.3, 424.8)
Anti-HPV 16						
Day 1	19	117.7	(70.3, 197.1)	13	94.2	(50.5, 175.7)
Month 7	12	2,142.2	(698.6, 6,568.6)	9	125.7	(34.5, 458.5)
Month 24	12	844.2	(490.6, 1,452.5)	12	80.7	(46.9, 138.9)
Month 36	9	704.3	(268.8, 1,845.3)	7	74.5	(25.0, 222.0)
Anti-HPV 18						
Day 1	6	81.7	(35.1, 189.9)	3	34.6	(10.5, 114.2)
Month 7	4	162.8	(<10, 6,830.7)	1	20.0	(<10, 35,204.0)
Month 24	4	117.6	(41.5, 333.3)	2	13.4	(<10, 58.5)
Month 36	4	84.3	(40.3, 176.6)	1	< 10	(<10, 21.9)

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 1 injection.

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; 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.

Table 10. Protocol 020. Summary of anti-HPV geometric mean titers by Vaccination group (Seronegative/PCR positive population).

Assay (cLIA) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	73	< 7	(<7, <7)	62	< 7	(<7, <7)
Month 7	50	331.8	(220.9, 498.3)	44	10.5	(<7, 16.2)
Month 24	50	94.5	(67.4, 132.6)	33	9.9	(<7, 15.1)
Month 36	40	73.5	(51.1, 105.9)	31	9.3	(<7, 14.1)
Anti-HPV 11						
Day 1	17	< 8	(<8, <8)	19	< 8	(<8, <8)
Month 7	11	237.5	(89.4, 630.8)	15	< 8	(<8, 16.4)
Month 24	11	156.7	(78.7, 312.0)	13	8.5	(<8, 16.0)
Month 36	7	99.1	(37.4, 262.4)	12	< 8	(<8, 14.6)
Anti-HPV 16						
Day 1	73	< 11	(<11, <11)	95	< 11	(<11, <11)
Month 7	52	2,427.9	(1,801.4, 3,272.2)	75	< 11	(<11, <11)
Month 24	50	357.5	(243.6, 524.7)	73	11.9	(<11, 16.4)
Month 36	39	337.0	(236.2, 480.9)	51	< 11	(<11, 13.5)
Anti-HPV 18						
Day 1	50	< 10	(<10, <10)	52	< 10	(<10, <10)
Month 7	33	317.9	(194.3, 520.2)	35	< 10	(<10, 14.4)
Month 24	32	53.0	(33.5, 83.9)	36	< 10	(<10, 13.7)
Month 36	24	50.8	(32.8, 78.7)	30	< 10	(<10, 11.4)

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 1 injection.

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; 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.

The GMTs, stratified by HM and MSM populations, are provided in Tables 11 and 12.

Table 11. Protocol 020. Summary of anti-HPV geometric mean titers for HM subjects by Vaccination group (HM Per Protocol Immunogenicity population).

Assay (cLIA) Study time	qHPV Vaccine (N=1,726) n	GMT (mMU/mL)	95% CI	Placebo (N=1,731) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	978	< 7	(<7, <7)	988	< 7	(<7, <7)
Month 7	978	473.9	(446.8, 502.7)	988	< 7	(<7, <7)
Month 24	851	81.6	(77.4, 86.1)	845	< 7	(<7, <7)
Month 36	792	73.4	(69.2, 77.8)	780	< 7	(<7, <7)
Anti-HPV 11						
Day 1	978	< 8	(<8, <8)	987	< 8	(<8, <8)
Month 7	978	651.5	(620.7, 683.7)	987	< 8	(<8, <8)
Month 24	851	94.9	(90.1, 100.0)	844	< 8	(<8, <8)
Month 36	792	83.8	(79.4, 88.5)	779	< 8	(<8, <8)
Anti-HPV 16						
Day 1	999	< 11	(<11, <11)	989	< 11	(<11, <11)
Month 7	999	2,622.1	(2,484.9, 2,766.9)	989	< 11	(<11, <11)
Month 24	869	355.7	(335.8, 376.7)	841	< 11	(<11, <11)
Month 36	811	309.3	(291.5, 328.1)	777	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,032	< 10	(<10, <10)	1,043	< 10	(<10, <10)
Month 7	1,032	439.3	(415.7, 464.3)	1,043	< 10	(<10, <10)
Month 24	897	39.4	(36.8, 42.2)	882	< 10	(<10, <10)
Month 36	836	33.9	(31.6, 36.4)	813	< 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 1 injection.

n = Number of subjects contributing to the analysis.

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

Table 12. Protocol 020. Summary of anti-HPV geometric mean titers for MSM subjects by Vaccination group (MSM Per Protocol Immunogenicity population).

