20 February 2014
EMA/CHMP/66618/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gardasil	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)
Silgard	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)

Procedure No. EMEA/H/C/xxxx/WS/0472

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 3 October 2013 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**Common name:**	**Presentations:**
Silgard	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)	See Annex A
Gardasil	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The WSA proposed the update of section 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) to include an alternative 2-dose vaccination schedule in children aged from 9 to 13 years. The Package leaflet was proposed to be updated accordingly.

In addition, the MAH proposed to express the quantity of aluminium salt in milligrams instead of micrograms in order to harmonise with the bivalent HPV vaccines in section 2 of the SmPC, PL and Labelling.

Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 9.0 and to implement minor linguistic changes.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Appointed Rapporteur for the WS procedure: Kristina Dunder

1.2. Steps taken for the assessment

Submission date:	3 October 2013
Start of procedure:	20 October 2013
Rapporteur's preliminary assessment report circulated on:	21 November 2013
Rapporteur's updated assessment report circulated on:	13 December 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	17 January 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	3 February 22014
Rapporteur's final assessment report on the MAH's responses circulated on:	14 February 2014
CHMP opinion:	20 February 2014

2. Scientific discussion

2.1. Introduction

Quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) recombinant vaccine, also referred to as qHPV vaccine, is a recombinant protein particulate (virus-like particle [VLP]) vaccine for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types and genital warts (condyloma acuminata) causally related to specific HPV types. Gardasil/Silgard is a vaccine for use from the age of 9 years for the prevention of:

- premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types
- genital warts (condyloma acuminata) causally related to specific HPV types

QHPV vaccine was evaluated in over 20,000 subjects in pre-licensure clinical trials when administered in 3 doses (0, 2, and 6 months). Gardasil/Silgard was licensed based on the safety, immunogenicity and efficacy of a 3-dose primary vaccination schedule.

Efficacy of qHPV in girls and boys 9- to 15-year old has been inferred based on demonstration of non-inferior antibody responses to 3 doses of qHPV vaccine when compared with antibody responses in young adult women 16 to 45 years of age, the populations in which efficacy has been shown. Moreover, ongoing follow-up studies of vaccinated cohorts have so far seen no breakthrough cases of cervical intraepithelial neoplasia (CIN) 2/3 caused by vaccine HPV types for up to 8 years for 3-dose recipients of qHPV vaccine and up to 9.5 years for recipients of a monovalent HPV 16 major capsid protein (L1) virus-like particles (VLP) vaccine. Similarly, there have not been breakthrough cases of vaccine type genital warts in follow-up studies in women or men who have received the 3-dose regimen of qHPV vaccine. Additionally, a long term follow-up study in young adolescents who were vaccinated at 9 to 15 years old (Protocol 018) has shown continuing effectiveness against high grade lesions after 8 years follow-up.

Despite the extensive experience and database demonstrating the protective efficacy of a 3-dose HPV vaccine regimen, public health authorities in several geographic regions are currently interested in using a 2-dose regimen to vaccinate young adolescents. Because there is no threshold level of antibody or other attribute of a vaccinated individual that can be characterized as a correlate of protection, the ultimate effectiveness and durability of alternative dosing regimens over the long term are unknown at this time. There are no specific data or text in the product labels to support these alternative regimens. Some governmental and public health authorities (e.g., Mexico, some Canadian provinces [Quebec and British Columbia]) have proposed a modified 3-dose regimen (0, 6, and 60 month) for girls 9 to 15 years of age. In May 2013 Quebec published their final decision to use 2 doses going forward. A third dose of vaccine at a 60-month interval is still under discussion in some regions outside of Quebec and has not been fully implemented because its need has not been demonstrated. Notably, there are no data on the immunogenicity of a 0, 6, 60 month regimen. The third dose is being considered as a safety net against potential poor effectiveness of a 2 doses schedule of HPV vaccine. The Swiss Federal Vaccination Committee (CFV) and the Swiss Federal Public Health Office (OFSP) recommend 2 doses at an interval of 4 to 6 months for girls 11 to 14 years of age. A third dose could be used for a subsequent dose if this should prove necessary. The Joint Committee on Vaccination and Immunisation (JCVI, UK) requested that HPV vaccine manufacturers provide available data and perspectives regarding 2-dose schedules and discussed this topic. On a global basis, there are indications that the World Health Organization Strategic Advisory Group of Experts (WHO SAGE) may also discuss this topic. Furthermore there is interest from public health authorities in Latin America.

