MEDICAL ADVISOR REPORT

TT50-7571/1

I.1 Type

NMA (abbreviated)

I.2 Medication

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

The HPV vaccine is an aluminium adjuvanted recombinant protein particulate (virus-like particle [VLP]) vaccine. The 9vHPV vaccine contains the same HPV types already represented in the qHPV vaccine (HPV 6, 11, 16, and 18), as well as five additional HR HPV types (31, 33, 45, 52, and 58).

I.3 Manufacturer

MSD

I.4 Background

This application follows previous approval of the quadrivalent HPV vaccine, marketed globally since 2006.

The application states that a similar submission for market approval of the nine valent vaccine has been made in the following countries/ regions:

Country	Submission date	Status
USA	10 Dec 14	Approved: 10 Dec 14
EU	7 Mar 14	Approved: 30 Mar 15
Canada	12 Feb 14	Approved: 12 Mar 15
Australia	5 June 2014	Approved: 22 June 2015

I.5 Indication

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

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

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

As part of the dosage, the datasheet notes that a three dose (0, 2, and 6 months) IM vaccination schedule is recommended.

I.6 Supporting documentation

In support of this application, the sponsor has provided the full submission as provided to the TGA, including the clinical evaluation report [document in AnnexII/14G].

I.6.1 Efficacy

The study programme consists of the following:

- Pivotal study 001
- Immunological Bridging (002 and 009)
- Prior exposure to Gardasil (006)
- Supporting Studies: concomitant use with other vaccines (005 and 007).

Non-inferior immunogenicity (4 original types) of 9vHPV in females (16 to 26 yrs) versus qHPV in 16 to 26 yrs

Pivotal study **Protocol V503-001**. Approximately 14,000 females 16 to 26 years of age were randomised to Gardasil9 or quadrivalent Gardasil.

The study sites were located in 6 countries in the Asia-Pacific region (Hong Kong, Japan, New Zealand, Republic of Korea, Taiwan, and Thailand), 5 countries in Europe (Austria, Denmark, Germany, Norway, and Sweden), 5 countries in Latin America (Brazil, Chile, Colombia, Mexico, and Peru) and 2 countries in North America (Canada and the United States, including US Territory Puerto Rico). Study dates were September 2007 to April 2013.

Study 001 study was designed as a combination of 3 sub-studies:

1. A Phase IIb dose-ranging sub-study including all subjects enrolled under Part A, to select a vaccine dose formulation for the 9vHPV vaccine program based on immunogenicity and safety assessment through Month 7.

   Women, 16 to 26 years of age, were randomized in equal numbers to 1 of 3 dose formulations of the 9vHPV vaccine or the comparator qHPV vaccine, in a 3-dose regimen.

   The **dose selected** for the second part of Study 001 was the mid-dose.

   The mid-dose formulation contains increased amounts of HPV 6, 16, and 18 VLPs than the qHPV vaccine and has an adjuvant-to-antigen ratio that is similar to that of the qHPV vaccine.

   This dose was then used in all subsequent studies.

2. A Phase III **efficacy** sub-study including those subjects enrolled under Part A who received the selected dose formulation of 9vHPV vaccine (mid-dose 9vHPV vaccine) or the qHPV vaccine control, and additional subjects enrolled under Part B, to assess the efficacy and safety objectives of the study.

   The additional healthy 16- to 26-year-old women were randomized in equal numbers to the selected 9vHPV vaccine dose formulation chosen from Part A or the comparator qHPV vaccine.

   Pelvic samples, including external genital and cervicovaginal swabs and Pap test samples, were to be collected at Day 1, Month 7, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, and Month 54. All subjects are to be followed for efficacy up to at least Month 42.

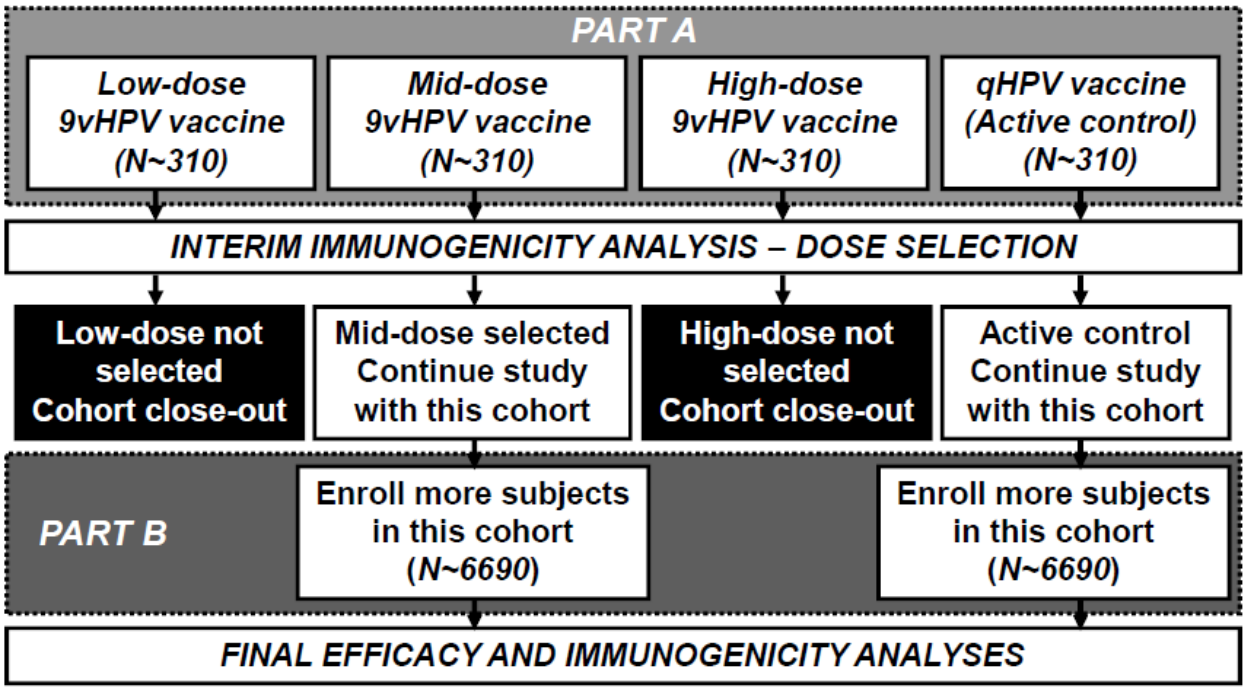
3. A Phase III **immunogenicity** sub-study, that included subjects enrolled under Part B, to assess the immunogenicity objectives of the study.