Assay (cLIA) Study time	qHPV Vaccine (N=299) n	GMT (mMU/mL)	95% CI	Placebo (N=299) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	114	< 7	(<7, <7)	120	< 7	(<7, <7)
Month 7	114	274.3	(222.5, 338.3)	120	< 7	(<7, <7)
Month 24	90	64.6	(53.7, 77.8)	104	< 7	(<7, <7)
Month 36	55	49.2	(37.3, 64.8)	54	< 7	(<7, <7)
Anti-HPV 11						
Day 1	114	< 8	(<8, <8)	120	< 8	(<8, <8)
Month 7	114	431.3	(348.2, 534.2)	120	< 8	(<8, <8)
Month 24	90	91.6	(76.7, 109.4)	104	< 8	(<8, <8)
Month 36	55	66.2	(51.8, 84.6)	54	< 8	(<8, <8)
Anti-HPV 16						
Day 1	136	< 11	(<11, <11)	138	< 11	(<11, <11)
Month 7	136	1,271.6	(996.0, 1,623.4)	138	< 11	(<11, <11)
Month 24	110	255.5	(219.5, 297.4)	110	< 11	(<11, <11)
Month 36	66	153.0	(116.1, 201.5)	62	< 11	(<11, <11)
Anti-HPV 18						
Day 1	142	< 10	(<10, <10)	159	< 10	(<10, <10)
Month 7	142	212.1	(170.0, 264.6)	159	< 10	(<10, <10)
Month 24	114	31.4	(25.9, 38.0)	128	< 10	(<10, <10)
Month 36	69	24.7	(19.0, 32.1)	69	< 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 1 injection.

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; MSM = Men having sex with men; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Evaluator's comment

The MSM substudy was pre specified and appropriately designed. The results support prophylactic efficacy (77.5%) against HPV 6/11/16/18 related AIN (Grades 1/2/3) in a MSM population who is seronegative at baseline, remain PCR negative to these serotypes and complete the 3 course vaccination with Gardasil at zero, 2 and 6 months. The efficacy against high grade AIN (Grades 2/3) which is more appropriate surrogate for progression to malignancy was also similar (74.9%) in the same population.

There was no occurrence of AC in either group at 36 months. Although this likely represents relatively short follow up period compared to the expected induction time for a malignant change, protection against AC cannot be claimed at this stage. It is understood that an extended follow up (10 years) of the participants in this trial has been planned.

The final results for the Protocol 020 controlled were included. The prophylactic efficacy against HPV 6/11/16/18 related EGL was observed to be 90.6% in adolescent and adult men (HM and MSM) who were baseline seronegative, remained PCR negative and completed the full course of vaccination.

In Protocol 020, the prophylactic efficacy against HPV 6/11/16/18 related penile/perineal/perianal intraepithelial neoplasia (PIN) (Grades 2/3) could not be confirmed (Tables 5 and 6) due to the low incidence.

The prophylactic efficacy of the vaccine in non S-/PCR- population was also not confirmed, neither overall or in the MSM substudy.

The immune response showed similar kinetics with respect to the four vaccine antigens; showing a peak after completion of vaccination and then a levelling off, with levels above baseline and seropositive cut offs at 24-26 months. The response was similar regardless of baseline serostatus or sexual orientation. The seroconversion rates were similar to those seen previously in studies in females.

Note that the immunological correlates of protection against HPV are not known. The HPV vaccine studies have not been able to determine the protective levels of antibodies due to the low incidence of events of interest.

The immune response was most robust against HPV 16 and mildest against HPV 18.

Safety

A cumulative total of 1346/2020 (69.2%) Gardasil recipients and 1252/2029 placebo recipients experienced one or more adverse event (AE).

The proportion experiencing injection site AEs was 60.1% and 53.7% in the two groups, respectively.

The proportion experiencing systemic AEs was 31.7% and 31.9% in the two groups, respectively.

Eight Gardasil subjects (0.4%) experienced serious AEs (SAEs) compared to 11 placebo subjects (0.6%). Three fatalities were reported in the Gardasil group (0.2%) and 10 fatalities were reported in placebo subjects (0.6%) and these were not considered treatment related.

Five Gardasil subjects (0.3%) and 14 placebo (0.6%) subjects discontinued the study due to an AE.

During Days 1-5 after any vaccination, 59.9% Gardasil subjects and 53.6% placebo subjects experienced an injection site AEs. Injection site pain (57.2% and 50.8%,

respectively) and injection site erythema (15.6% and 14.1%, respectively) were the most common local AEs in both groups.

During Days 1-15 after any vaccination, 31.7% Gardasil subjects and 31.4% placebo subjects experienced one or more systemic AEs. Headache (9.2% and 10.6%, respectively) and pyrexia (6.2% and 6.4%, respectively) were the most common systemic AEs in both groups (Table 13).

Table 13. Protocol 020. 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	616	(31.7)			613	(31.4)		
Number (%) of Subjects with no systemic adverse experience	1329	(68.3)			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	**161**	**(8.3)**	**110**	**(5.7)**	**169**	**(8.7)**	**122**	**(6.3)**
Fatigue	13	(0.7)	6	(0.3)	19	(1.0)	15	(0.8)
Pyrexia	120	(6.2)	93	(4.8)	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)**	**137**	**(7.0)**
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)**
Oropharyngeal 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.

Adverse experience terms are from MedDRA Version 12.0

No other significant safety outcomes were reported in this trial.

Evaluator's comment

No unexpected safety signal was reported in the final report of Protocol 020.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Clinical Evaluator Question

It was not clear how 'persistent infection' was defined. The sponsor was requested to clarify this measure both in the overall Protocol 020 population and the MSM substudy.

Sponsor's Answer

The sponsor provided the definition of HPV 6, 11, 16, 18 related persistent infection based on PCR detection of at least one common gene for the same HPV type in swab or biopsy samples collected at least 6 months apart.

Clinical Summary and Conclusions

HPV is a tissue specific, DNA virus that infects epithelial cells. It is highly prevalent with sub clinical infections often occur early on with onset of sexual activity. Most infections clear spontaneously and long term cytological changes are likely associated with persistent infection only.