Investigations of reduced dosing regimens began just as the long term follow-up studies of young adolescents and sexually active women who received 3 doses of the qHPV vaccine were getting underway.

Data from these studies are becoming available at this time and show that 3 doses of vaccine provide durable protection against high grade disease and genital warts over 6 to 8 years following vaccination. Serological evidence also shows seropositivity against the HPV types in the vaccine at 8 and 9 years following vaccination in young adolescents and sexually active young women, respectively. These studies are ongoing.

This variation application is supported by a clinical study entitled: A Randomized Clinical Trial to Assess the Immunogenicity of a 2-Dose Schedule of the Quadrivalent Human Papillomavirus Vaccine in Younger Adolescents compared to a 3-Dose Schedule in Young Women. In addition, reference is made to published studies with different vaccination schedules of qHPV vaccine and the bivalent HPV vaccine.

As a consequence of this data, the MAH proposed the update of the SmPC sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) to include an alternative 2-dose vaccination schedule in children aged from 9 to 13 years.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Study objectives:

Primary Objective Part 1: To determine if antibody responses to HPV types 16 and 18 are non-inferior after a 2-dose paediatric regimen as compared to a 3-dose adult regimen of qHPV vaccination, with responses measured at Month 7.

Primary Objective Part 2: To compare the serum antibody responses to HPV 6, 11, 16 and 18 at months 18, 24 and 36 after a 2-dose adolescent, 3-dose adolescent or 3-dose adult regimen of qHPV vaccine.

Secondary Objectives Part 1: (1) To demonstrate that 2-doses of qHPV vaccine administered to 9 to 13 year old females produced a serum antibody response to HPV 6 and 11 that was similar to the response seen in 16 to 26 year old females; (2) To evaluate the antibody response to HPV 16 and 18 in 9 to 13 year old females after a 2-dose versus a 3-dose qHPV regimen; (3) To evaluate seroconversion rates to HPV 6, 11, 16 and 18 at 7 months; (4) To evaluate the memory B cell and T helper cell mediated immune response to qHPV vaccine in the 2-dose adolescent, 3-dose adolescent and 3-dose adult arms.

Secondary Objectives Part 2: To evaluate the memory B cell and T helper cell mediated immune response to qHPV vaccine in the 2-dose adolescent, 3-dose adolescent and 3-dose adult arms.

Study design*:*

Post licensure, randomized, controlled, multi-centre study with 3 parallel groups in 2 age strata receiving open label qHPV vaccine. There were 3 study centres with approximately 1/3 of the total number of subjects enrolled at each site.

Subjects aged 9 to 13 were randomly assigned to receive either 2 or 3 doses of qHPV vaccine and subjects aged 16 to 26 received 3 doses of qHPV vaccine. During Part 1 subjects in all groups had two 10 mL blood samples collected. Subjects at Centre 01 provided an additional 10 mL blood sample collected to facilitate additional immunoassay in that subset of participants. At the study visits on Month 0, Month 2 and Month 6 all examinations and specimen collections took place prior to vaccination.

Diagnosis / Inclusion criteria: Subjects who the investigator believed could and would comply with the requirements of the protocol may have enrolled in the study; females between, and including, 9 to 13 years (before 14th birthday) and 16 to 26 years of age (before 27th birthday) at the time of the first vaccination; ability to provide written informed consent (and assent where applicable); Healthy (stable chronic conditions acceptable) at Visit 1 (Month 0); Not pregnant (as determined by negative urine pregnancy test); Four or

fewer sexual partners over lifetime as reported by subject (sexual intercourse defined as penetrative vaginal intercourse).

Evaluation criteria: The primary immunogenicity endpoints are serum antibody concentrations to HPV (Types 16 and 18) at Month 7. The per-protocol immunogenicity (PPI) population will serve as the primary population for the analysis of serum antibody concentrations to the 4 HPV types (6, 11, 16, and 18). To be included in this population, subjects must: (1) Have seronegative (below the serostatus cut-off) results to each HPV type at study enrolment (according to the cLIA) and for women, have PCR negative results to each HPV type at study enrolment. Individuals who, at study enrolment, are positive for antibodies to any of HPV 6, 11, 16, or 18 (according to the cLIA) or women who are PCR positive to HPV 6, 11, 16 or 18 will be excluded from the per-protocol analysis of vaccine response for the same antigen; (2) Have no other protocol violations at study enrolment or at specific visits. Generally, the protocol violators included subjects who did not receive all injections with the correct dose of the correct clinical material and/or did not adhere to all study procedures.