A 3-dose regimen (0, 2 and 6 months) was followed-up for safety and efficacy for 54 months. Immunogenicity was assessed at Month 7, followed by assessment of persistence of antibody responses through Month 42.

The diagram in Figure 9-1 summarizes the study enrollment and indicates that the middose 9vHPV vaccine formulation was selected.

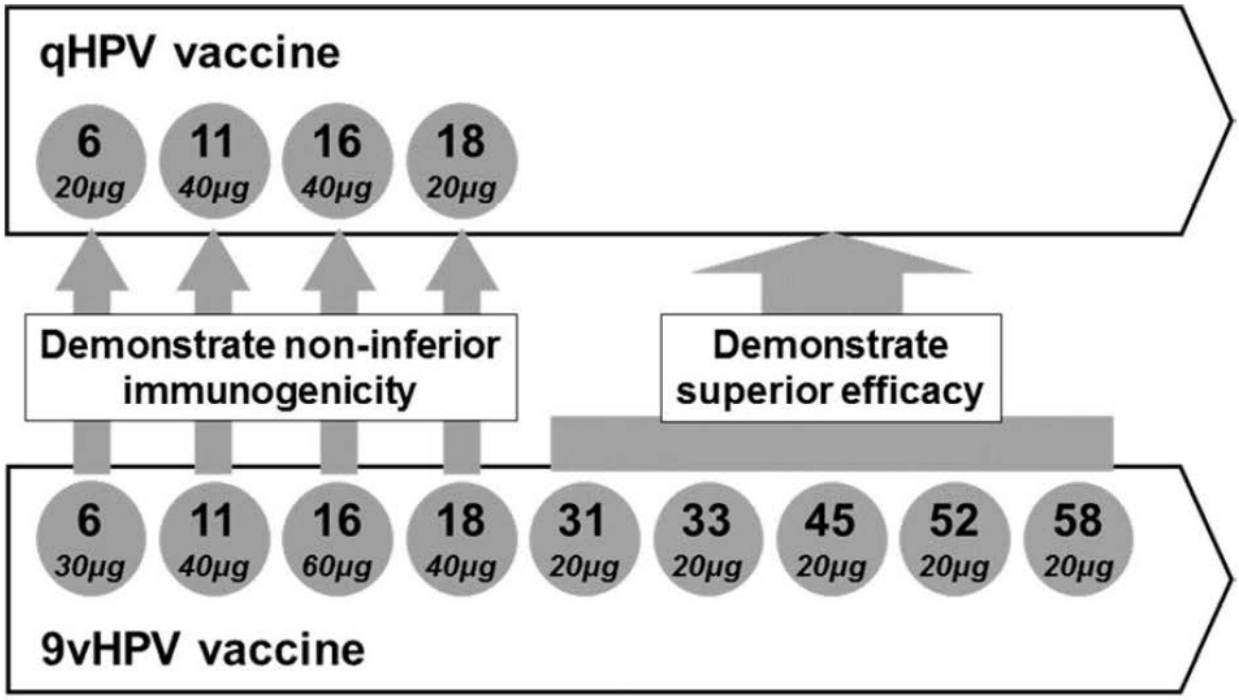
Figure 9-1

Study Enrollment



The 2 primary objectives of V503-001, immunological bridging with respect to HPV 6, 11, 16, and 18 and demonstration of efficacy with respect to HPV 31, 33, 45, 52, 58, are illustrated in [Figure 2.7.3-hpvdiseases: 2].

Figure 2.7.3-hpvdiseases: 2
Primary Efficacy Objectives of Protocol V503-001



The 001 study also had the following (supportive) analysis

Non-inferior immunogenicity (4 original types) of 9vHPV in females (9 to 15 yrs) versus qHPV in 16 to 26 yrs

Immunogenicity endpoint

Neutralizing antibodies are recognized as the vaccine-induced immune mechanism of protection against HPV infection and disease. Since no immune threshold of protection has been identified for HPV vaccines, immunogenicity of the 9vHPV vaccine was compared to that of the qHPV vaccine.