The estimates of prevalence of HPV in men are described n Table 14 below.

Table 14. Prevalence of HPV in men

HPV Type	Prevalence of HPV by PCR	
	Any genital site	
	HM[6]	MSM[7]
6/11/16/18	19%	31%
16/18	15%	19%
16	13%	14%
18	3%	8%
6/11	5%	18%
6	5%	13%
11	0%	7%

Estimates of prevalence in females are not available and generally anal intercourse among heterosexual men and women is not controlled for in the studies.

Approximately 88-94% anal cancers test positive for HPV DNA with HPV 16 being the most common followed by HPV 18[8].

The Protocol 020 successfully demonstrated prophylactic efficacy of Gardasil (given as a course of 3 separate injections at 0, 2 and 6 months) in HPV naive population of men. The observed estimate of VE against EGL was 90.6% (95% CI 70.1%, 98.2%) in HPV naive men. The observed estimate of VE against AIN was 77.5% (95% CI 39.6%, 93.3%) in HPV naive MSM population. Anal Cancer had not been reported in any group by the end of 36 months of controlled observation. The design was adequate and the estimates were considered

[6] Journal of Infectious Diseases 2008;197:1676-84

[7] Journal of Infectious Diseases 2011;203:66-74

[8] Vaccine 24S3 (2006) S3/1–S3/10

reliable for these outcomes in the specified population. There were no new safety signals in this trial.

The sponsor is proposing expansion of the current indication with extrapolation of effect to men and women. The clinical evaluator accepted that pathogenesis, clinical presentation and progression of HPV related anal disease can be expected to be similar across genders and sexual orientation.

However, the following points were noted:

(1) The currently approved indication(s) for Gardasil in men and women are already broad and capture the intended use of this vaccine based on the results observed in Protocol 020. No change in the indications as currently approved was considered necessary.
(2) An 'at risk population' has been identified and estimate of vaccine efficacy has been determined. The risk of anal cancer in MSM is stated to be as high as 60 times that in the general population[9]. It will therefore be appropriate to identify information this in the therapeutic indication.
(3) The observation time in the study was too short to distinguish between vaccinated and non vaccinated cohorts with respect to progression to anal cancer. Hence, usage recommendation should relate to protection against AIN and should also identify the intended population, that is, HPV naive MSM.

Recommendation

Based on comments above, the clinical evaluator recommended the extension of indication as follows:

> 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.
>
> *There is also evidence of efficacy in prevention of HPV 6, 11, 16 and 18 related anal intraepithelial neoplasia based on a substudy in men who have sex with men and were naive to these HPV types at baseline (see Clinical Trials).*
>
> *Immunogenicity studies have been conducted to link efficacy in females and males aged 16 to 26 years to the younger population.

V. Pharmacovigilance Findings

There was no Risk Management Plan (RMP) submitted with this application. The Office of Product Review (OPR) decided that a RPM was not required because the application sought to extend the indication for use in the same population for which a RMP evaluation and approval had previously been undertaken.

VI. Overall Conclusion and Risk/Benefit Assessment

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

[9] Journal of Infectious Diseases 2011;203:66-74

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Clinical data only were submitted with the current Australian submission. The clinical data for this submission are based on Protocol 020. Protocol 020 was a multicentre, randomised, placebo controlled, double blind, parallel group study assessed efficacy, safety and immunogenicity of Gardasil (qHPV). In this study, 4065 male subjects in the age range of 15-26 years, with heterosexual men (HM) and male sex with men (MSM) subgroups, were randomised to receive qHPV or placebo in a 1:1 ratio. The Month 7 and Month 24 results for Protocol 020 have been submitted previously to the TGA and formed the basis for the approval of qHPV for prevention of external genital lesions and infections in males. The data submitted with the current Australian submission includes results of substudy of men who have sex with men (MSM) within Protocol 020. MSM have a higher risk of AIN/AC than heterosexual men.

The objective of the MSM substudy within Protocol 020 was to determine prophylactic effect of the vaccine on incidence of HPV 6,11,16,18 related AIN or AC. A total of 602 MSM aged 16 to 26 years participated in the substudy. The duration of follow up for each participant was 36 months. The sponsor's report provided the final report of controlled data at 36 months.

The definition of the AIN/AC efficacy outcome was the combined incidence of HPV 6,11,16 or 18 related AIN or Anal Cancer in MSM who were seronegative at baseline and PCR negative to relevant HPV types from Day 1 through Month 7. Results in an ITT population are provided as secondary outcomes. Additional procedures for MSM subjects included intra anal swab for HPV PCR and anal cytology at Day 1 and then approximately 6 monthly through to Month 36. Subjects also underwent digital rectal examination and, if indicated, anoscopy. High resolution anoscopy was scheduled according to a prespecified algorithm based on anal cytology results.

The PPE Population comprised 418 of 602 randomised participants (69%) for the MSM objective (AIN/AC).

Efficacy results in the MSM substudy are described in clinical evaluation report (CER).

For the primary efficacy endpoint based on the PP population the incidence rate of HPV 6/11/16/18 related AIN/AC was 1.3/100 PY in the Gardasil group compared to 5.8/100 PY in the placebo group representing a VE of 77.5% ($p < 0.001$) and a 95% CI of 39.6% to 93.3%. There were 5 cases of HPV 6/11/16/18 AIN/AC in the qHPV group and 24 such cases in the placebo group. The VE (6/11/16/18) against AIN (Grade 2 or worse) was 74.9% (95% CI: 8.8%, 95.4%) using the PPE population data. In the qHPV group there were 3 cases of AIN Grade 2 or worse and in the placebo group there were 13 cases of AIN Grade 2 or worse. There were no reports of AC in either group at the 36 month timepoint.