Statistical planning and analysis: The primary endpoint analysis is an Analysis of Variance (ANOVA) to test differences in the Geometric Mean Titers (GMTs) of HPV 16 and 18 at Month 7. Non-inferiority of any treatment arm was declared if lower bounds of the multiplicity-adjusted 95% CIs of GMT ratios (study arm/control arm) for HPV16 and 18 were greater than 0.5.

2.2.2. Results

Study Subjects/Patients and Data Sets Analysed

The number of subjects by treatment group and vaccination number is as follows:

- 2 dose girls: 259 subjects had their first vaccination; 253 subjects had their second vaccination.
- 3 dose girls: 261 subjects had their first and second vaccinations; 254 subjects had their third vaccination.
- 3 dose women: 310 subjects had their first vaccination; 304 subjects have their second vaccination; 301 subjects had their third vaccination.

The primary analysis of immunogenicity was based on the HPV type-specific Per- Protocol Immunogenicity (PPI) population. HNRT (HPV Naive to the Relevant Type) immunogenicity population was used for supportive analyses.

One exception to the PPI is Patient 2113. Her planned randomization was the 2 Dose Girls group but she received 3 doses so she is included in the 3 Dose Girls group.

Exceptions were made to the protocol defined visit windows in order to match publication results (Dobson et al., JAMA 2013). The Month 18 visit window was changed relative to the study protocol from 504 ± 56 days to 547 ± 56 days, to more accurately reflect an 18 month interval.

Demographic and Other Subject Characteristics

The two groups of girls were well balanced with respect to the demographic and sexual history characteristics (not shown in this AR).

Immunogenicity results

Primary Objectives: Anti-HPV 16 and 18 2-Dose Girls / 3-Dose Women at Month 7

In order to address the primary immunogenicity objectives of this study, anti-HPV 16 and 18 serum Competitive Luminex immunoassay (cLIA) GMTs at Month 7 were compared between the 2-dose girls vaccine group and the 3-dose women vaccine group. A one-sided test of non-inferiority was conducted.

Table 2 presents the results of the per-protocol analysis. The estimated GMTs, fold-difference in GMTs, associated 95% confidence interval, and p-value for testing the null hypothesis of inferiority of anti-HPV 16 and 18 responses are shown. The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% confidence interval for the fold difference in anti-HPV 16 and 18 GMTs (2-dose girls / 3-dose women) is greater than or equal to 0.5. The table shows that non-inferiority of the anti-HPV 16 and 18 GMT response in the 2-dose girls vaccine group, relative to 3-dose women vaccine group, is demonstrated. In fact, the estimated Month 7 anti-HPV 16 and 18 GMTs were numerically higher in the 2-dose girls vaccine group, than the 3-dose women vaccine group. Results are similar after adjusting for investigative site. Results are similar for the HPV Naive to the Relevant Type (HNRT) population. The same analysis was performed using the IgG assay; the fold-differences for types 16 and 18 were 2.13 (95% CI: 1.81; 2.49) and 1.88 (95% CI: 1.58; 2.24) respectively. Conclusions do not change for the PPI and HNRT populations.

Table 1. Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titers (HPV-types 16 and 18) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population)†

	Comparison Group					
	2-Dose Girls (Comparison Group) (N = 259)		3-Dose Women (Reference Group) (N = 310)		Estimated Fold Difference Comp Grp / Ref Grp	p-Value for
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	(95% CI)	Non-Inferiority‡
Anti-HPV 16	243	7,456.6	246	3,574.5	2.09 (1.68, 2.60)	<0.001
Anti-HPV 18	243	1,207.3	264	661.4	1.83 (1.52, 2.19)	<0.001
Overall conclusion: The non-inferiority criteria were met for both HPV types.						