Prophylactic Efficacy

HPV 31/33/45/52/58-Related High Grade Cervical, Vulvar, or Vaginal Lesions

Results in the PPE (per-protocol efficacy) Population

All subjects in the PPE population were required to be seronegative to the relevant HPV type at Day 1 and PCR-negative to the relevant HPV type from Day 1 through Month 7, have received all 3 vaccinations within protocol-specified visit windows, and have no protocol violation.

Table 11-1 presents the results of evaluation of efficacy against the primary efficacy endpoint of high grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58 in the PPE population.

As shown in the table, the 9vHPV vaccine is efficacious in preventing the incidence of the primary efficacy endpoint among subjects who were naïve to the relevant HPV type during the vaccination period.

Table 11-1

Analysis of Efficacy Against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer
(Per-Protocol Efficacy Analysis Population)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI	P-value[†]
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6,016	1	19,005.1	0.0	6,017	30	18,976.6	0.2	96.7	(80.9, 99.8)	< 0.0001
By HPV Type											
HPV 31-Related	5,308	0	16,744.4	0.0	5,252	7	16,560.7	0.0	100	(40.1, 100)	
HPV 33-Related	5,624	0	17,771.4	0.0	5,628	7	17,803.0	0.0	100	(39.3, 100)	
HPV 45-Related	5,724	0	18,102.7	0.0	5,724	2	18,079.2	0.0	100	(-246.8, 100)	
HPV 52-Related	5,320	0	16,777.1	0.0	5,216	11	16,473.6	0.1	100	(67.3, 100)	
HPV 58-Related	5,361	1	16,902.7	0.0	5,340	6	16,842.4	0.0	83.4	(-23.9, 99.3)	
By Lesion Type											
CIN 2 or worse	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2/3 or AIS	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2/3	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2	5,948	1	17,407.0	0.0	5,943	23	17,430.9	0.1	95.6	(76.3, 99.8)	
CIN 3	5,948	0	17,407.0	0.0	5,943	5	17,438.1	0.0	100	(-0.2, 100)	
AIS	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA	NA	
Cervical Cancer	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA	NA	
VIN 2/3 or VaIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
VIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
VIN 2/3	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
Vulvar Cancer	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
VaIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
VaIN 2/3	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
Vaginal Cancer	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	

[†] P-value calculated for the lower bound of the two sided 95% confidence interval for the vaccine efficacy being greater than 25%.

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 Month 7.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia

The point estimate of vaccine efficacy is highly statistically significant. The pre-specified success criterion was that the lower bound of the 95% confidence interval (CI) of vaccine efficacy (VE) be greater than 25%, has been met.

Evaluator's comment

In the pivotal study Protocol V503-001, the Gardasil9 protected against cervical lesions of the new serotypes when compared against the quadrivalent Gardasil which did not include these HPV types.

HPV 6/11/16/18-Related Endpoints

Both the 9vHPV and qHPV vaccines contain virus-like particles of HPV 6, 11, 16, and 18.

As shown in Table 2.5: 4, the 9vHPV vaccine induced non-inferior anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 responses compared to qHPV vaccine in females 16 to 26 years of age.

The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the fold-difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs (9vHPV vaccine vs. qHPV vaccine) be above 0.67, to exclude a decrease of 1.5-fold or more.

Table 2.5: 4

Non-Inferior Month 7 HPV cLIA Geometric Mean Titers in Females 16 to 26 Years of Age Who Received 9vHPV Vaccine vs. Females 16 to 26 Years of Age Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-001)

	9vHPV Vaccine (N = 6,792)		qHPV Vaccine (N = 6,795)		9vHPV Vaccine / qHPV Vaccine	
Assay	**n**	**GMT mMU/mL**	**n**	**GMT mMU/mL**	**GMT Ratio**	**95% CI**
Anti-HPV 6	3,993	893.1	3,975	875.2	1.02	(0.99, 1.06)*
Anti-HPV 11	3,995	666.3	3,982	830.0	0.80	(0.77, 0.83)*
Anti-HPV 16	4,032	3,131.1	4,062	3,156.6	0.99	(0.96, 1.03)*
Anti-HPV 18	4,539	804.6	4,541	678.7	1.19	(1.14, 1.23)*

* p-value <0.001

N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titer; CI = Confidence interval; mMU = milli-Merck units; HPV = Human papillomavirus

Evaluator's comment

In the pivotal study Protocol V503-001, the Gardasil9 showed similar immunogenicity as that provided by the quadrivalent Gardasil for the original four HPV types.

Two Immunological Bridging Studies

In these two studies, safety as well as immunogenicity of Gardasil 9 in Girls and Boys (9-15 years) was compared to that in young women (16-26 years).

[Preadolescents and adolescents could not be included in original Gardasil studies as these studies involved gynaecological and genital examination and sampling for HPV infection endpoints. While efficacy of qHPV was initially established in women aged 16 to 26 year old, bridging with immunogenicity data was used for preadolescents and adolescents.]