Using the Full Analysis Set (ITT) the incidence rates were 6.3 and 12.6 per 100 PY in the two groups, respectively, representing a VE of 50.3% with a 95% CI of 25.7% to 67.2%. For the FAS population, the VE (6/11/16/18) against AIN (Grade 2 or worse) was and 54.2% (95% CI: 18.0%, 75.3%).

The incidence rate of intra anal persistent infection (HPV Types 6/11/16/18) was 0.5 and 10.2 per 100 PY in the Gardasil and placebo groups, respectively representing VE of 94.9% with a 95% CI of 80.4% to 99.4% using the PPE population data.

The incidence rate of HPV 6/11/16/18 persistent infection was 1.3 and 10.8 per 100 PY in the Gardasil and placebo groups, respectively, representing a VE of 88.0% with a 95% CI of 69.5% to 96.3% using the PPE population data. The VE was 52.0% (95% CI 34.2%, 65.3%) using the FAS population data.

The CER presented the 36 month efficacy results for the full study population in Protocol 020 and also immunogenicity results to Month 36.

A cumulative total of 1346/2020 (69.2%) qHPV recipients compared to 1252/2029 placebo recipients experienced one or more AEs. The proportions experiencing injection site AEs was 60.1% and 53.7% in the two groups, respectively. The proportions experiencing systemic AEs were 31.7% and 31.9% in the two groups, respectively.

Eight qHPV subjects (0.4%) and 11 placebo subjects (0.6%) experienced SAEs. Three fatalities were reported in the qHPV group (0.2%). Ten fatalities were reported in the placebo group (0.6%) and these were not considered treatment related.

Five Gardasil subjects (0.3%) and 14 placebo (0.6%) subjects discontinued the study due to an AE.

Clinical evaluator's Conclusion

The clinical evaluator (CE) considered the MSM substudy was appropriately designed with prespecified endpoints. The results support prophylactic efficacy (77.5%) against HPV 6/11/16/18 related AIN (Grades 1/2/3) in MSM population who is seronegative at baseline, remain PCR negative to these serotypes and complete the 3 course vaccination with Gardasil at zero, 2 and 6 months. The efficacy against high grade AIN (Grades 2/3) which is more appropriate surrogate for progression to malignancy was also similar (74.9%) in the same population. No unexpected safety signal was reported in this final report of Protocol 020.

The CE concluded that currently approved indications for Gardasil in men and women are broad and capture the intended use of the vaccine based on results observed in Protocol 020. The CE considered that no change in the currently approved indications was necessary. The CE noted that the observation time in the study was too short to distinguish between vaccinated and non-vaccinated cohorts with respect to progression to anal cancer. Hence, usage recommendation should relate to protection against Anal Intraepithelial Neoplasia and should also identify the intended population, that is, HPV naive MSM. The CE recommends an extension of indications worded

> "*There is also evidence of efficacy in prevention of HPV 6, 11, 16 and 18 related anal intraepithelial neoplasia based on a substudy in men who have sex with men and were naive to these HPV types at baseline (see Clinical Trials)".*

Risk Management Plan

There was no Risk Management Plan (RMP) submitted with this application. The Office of Product Review (OPR) decided that a RPM was not required because the application sought to extend the indication for use in the same population for which a RMP evaluation and approval had previously been undertaken.

Risk-Benefit Analysis

Delegate Considerations

The clinical evaluator (CE) commented that approximately 88-94 % of anal cancers test positive for HPV DNA.

The Delegate accepted the sponsor's argument that efficacy against AIN Grades 2/3 is an appropriate surrogate marker for progression to anal cancer. In Protocol 020, the

demonstrated VE (6/11/16/18) against AIN (Grades 2/3 or worse) was 74.9% (95% CI 8.8%, 95.4%) using PPE population data. The wide confidence intervals reflect the small number of AIN Grades 2/3 cases in Protocol 020. In Protocol 020, a substantial proportion of AIN cases were AIN Grade 1, which may regress. Demonstration of efficacy of qHPV against CIN Grades 2/3 was considerably more robust with much larger numbers of study participants followed for longer time periods.

An analysis of data from placebo arms of the Gardasil studies shows the likelihood ratio of developing 16/18 related AIN Grades 2/3 given persistent HPV 16/18 infection is 6.7% (95% CI 3-1-11.1) in 16 to 26 year old MSM which is similar to the likelihood of developing 16/18 related CIN Grades 2/3 given persistent HPV 16/18 infection (7.2; 95% CI: 6.4-8.2) in 16 to 26 year old females. The negative likelihood ratio of developing AIN Grades 2/3 given no persistent HPV 16/18 infection was 0.34 (95% CI <0.01-0.76) whereas the negative likelihood ratio of developing CIN Grades 2/3 given no persistent HPV 16,18 infection was 0**.**

Taken together with other sponsor arguments, the Delegate considered that the demonstrated efficacy of 4vHPV against AIN Grades 2/3 in the MSM population can be generalised to males and females regardless of sexual orientation.

Delegate's Proposed Action

The Delegate proposed to register the extension of indication for quadrivalent human papillomavirus (Types 6,11,16 7 18) (qHPV) recombinant vaccine, Gardasil, as follows:

> *Gardasil is indicated in females aged 9 through 45 years * for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).*
>
> *Gardasil is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV Types 6, 11, 16, 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.*

The advice of ACSM was requested particularly on the wording of the extension of indications the Delegate proposed to accept compared to indications recommended in the clinical evaluation report.

Response from Sponsor

Clinical evaluation

The sponsor has provided a response to conclusions made in the clinical evaluation report (CER). The sponsor (MSD) wishes to pursue the originally proposed indications on the basis that high grade AIN is an appropriate surrogate marker for cancer. The sponsor comments on the strong rationale for use of surrogate outcomes based on what is known for HPV and neoplasias in cervical, vulval and vaginal cancers. A body of natural history, anatomical and pathological data provide evidence that HPV is the initial event that can lead to persistent infection, high grade AIN and ultimately anal cancer. The evidence was summarised in a briefing document submitted FDA on 17 November 2010.

MSD also argued that effect of qHPV in the MSM population may be extrapolated to males and females. Pathogenesis, clinical presentation and progression of HPV related anal disease can be expected to be similar across genders and sexual orientation. The sponsor provided evidence that heterosexual males and females, not just MSM, are at risk for acquiring anal HPV infections and also acquire these infections at a substantial rate.

Studies have shown anal intercourse is not required for acquisition of anal HPV infection or development of anal cancer in men and women. The anatomical location, histologic and molecular characteristics of HPV related anal cancer are the same in men and women, also supporting the same role of HPV in developing anal disease regardless of gender.

MSD does not consider a HPV naive population to be the appropriate intended population. Including males rather than MSM in the indication is non discriminatory to sexual preferences and enables vaccination prior to onset of sexual activity.

Pre ACPM Response

The sponsor noted that there were no outstanding efficacy or safety issues pertaining to this proposed extension of indications. The sponsor also noted that the Delegate has accepted that:

1. high grade anal intraepithelial neoplasia (AIN Grades 2/3) is an appropriate surrogate marker for progression to anal cancer, and
2. the demonstrated efficacy of qHPV against AIN Grades 2/3 in the MSM population can be generalised to males and females regardless of sexual orientation.

The sponsor noted that the Delegate is seeking the advice of the ACPM particularly on the wording of the extension of indications, as proposed above.

The purpose of this response document is

- to outline the burden of anal cancer and pre cancers and the limitations of currently available interventions;
- emphasise the importance of having the approved indications accurately reflect the intended use and benefit of the vaccine;
- summarise the efficacy of Gardasil;
- reiterate the relevance and importance of generalising Gardasil data to both males and females irrespective of sexual orientation; and
- reaffirm the safety profile of the vaccine.

There is a substantial and increasing burden of anal cancer in men and women with limited options for intervention.

Almost all (approximately 88-94%) anal cancer cases test positive for HPV DNA, with HPV 16 and HPV 18 being the most common associated types.

Data from Europe, the USA and Australia consistently show that the incidence of anal cancer has increased substantially in men and women over the past 30 to 50 years. In most settings, the incidence of anal cancer is higher in women than in men. In Australia, the incidence of anal cancer increased significantly in both sexes from less than 1 per 100,000 in 1982 to around 1.5 per 100,000 in 2005, when a total of 176 women and 149 men were diagnosed with anal cancer.[10]

A large body of natural history, anatomical and pathological data provides evidence that HPV infection is the initial event that can lead to persistent infection, high grade AIN and ultimately, malignant transformation to invasive anal cancer. Treatment of high grade AIN however, while currently performed in high risk populations, has not been prospectively proven to eliminate anal cancer development. For those who progress from high grade

[10] AE Grulich *et al*, "Cancers attributable to human papillomavirus infection", Sexual Health (CSIRO), no. 7, pp. 244-252.

AIN to malignancy, treatment (which may include radiation, chemotherapy and/or surgery depending on the size and spread of the cancer) is associated with significant morbidity and long term sequelae.

Although public health authorities recognise that anal cancer is an important entity for which screening should be considered, there is currently no standardised screening method for anal disease. The limitations of cytologic screening for anal pre malignant and malignant disease in a generally healthy population was demonstrated during the sponsor's study when a number of AIN cases were diagnosed at mandatory anoscopies conducted at the end of the study.

> *A broad strategy of vaccinating males and females prior to sexual debut and potential*
>
> *HPV infection, that is, during the adolescent years, is an effective and optimal approach to anal cancer prevention.*

It is important that the Indications accurately reflect the intended use and benefit of the vaccine.

The current indications of Gardasil do not include the prevention of anal infection, AIN and anal cancer. Furthermore, identification of a sub population of males who have sex with men (MSM) in adolescents prior to sexual debut and potential exposure to HPV poses practical and ethical problems.

Without the requested new indications, the use of Gardasil to prevent AIN and anal cancer in males and females cannot be recommended to healthcare professionals. Failure to extend the indications may impact the accessibility and acceptability of the vaccine to some people, since there are sections of the populace at risk of anal cancer who would not present for vaccination under the current limited indications.

Males and females vaccinated with Gardasil will be afforded the knowledge that vaccination can protect against HPV related genital, cervical and anal diseases.