Non-inferior immunogenicity (9 types) of 9vHPV in females (9 to 15 yrs) versus 9vHPV in 16 to 26 yrs

Non-inferior immunogenicity (9 types) of 9vHPV in males (9 to 15 yrs) versus 9vHPV in females 16 to 26 yrs

Protocol V503-**002**: 600 girls and 600 boys (9 to 15 years of age) the comparison was with 400 young women (16 to 26 years of age) who were also enrolled in the study. A manufacturing consistency sub-study enrolled a further 1800 girls. Subjects were followed for immunogenicity for 7 months and safety for 12 months.

Administration of 9vHPV vaccine to baseline HPV 6-, HPV 11-, HPV 16-, HPV 18-, HPV 31-, HPV 33-,HPV 45-, HPV 52-, and/or HPV 58-naïve females and males 9 to 15 years of age, results in anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 antibody responses (GMTs) at 4 weeks postdose 3 that are approximately 2- to 3-fold higher than those observed among baseline HPV 6-, HPV 11-, HPV 16-, HPV 18-, HPV 31-, HPV 33-, HPV 45-, HPV 52-, and/or HPV 58-naïve females 16 to 26 years of age.

The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the fold-difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti- HPV 45, anti-HPV 52, and anti-HPV 58 GMTs (adolescents vs. adult) be above 0.67.

These results are displayed in Table 2.5: 6 (females) and Table 2.5: 7 (males).

Table 2.5: 6
Non-Inferior Month 7 HPV cLIA Geometric Mean Titers in Females 9 to 15 Years of Age Who Received 9vHPV Vaccine vs. Females 16 to 26 Years of Age Who Received 9vHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-002)

Assay	Females 9 to 15 Years of Age (N = 646)		Females 16 to 26 Years of Age (N = 468)		Females 9 to 15/ Females 16 to 26	
	n	GMT mMU/mL	n	GMT mMU/mL	GMT Ratio	95% CI*
Anti-HPV 6	517	1,715.4	328	900.8	1.90	(1.70, 2.14)
Anti-HPV 11	517	1,295.1	332	706.6	1.83	(1.63, 2.06)
Anti-HPV 16	529	6,979.8	329	3,522.6	1.98	(1.77, 2.22)
Anti-HPV 18	531	2,153.7	345	882.7	2.44	(2.13, 2.80)
Anti-HPV 31	522	1,891.6	340	753.9	2.51	(2.21, 2.85)
Anti-HPV 33	534	980.4	354	466.8	2.10	(1.87, 2.36)
Anti-HPV 45	534	714.4	368	272.2	2.62	(2.27, 3.03)
Anti-HPV 52	533	932.9	337	419.6	2.22	(1.97, 2.51)
Anti-HPV 58	531	1,286.7	332	590.5	2.18	(1.93, 2.45)

* p-value <0.001
N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titer; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus

Table 2.5: 7
Non-Inferior Month 7 HPV cLIA Geometric Mean Titers in Males 9 to 15 Years of Age Who Received 9vHPV Vaccine vs. Females 16 to 26 Years of Age Who Received 9vHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-002)

	Males 9 to 15 Years of Age (N = 666)		Females 16 to 26 Years of Age (N = 468)		Males 9 to 15/ Females 16 to 26	
Assay	n	GMT mMU/mL	n	GMT mMU/mL	GMT Ratio	95% CI*
Anti-HPV 6	559	2,084.7	328	900.8	2.31	(2.07, 2.59)
Anti-HPV 11	559	1,487.1	332	706.6	2.10	(1.88, 2.36)
Anti-HPV 16	569	8,628.9	329	3,522.6	2.45	(2.19, 2.74)
Anti-HPV 18	567	2,822.8	345	882.7	3.20	(2.80, 3.65)
Anti-HPV 31	564	2,221.2	340	753.9	2.95	(2.60, 3.34)
Anti-HPV 33	567	1,198.7	354	466.8	2.57	(2.29, 2.88)
Anti-HPV 45	570	907.0	368	272.2	3.33	(2.89, 3.84)
Anti-HPV 52	568	1,037.8	337	419.6	2.47	(2.19, 2.79)
Anti-HPV 58	566	1,567.7	332	590.5	2.66	(2.37, 2.98)

* p-value <0.001
N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titer; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus

Non-inferior immunogenicity (HPV 16 and 18) of 9vHPV in females (9 to 15 yrs) versus qHPV in 9 to 15 yrs

Protocol V503-**009**/GDS01C: In this immunogenicity and safety/tolerability study involving 600 girls aged 9-15 years who were followed for 7 months.

Subjects were randomised to receive a 3-dose regimen of 9vHPV vaccine or qHPV vaccine (at Day 1, Month 2, and Month 6). Immune responses were compared to those in recipients of Gardasil.

Administration of 9vHPV vaccine to baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve females 9 to 15 years of age who received 9vHPV vaccine results in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody responses (GMTs) at 4 weeks post-dose 3 that are comparable to those observed among baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve females 9 to 15 years of age who received qHPV vaccine (Table 2.5: 8).

Table 2.5: 8

Non-Inferior Month 7 HPV cLIA Geometric Mean Titers in Females 9 to 15 Years of Age Who Received 9vHPV Vaccine vs. Females 9 to 15 Years of Age Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-009/GDS01C)

Assay	9vHPV Vaccine (N = 300)		qHPV Vaccine (N = 300)		9vHPV Vaccine / qHPV Vaccine	
	n	GMT mMU/mL	n	GMT mMU/mL	GMT Ratio	95% CI
Anti-HPV 6	273	1679.4	261	1565.9	1.07	(0.93, 1.23)
Anti-HPV 11	273	1315.6	261	1417.3	0.93	(0.80, 1.08)
Anti-HPV 16	276	6739.5	270	6887.4	0.97	(0.85, 1.11)*
Anti-HPV 18	276	1956.6	269	1795.6	1.08	(0.91, 1.29)*

* p-value <0.001

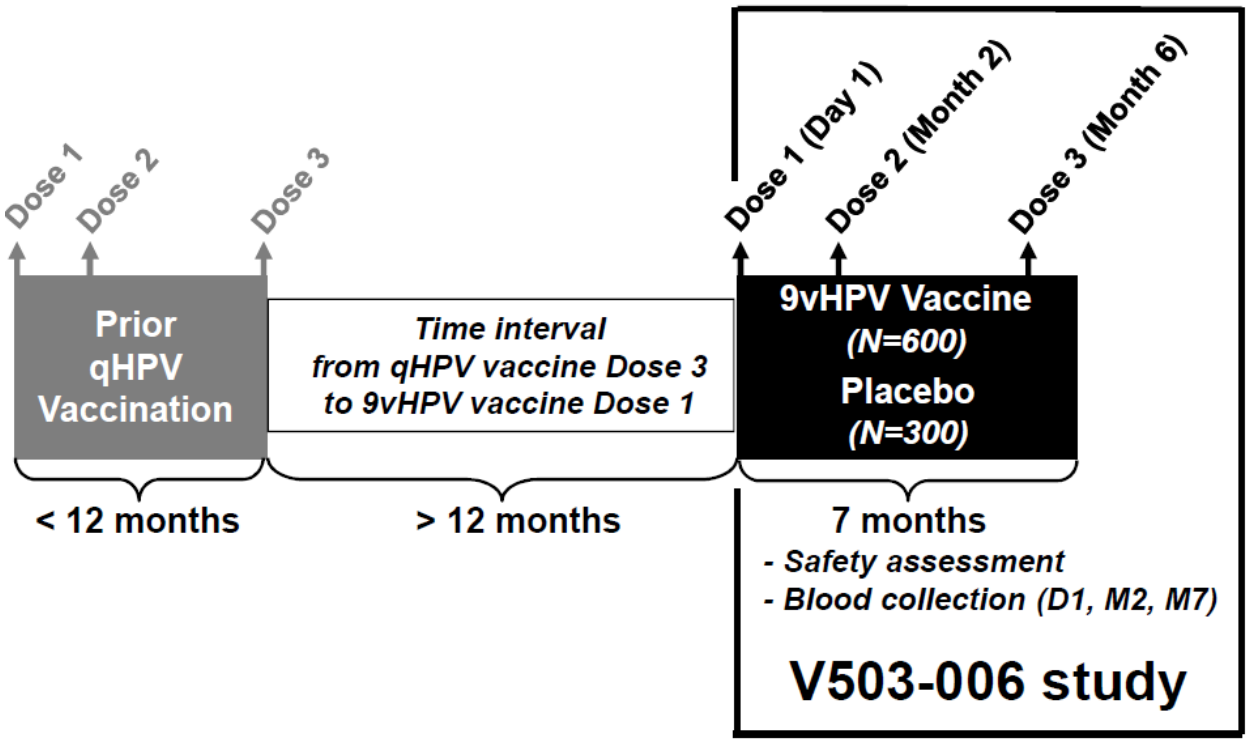
N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titer; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus

Prior exposure to Gardasil

Protocol V503-**006**: 924 adolescent girls and young women (12 to 26 years of age) who were previously vaccinated with Gardasil received Gardasil 9. Subjects were followed for 7 months for immunogenicity and safety.

The study was double-blinded, placebo-controlled (saline placebo) [Figure 2.7.3-hpvdiseases: 8].

Figure 2.7.3-hpvdiseases: 8
Protocol V503-006 Study Design



In the study, 9vHPV vaccine given to women who previously received the qHPV vaccine elicited a greater immune response compared to 9vHPV vaccine given to women naïve to HPV vaccination. There was an adequate immune response to the new HPV types, in previously fully primed qHPV individuals.

Supporting Studies: concomitant use with other vaccines

Protocol V503-**005** & **Protocol** V503-**007**: The tolerability and immunogenicity of concomitant administration of the first dose of Gardasil 9 with adolescent vaccines **Menactra** and **Adacel** [Protocol 005] and Repevax [Protocol 007] was evaluated (compared to non-concomitant administration). Non-interference was demonstrated based on pre-defined criteria of non-inferior immunogenicity for all components. Co-administration was well tolerated.

Protocol 005 enrolled 620 males and 621 females and Protocol 007 enrolled 526 males and 528 females, all aged 11 to 15 years. Subjects were followed for immunogenicity and safety for 7 months. This supportive study demonstrated non-inferior immunogenicity for all components of the two vaccines. Co-administration was well tolerated.

I.6.2 Safety

The population considered for evaluation of safety ('Safety Population') included subjects who received the mid-dose formulation (30/40/60/40/20/20/20/20/20-mcg) of the 9vHPV vaccine or qHPV vaccine.