> *Approval of MSD's application to extend the wording of the Indications to include prevention of anal cancer, precancerous or dysplastic lesions regardless of gender and sexual orientation will accurately reflect the product's intended use.*

Efficacy of Gardasil qHPV vaccine in prevention of anal cancer, precancerous or dysplastic lesions has been accepted.

The clinical evaluator and the Delegate have agreed with the sponsor that high grade AIN is an appropriate surrogate marker for anal cancer. Therefore, prophylactic efficacy against AIN Grades 2/3 is a similar marker for prevention of anal cancer.

The analysis focuses on the substudy involving 602 MSM in the Protocol 020 study, since MSM have a significantly elevated risk of anal infection, AIN and anal cancer. The results from this substudy support the vaccine's efficacy against high grade AIN (74.9% in the PPE population).

There is already a strong rationale for the use of the surrogate outcomes based on what is known for HPV infection and neoplasias in cervical, vulvar and vaginal cancers. The relationships between persistent HPV infection, cervical intraepithelial neoplasia (CIN) and cervical cancer have been clearly established.

Although HPV associated anal cancers have not been studied as extensively as cervical cancer, all the evidence points to similar biological processes. There are notable similarities between the anatomy of the anus and cervix; biological, histological and

molecular characteristics between AIN and CIN; similarities in etiological fractions of anal and cervical cancer caused by HPV; the proportion of AIN and CIN that are HPV related; and risk factors for both anal and cervical disease.

Protocol 020 has demonstrated that in addition to high efficacy in males against external genital lesions, Gardasil is also efficacious against HPV related AIN (Grades 1/2/3), has statistically significant efficacy against high grade AIN, and consequently anal cancer.

> *The data supports the potential extended benefits of Gardasil to address the important unmet medical need for prevention of anal HPV-related cancer and precancers, given its similarities to cervical cancer prevention.*

Efficacy in MSM can be generalised to males and females regardless of sexual orientation.

Although the Protocol 020 substudy was conducted in MSM, there is no evidence to indicate that the natural history and biology of anal HPV associated disease in MSM differs from that in heterosexual men and women in the general population.

HPV is one of the most common sexually transmitted infections and it is well documented that anal intercourse is not required for anal HPV acquisition. All sexually active individuals, regardless of gender or sexual orientation, are potentially at risk for anal HPV infection and subsequent disease.

Risk factors for high grade AIN and anal cancer are not specific to either gender or sexual preference. These factors include: higher number of sex partners, history of anal intercourse, tobacco use, HPV associated anogenital infections or diseases, sexually transmitted diseases and immunosuppression related to HIV seropositivity or organ transplantation.

The risk of anal HPV related infection and disease is not limited to HPV naïve MSM. Anal infection, in particular HPV type 16 positive, is common and can lead to cancer in heterosexual men and women, as well as MSM. The predominant HPV types that cause anal cancer are the same in men and women. The pathogenesis, histopathological and clinical presentation of HPV related anal disease is identical across genders and populations (women, heterosexuals and MSM).

An analysis of data from the placebo arms of the Gardasil studies shows the likelihood ratio of persistent HPV16/18 infection in the 16 to 26 year old MSM population developing into HPV16/18 related high grade AIN to be 6.7%. This is very similar to the likelihood ratio of 7.2% for persistent HPV16/18 infection developing into HPV16/18-related CIN Grades 2/3 in 16 to 26 year old females. The negative likelihood ratios of high grade AIN or CIN given no persistent HPV16/18 infection was similar in the MSM and female populations, respectively.

> *Extrapolation of Gardasil's efficacy against AIN 2/3 in the MSM population to males and females regardless of sexual orientation is justified.*

The safety of Gardasil qHPV vaccine is well established.

The clinical trial safety data, passive post licensure safety surveillance and active controlled evaluations of selected conditions of clinical interest continue to support the overall positive safety profile of Gardasil.

> *No unexpected safety signals have been reported in the final report of Protocol 020.There are no other outstanding safety issues.*

Conclusion

The sponsor therefore supported the Delegate's proposal to accept the extension of indications for Gardasil as follows:

> *Gardasil is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).*
>
> *Gardasil is indicated in males aged 9 through 26 years for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by 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.*

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy and Safety

The ACPM agreed with the Delegate that the submission provided sufficient evidence of efficacy and safety to support the broader indication proposed. The ACPM supported the Delegate that limiting the use to patients in the proven HPV naïve population, or by sexual orientation, is not appropriate in view of the evidence of the larger population benefit.

Indication

The ACPM considered this product to have a positive benefit risk profile for the indication of:

> *Gardasil is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16 and 18 (which are included in the vaccine).*
>
> *Gardasil is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV Types 6, 11, 16 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.*

Conditions of Registration:

The ACPM agreed with the conditions proposed by the Delegate.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Gardasil would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approve 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 indications.

The full indications are now read as:

> Gardasil is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).
>
> Gardasil is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV Types 6, 11, 16, 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.

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.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #

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 aluminium-containing adjuvant (amorphous aluminium hydroxyphosphate sulfate, or AAHS). The quadrivalent HPV VLP vaccine is prepared by combining the adsorbed VLPs of each HPV type, the aluminium-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 aluminium (as amorphous aluminium hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of 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 study, Protocol 020, evaluated GARDASIL in 4055 males, including a subset of 598 men (GARDASIL = 299; placebo = 299) who self-identified as having sex with men (MSM population). Together, these studies evaluated 24,358 females 16 through 45 years of age 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, 4.0 and 2.9 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. Among 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.

†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 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.

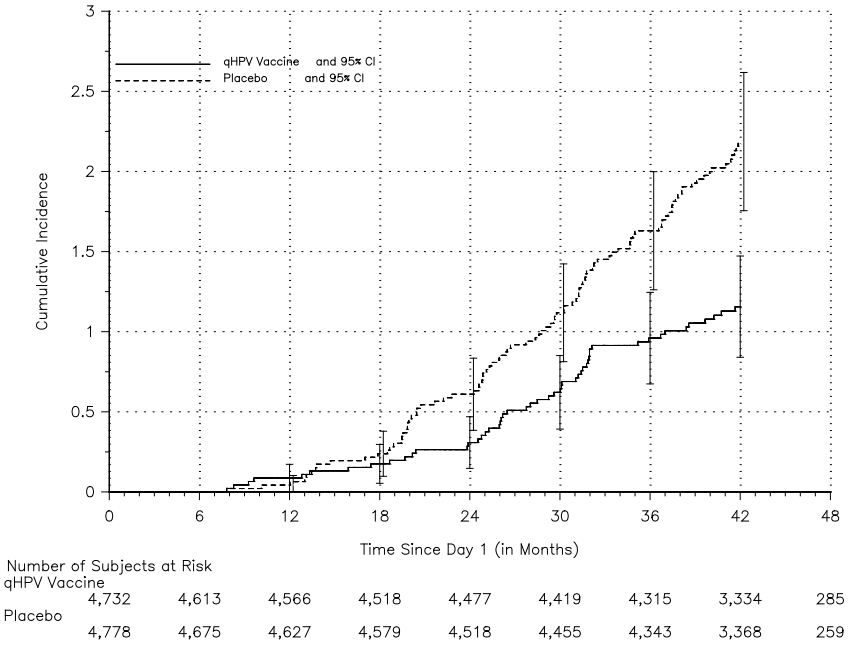
Subjects, who had early HPV infection at the time of enrolment and who received GARDASIL did not show a statistically significant reduction of CIN or AIS compared to placebo. Estimated vaccine efficacy was 21.6% (95% CI: <0.0%, 42.1%). Early infection was defined as infection with a vaccine HPV type 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	1,601	10*	1,599	86	88.7 (78.1, 94.8)
HPV 16- or 18-related CIN (any grade), Persistent Infection, or EGL	1,587	8*	1,571	51	84.7 (67.5, 93.7)
HPV 6- or 11-related CIN (any grade), Persistent Infection, or EGL	1,316	2	1,316	38	94.8 (79.9, 99.4)
HPV 16/18-related Pap Diagnosis of ASC-US Positive for High-risk HPV	1,565	1	1,557	27	96.3 (77.7, 99.9)

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

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 (N = 2025)		AAHS Control (N = 2030)		% Efficacy (95% CI*)
	N	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (<0.0, 100.0)
PIN 2/3	1394	0	1404	2	100.0 (<0.0, 100.0)
Persistent Infection**					
HPV 6, 11, 16, or 18-related	1390	21	1402	140	85.5 (77.0, 91.3)
HPV 6-related	1238	5	1242	50	90.1 (75.3, 96.9)
HPV 11-related	1238	1	1242	18	94.4 (64.7, 99.9)
HPV 16-related	1288	13	1268	61	79.3 (61.9, 89.6)
HPV 18 -related	1327	2	1350	33	93.9 (76.3, 99.3)

*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 Aluminium Hydroxyphosphate Sulfate

Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 Through 26 Years of Age in the MSM Sub-study

A sub-study of Protocol 020 evaluated the efficacy of GARDASIL against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 MSM. In this sub-study, cases of AIN 2/3 were the efficacy endpoints used to assess prevention of HPV-related anal cancer. The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population of Protocol 020.

GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline (Table 7).

Table 7
Analysis of Efficacy of GARDASIL for Anal Disease in the PPE Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types

HPV 6, 11, 16, or 18-related Endpoint	GARDASIL (N = 299)		AAHS Control (N = 299)		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)

N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
AAHS Control = Amorphous Aluminium 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 8). This

finding is expected, as the immune responses to vaccines generally decrease was 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 45-Year-Old Girls and Women

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year-old girls	1,122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
16- through 26-year-old girls and women	9,859	3,329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
27- through 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
35- through 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
Anti-HPV 11				
9- through 15-year-old girls	1,122	917	99.9 (99.4, 100.0)	1,304.6 (1,224.7, 1,389.7)
16- through 26-year-old girls and women	9,859	3,353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
27- through 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
35- through 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
Anti-HPV 16				
9- through 15-year-old girls	1,122	915	99.9 (99.4, 100.0)	4,918.5 (4,556.6, 5,309.1)
16- through 26-year-old girls and women	9,859	3,249	99.8 (99.6, 100.0)	2,409.2 (2,309.0, 2,513.8)
27- through 34-year-old women	667	435	99.3 (98.0, 99.9)	2,342.5 (2,119.1, 2,589.6)
35- through 45-year-old women	957	657	98.2 (96.8, 99.1)	2,129.5 (1,962.7, 2,310.5)
Anti-HPV 18				
9- through 15-year-old girls	1,122	922	99.8 (99.2, 100.0)	1,042.6 (967.6, 1,123.3)
16- through 26-year-old girls and women	9,859	3,566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
27- through 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
35- through 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