Overall, 13,360 subjects from these 6 studies received 9vHPV vaccine (including

- 8,053 females 16 to 26 years of age,
- 3,498 females 9 to 15 years of age, and

- 1,809 males 9 to 15 years of age).

There were 7,391 subjects from Protocols V503-001 and V503-009/GDS01C who received **qHPV vaccine** (including 7,093 females 16 to 26 years of age, and 298 females 9 to 15 years of age).

Analysis of Adverse Experiences in Subjects 9 to 26 Years of Age

Overall 5 serious adverse experiences were determined to be related to 9vHPV vaccine.

Few subjects (0.1%) discontinued due to an adverse experience.

[Appendix 2.7.4: 53] summarizes adverse experiences for the entire study period in subjects enrolled in Protocol V503-001 who received 9vHPV vaccine or qHPV vaccine.

Appendix 2.7.4: 53

Adverse Event Summary
(Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more adverse events	6,661	(94.2)	6,444	(91.0)
injection-site	6,423	(90.8)	6,024	(85.1)
non-injection-site	4,052	(57.3)	3,957	(55.9)
with no adverse event	410	(5.8)	634	(9.0)
with vaccine-related† adverse events	6,519	(92.2)	6,202	(87.6)
injection-site	6,422	(90.8)	6,024	(85.1)
non-injection-site	2,088	(29.5)	1,930	(27.3)
with serious adverse events	233	(3.3)	183	(2.6)
with serious vaccine-related adverse events	2	(0.0)	2	(0.0)
who died	5	(0.1)	5	(0.1)
discontinued‡ due to an adverse event	8	(0.1)	4	(0.1)
discontinued due to a vaccine-related adverse event	5	(0.1)	3	(0.0)
discontinued due to a serious adverse event	3	(0.0)	1	(0.0)
discontinued due to a serious vaccine-related adverse event	1	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

The frequencies of adverse experiences were generally comparable between the two vaccination groups.

Injection-Site Adverse Experiences

The most common injection-site adverse experiences occurring in subjects who received 9vHPV vaccine were erythema (32%), pain (85%), and swelling (38%).

> [percentages sourced from the following Table: Table 2.7.4: 14 Subjects With Injection Site Adverse Events (Incidence >0% in One or More Vaccination Groups) Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009) (Days 1 To 5 Following Any Vaccination Visit)]

In Protocol V503-001, 16 to 26 year old females who received 9vHPV vaccine were more likely to report injection-site adverse experiences compared with subjects who received qHPV vaccine (especially with respect to the injection-site adverse experiences of erythema [34% for those receiving 9vHPV vs 26% receiving qHPV], pain [90% 9vHPV vs 84% qHPV] and swelling [40% 9vHPV vs 29% qHPV]).

> Appendix 2.7.4: 54 Subjects With Injection Site Adverse Events (Incidence >0% in One or More Vaccination Groups) (Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy

The frequencies of injection-site pain of severe intensity were 4.3% and 2.6% in the 9vHPV vaccine group and qHPV vaccine group, respectively. Frequencies of injection-site erythema greater than 2 inches [5 cm] in maximum size were 1.6% and 0.8% in the 9vHPV vaccine group and qHPV vaccine group, respectively. Frequencies of injection-site swelling greater than 2 inches [5 cm] in maximum size were 3.8% and 1.5% in the 9vHPV vaccine group and qHPV vaccine group, respectively.

Systemic Adverse Experiences.

In Protocol V503-001, the proportions of subjects who reported systemic adverse experiences were generally comparable between those who received 9vHPV vaccine or qHPV vaccine.

Fever

Overall, 6.6% of subjects who received 9vHPV vaccine reported a temperature ≥37.8°C and <38.9°C, and 1.4% of subjects reported a temperature of ≥38.9°C, oral equivalent.

The number and percentage of subjects in Protocol V503-001 who experienced fever was generally comparable between 9vHPV vaccine and qHPV vaccine recipients.

Deaths, Serious Adverse Experiences, and Discontinuations.

A total of five subjects who received 9vHPV vaccine died during the entire study period. All deaths reported were from subjects in Protocol V503-001. None of the deaths were considered to be vaccine-related.

The causes of death for the subjects who received 9vHPV vaccine are as follows: One death each due to trauma (road traffic accident); intentional overdose (non-study medications) or suicide; cancer (acute lymphocytic leukemia); hypovolemic and septic shock; and sudden death (occurring 678 days postdose 3).

A total of five subjects who received 9vHPV vaccine had at least one **serious adverse experience** that was determined to be related to the vaccine (one event each of pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis).

A total of 15 subjects (0.1%) who received 9vHPV vaccine **discontinued** from further study vaccination due to an adverse experience, including 11 subjects who discontinued study vaccination due to a vaccine-related adverse experience.

In Protocol V503-001, 12 subjects, 8 (5 and 3 in subjects who received 9vHPV vaccine or qHPV vaccine, respectively) discontinued due to a vaccine related adverse experience [refer to Table Appendix 2.7.4: 53 above].

Two long-term safety studies are planned. There will be a 10 year follow-up of Scandinavian subjects in study 001 through the Nordic Cancer Registry Programs. In addition, subjects of study 002 will be followed for 10 years post-dose 3.