*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 9). 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 9
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	1,072	884	99.9 (99.4, 100.0)	1,037.5 (963.5, 1,117.3)
16- through 26-year old boys and men	2,026	1093	98.9 (98.1, 99.4)	447.8 (418.9, 478.6)
Anti-HPV 11				
9- through 15-year old boys	1,072	885	99.9 (99.4, 100.0)	1,386.8 (1,298.5, 1,481.0)
16- through 26-year old boys and men	2,026	1,093	99.2 (98.4, 99.6)	624.3 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year old boys	1,072	882	99.8 (99.2, 100.0)	6,056.5 (5,601.3, 6,548.7)
16- through 26-year old boys and men	2,026	1,136	98.8 (97.9, 99.3)	2,403.3 (2,243.4, 2,574.6)
Anti-HPV 18				
9- through 15-year old boys	1,072	887	99.8 (99.2, 100)	1,357.4 (1,249.4, 1,474.7)
16- through 26-year old boys and men	2,026	1,175	97.4 (96.3, 98.2)	402.6 (374.6, 432.7)

*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.

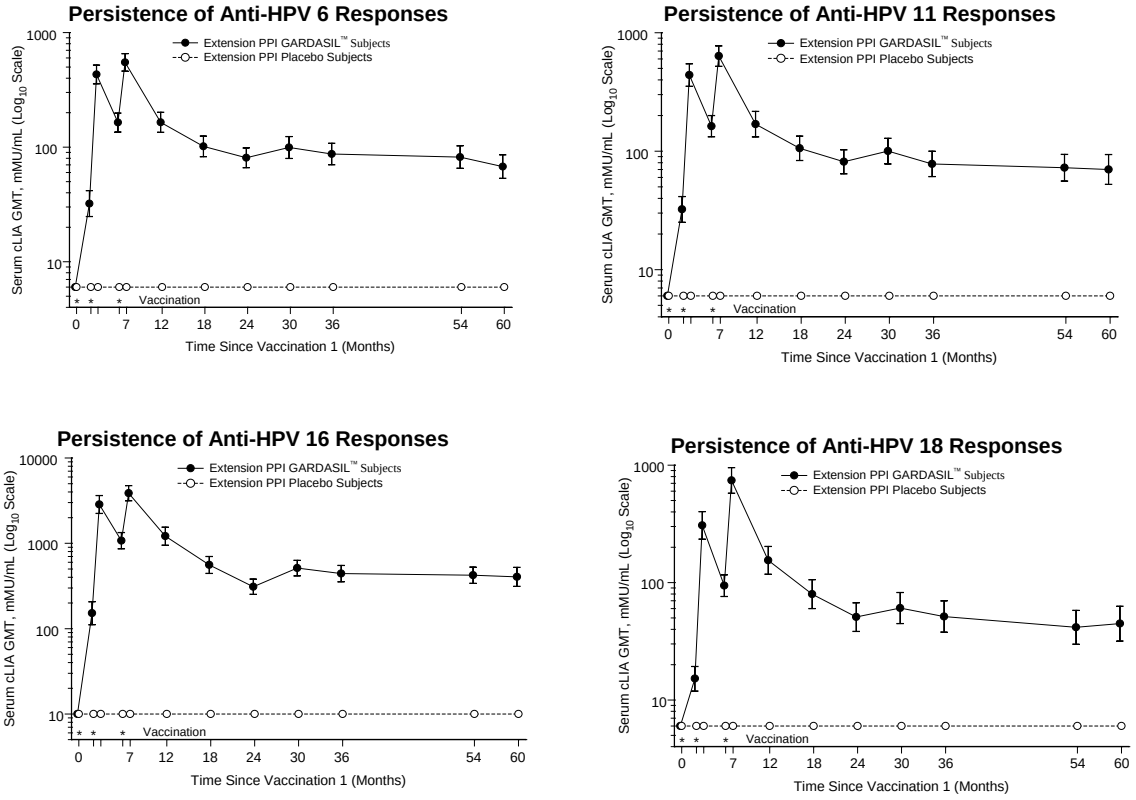
Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses (GMTs) were compared between 9- through 15-year-old males and 16- through 26-year-old males. Among males who received GARDASIL, 97.4% to 99.9% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month postdose 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 10).

Table 10
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, vaginal and anal 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 anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by 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.

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, vaginal or anal cancers; CIN, VIN, VaIN, or AIN 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 foetal 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, 3,819 women (vaccine N = 1,894 vs. placebo N = 1,925) reported at least one pregnancy. The overall proportions of pregnancies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late foetal death, congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22.6% (446/1,973) in subjects who received GARDASIL and 23.1% (460/1994) 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, 40 cases of congenital anomaly were observed in the group that received GARDASIL compared with 33 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women 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 1,133 women who were breast feeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination

groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

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 (aluminium or non-aluminium 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 11 and 12.

Table 11
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 12
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	61.5	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2
Haematoma	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 aluminium 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 13 and 14.

Table 13
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
Diarrhoea	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

*Aluminium and/or non-aluminium containing placebo

Table 14
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
Diarrhoea	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

*Aluminium and/or non-aluminium 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.

Infections and infestations: cellulitis

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy

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

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

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

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

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 discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured.

Prefilled Syringe Use
Inject the entire contents of the syringe.

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.

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Auckland

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POISONS SCHEDULE

Schedule 4 – Prescription Medicine

This product information was approved by the Therapeutic Goods Administration on 21 December 2011.