Post-marketing data: recent concerns regarding complex regional pain syndrome

A Medscape article reports that the EMA, at the request of Denmark, has in 2015 started a review of the safety profile of the HPV vaccine.

Concerns have been raised regarding case-reports of:

- complex regional pain syndrome (CRPS), a chronic pain condition affecting the limbs, and
- postural orthostatic tachycardia syndrome (POTS), a condition in which the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain, and weakness.

In response to publicity of case reports of 'syndrome' following HPV vaccination, the FDA told *Medscape Medical News* (among other information) that since licensure (Gardasil in 2006), no causal association between HPV vaccines and a patterned illness of neuropathic pain and autonomic dysfunction, CRPS, POTS, or fibromyalgia has been identified in either the pre-licensure clinical trials evaluated by the FDA or in post-licensure safety monitoring conducted by the CDC and FDA."

The Medscape article further notes that the FDA and CDC monitor the safety of all vaccines, including each HPV vaccine, using multiple safety systems: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system, and the Clinical Immunization Safety Assessment (CISA) network.

I.7 Product information

The datasheet v0.1 is satisfactory.

I.8 Risk management plan

The RMP includes routine PhV, including comparison of the spontaneous reported AE experience with 9vHPV to the AE experience with other Human Papillomavirus vaccines.

In addition to ongoing studies, there is also information from the pregnancy registry which gathers data from women exposed to the vaccine during pregnancy that is included in ongoing PSUR reporting

I.9 Benefit risk assessment

The benefit risk balance of Gardasil [Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine] in females and males for the for the prevention of HPV-related lesions is positive.

The HPV9 vaccine provides protection against a greater range of disease associated with HPV, while the safety profile of the 9vHPV vaccine is similar to that of the well characterised qHPV vaccine. Note, however, that reactivity was more common following vaccination with the nine-valent than with the quadrivalent HPV vaccine. Local symptoms such as pain (90%) and swelling (40%) following 9vHPV vaccination were very common. Fever following vaccination with the 9vHPV vaccine was common (7%).

Efficacy

The following study programme demonstrated efficacy.

In the pivotal study Protocol V503-001, women 16 to 26 years of age were randomised to Gardasil9 or quadrivalent Gardasil.

- A comparison of immune response to the 4 original HPV types showed 9vHPV to be non-inferior to qHPV in women 16 to 26 yrs of age.
- A comparison of Cervical, Vulvar, or Vaginal Lesions of new HPV types showed that the women randomised to 9vHPV had a high level of protection when compared to women who had received qHPV (which does not cover the vaccine types tested; new HPV types).

In two so called Immunological Bridging studies, safety as well as immunogenicity of Gardasil 9 in Girls and Boys (9-15 years) was compared to that in young women (16-26 years).

- Protocol V503-002: compared immunogenicity in girls and boys (9 to 15 years of age) to that of females 16 to 26 yrs.
- Protocol V503-009/GDS01C compared immunogenicity of 9vHPV and qHPV in girls aged 9-15 years.

Safety

While injection-site AEs were very common with the 9vHPV vaccine (eg pain in 85%, and swelling in 38%), such AEs were only slightly more common than with the qHPV vaccine.

In Protocol V503-001, 16 to 26 year old females who received 9vHPV compared to qHPV reported:

- erythema [34% vs 26%]
- pain [90% vs 84%]
- swelling [40% vs 29%]
- injection-site pain of severe intensity [4.3% vs 2.6%]
- injection-site erythema greater than 5 cm in maximum size [1.6% vs 0.8%]
- injection-site swelling greater than 5 cm in maximum size were [3.8% vs 1.5%].

Fever; overall, 6.6% of subjects who received 9vHPV vaccine reported a temperature ≥ 37.8°C and <38.9°C, and 1.4% of subjects reported a temperature of ≥ 38.9°C, oral equivalent. The number and percentage of subjects in Protocol V503-001 who experienced fever was generally comparable between 9vHPV vaccine and qHPV vaccine recipients.

I.10 Conclusion

Based on review of the information provided, and taking account of the information relating to the TGA assessment, the Evaluator considers that under Section 20 of the Medicines Act consent to distribute Gardasil [Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine] can be recommended for the following indication:

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

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

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

A three dose (0, 2, and 6 months) IM vaccination schedule is recommended.

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Reviewer	
Evaluator	

I.10.1 Appendix

Limited glossary

AAHS adjuvant	amorphous aluminum hydroxyphosphate sulphate adjuvant
AIS	adenocarcinoma in situ
CIN	Cervical intraepithelial neoplasia
HR HPV	high risk HPV types
HNTS population	HPV Naïve Type Specific Population; seronegative and PCR-negative to the relevant HPV type at Day 1. The HN-TS analysis differed from the PPE analysis in that it included subjects with major protocol violations and subjects who became infected with a vaccine HPV type during the vaccination period.
L1 viral protein	capsid protein, virus-like particles of which the HPV vaccine is prepared
RRP	Recurrent Respiratory Papillomatosis
VIN	Vulvar Intraepithelial Neoplasia
VLPs	virus like particles

Background

The manufacturing process of the 9vHPV vaccine is similar to that of the qHPV vaccine, which facilitates development. It consists of three main steps:

(1) Fermentation and harvest of the recombinant yeast cell slurry for each of the vaccine types;

(2) Purification of the VLPs from the cell slurry and adsorption onto AAHS to form the monovalent bulk alum-adsorbed products (MBAP); and

(3) Formulation of the MBAPs into the multivalent bulk alum-adsorbed product and subsequent filling into market containers.

The HPV9 application notes that results from recent interim analyses show no breakthrough of HPV-related disease and statistically significant demonstration of sustained vaccine effectiveness after up to 6 years of follow-up.

The 9vHPV vaccine compared to the qHPV increases cervical cancer coverage from ~70% to ~90% worldwide.

HPV Molecular Structure

HPV consist of a family of small, nonenveloped icosahedral capsid viruses containing double-stranded DNA composed of 8 early transcribed open reading frames, two late open reading frames, and a non-coding long control region.

The Late (L) genes encode the 2 capsid proteins (L1, major capsid protein) and L2 (minor capsid protein). [The HPV vaccine is prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of particular HPV types.]

Mature viral particles are composed of 72 pentamers of L1 proteins arranged in icosahedral symmetry.

Proteins encoded on the early (E) portion of the genome are involved in viral DNA synthesis. E6 and E7 proteins induce epithelial cell hyperproliferation by inhibiting cell cycle regulatory proteins, a likely mechanism by which all HPV types cause aberrant proliferation of infected cells.

The proportion of cervical cancers caused by types other than HPV 16 varies by region. For example, in Western countries, HPV 18 is the second most common cause of cervical cancer. However, in East Asia, HPV 52 and 58 are responsible for a higher proportion of cervical cancers than HPV 18. Species A10 contains LR HPV Types 6 and 11, which are responsible for over 90% of anogenital warts and RRP cases.

HPV Infection and Replication

HPV infection and replication is entirely intraepithelial. The basal cell of the epithelium is the primary target of HPV infection. A minor lesion in the epithelium is sufficient to allow HPV to access this layer of cells. HPV binds to heparin sulfate proteoglycans of the basement membranes exposed after epithelial micro-trauma; then capsid protein L2 undergoes a conformational change that makes it susceptible to proteolysis, which in turn exposes a portion of capsid protein L1 that binds to an undetermined epithelial cell surface receptor [Ref. 5.4: 03RVHV]. Because of this complex, multistep mechanism, the infection process is particularly slow, and transcription is not initiated before 12 to 24 hours.

Viral replication occurs only at a low level in the basal cells. High-level viral protein expression is achieved in the middle or upper layers of the epithelium. These layers of epithelial cells are normally terminally differentiated. However, with the up-regulation of viral proteins E6 and E7 that takes place during HPV infection, these cells are maintained in a mitotically active state that is conducive to viral DNA and protein synthesis. Viral assembly takes place only in terminally differentiated cells at the epithelium surface. Viral shedding occurs through the routine desquamation of dead epithelial cells.

HPV Persistence and Progression to Cancer

Most HPV infections are asymptomatic and resolve spontaneously. In some cases, HPV infection is not cleared, resulting in persistent HPV infection. With time, persistent HR HPV infection produces elevated expression of the E6 and E7 viral proteins, viral deregulation, and progression toward high-grade dysplasia, which can lead to the development of cervical cancer, usually after 1 to 3 decades.

An extension of the main Phase III efficacy study of the qHPV vaccine (**Protocol V501- 015**, conducted in female subjects vaccinated at 16 to 23 years of age) is ongoing to assess long-term effectiveness of the qHPV vaccine. Results from recent interim analyses show no breakthrough of HPV-related disease and statistically significant demonstration of sustained vaccine effectiveness after up to 6 years of follow-up.

Extension of the Phase III studies of qHPV vaccine in adolescent boys and girls vaccinated at 9 to 15 years of age (**Protocol V501-018**) and young men vaccinated at 16 to 23 years of age

(**Protocol V501-020**) are also ongoing. Results from recent interim analyses show no breakthrough of HPV disease in these studies after up to more than 6 years of follow-up.

Immune Response to HPV Natural Infection versus HPV Vaccination

By remaining exclusively intraepithelial, HPV largely avoids exposure to the host immune system and largely evades immune recognition, which allows HPV infection to proceed.

Immune responses to natural viral infection are poor. In particular, low-level antibody responses to HPV become detectable only several months after the infection and in only approximately 50% of those infected. Nonetheless, most HPV infections are eventually cleared.

Immune Mechanisms of Vaccine-Induced Protection Against HPV Disease

Protection induced by HPV L1 VLP-based vaccination is thought to be primarily antibody-mediated, since passive immunization (i.e., passive transfer of serum from vaccinated animals) is protective in animal models.

Antibody-dependent cell-mediated cytotoxicity (ADCC) is unlikely to be involved because HPV virions assemble in the nucleus, and therefore L1 is not displayed on the surface of infected cells.

Even though prophylactic HPV vaccination induces robust T-cell responses to L1, these are probably not directly implicated in qHPV vaccine-induced protection because:

1) HPV infection is confined to epithelia (is intra-epithelial) and does not involve a viremic phase (haemaogenous systemic viral spread), and

2) L1 is only expressed in the upper differentiating and dying epithelial layers but not detectable in basal epithelial cells where infection is maintained.