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
‡ Non-inferiority for GMTs is defined as the lower bound of the 95% confidence interval greater than or equal to 0.5. The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Secondary Objectives: Anti-HPV 6 and 11 2-Dose Girls / 3-Dose Women at Month 7

In order to address the secondary immunogenicity objectives of this study, anti-HPV 6 and 11 serum cLIA GMTs at Month 7 were compared between the 2-dose girls vaccine group and the 3-dose women vaccine group. Table 3 presents the results of the per-protocol analysis. The estimated GMTs, fold difference in GMTs, and associated 95% confidence intervals for comparing the 2-dose girls vaccine group and the 3-dose women vaccine group for anti-HPV 6 and 11 responses are shown. The lower bound of the 95% confidence interval for the fold difference in anti-HPV 6 and 11GMTs (2-dose girls / 3-dose women) is greater than or equal to 0.5. In fact, the estimated Month 7 anti-HPV 6 and11 GMTs were numerically higher in the 2-dose girls vaccine group, than the 3-dose women vaccine group. Results are similar for the HPV Naive to the Relevant Type (HNRT) population. The same analysis was performed using the IgG assay; the fold-differences for types 16 and 18 were 1.96 (95% CI: 1.67; 2.31) and 2.08 (95% CI: 1.79; 2.41) respectively. Conclusions do not change for the PPI and HNRT populations.

Table 2. Statistical Analysis Comparing Month 7 HPV cLIA Geometric Mean Titers (HPV-types 6 and 11) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population)†

	Comparison Group				
	2-Dose Girls (Comparison Group) (N = 259)		3-Dose Women (Reference Group) (N = 310)		Estimated Fold Difference Comp Grp / Ref Grp
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	(95% CI)
Anti-HPV 6	241	2,186.1	256	938.3	2.33 (1.83, 2.96)
Anti-HPV 11	243	2,348.1	269	1,277.5	1.84 (1.56, 2.16)

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Summary of GMTs

Table 4 presents a summary by vaccination group of the serum cLIA geometric mean titers (GMTs) for the immune responses to HPV 6, 11, 16, and 18 at Day 1, Month 7, Month 18, Month 24, and Month 36, with associated 95% CIs. The table shows that GMTs for HPV Types 6, 11, 16, and 18 peaked following the 2nd or 3rd vaccine administrations in all vaccine groups at Month 7. The GMTs declined, as expected, during follow-up (Month 18, Month 24, and Month 36).

Table 3. Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population)†

Assay (cLIA)	2 Dose Girls (N=259)			3 Dose Girls (N=261)			3 Dose Women (N=310)		
Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6									
Day 1	239	< 7	(<7, <7)	245	< 7	(<7, <7)	255	< 7	(<7, <7)
Month 07	241	2,186.1	(1,846.3, 2,588.4)	248	1,856.1	(1,571.4, 2,192.5)	256	938.3	(796.5, 1,105.4)
Month 18	96	347.3	(291.2, 414.2)	97	350.6	(294.2, 417.8)	93	200.5	(167.6, 239.8)
Month 24	193	275.6	(242.5, 313.3)	186	359.1	(315.2, 409.1)	195	196.9	(173.4, 223.7)
Month 36	84	239.0	(195.3, 292.4)	83	372.1	(303.8, 455.8)	92	175.7	(144.9, 213.0)
Anti-HPV 11									
Day 1	241	< 8	(<8, <8)	246	< 8	(<8, <8)	268	< 8	(<8, <8)
Month 07	243	2,348.1	(2,090.3, 2,637.7)	251	2,095.7	(1,869.1, 2,349.8)	269	1,277.5	(1,143.8, 1,426.8)
Month 18	96	450.7	(380.1, 534.6)	99	424.2	(358.6, 501.8)	98	281.3	(237.6, 333.1)
Month 24	195	368.5	(323.6, 419.6)	186	422.0	(369.4, 482.0)	206	266.6	(235.0, 302.6)
Month 36	86	297.9	(244.1, 363.6)	82	410.2	(334.5, 503.1)	97	207.7	(172.2, 250.6)
Anti-HPV 16									
Day 1	241	< 11	(<11, <11)	246	< 11	(<11, <11)	245	< 11	(<11, <11)
Month 07	243	7,456.6	(6,387.6, 8,704.5)	251	7,639.8	(6,560.8, 8,896.2)	246	3,574.5	(3,064.9, 4,168.7)
Month 18	96	1,598.1	(1,332.8, 1,916.3)	98	1,804.4	(1,507.6, 2,159.7)	92	837.1	(695.4, 1,007.7)
Month 24	195	1,413.7	(1,234.9, 1,618.3)	186	1,739.3	(1,514.5, 1,997.5)	189	813.3	(708.9, 933.0)
Month 36	86	1,151.1	(917.6, 1,443.9)	83	1,413.4	(1,122.2, 1,780.2)	86	677.8	(540.3, 850.3)
Anti-HPV 18									
Day 1	241	< 10	(<10, <10)	247	< 10	(<10, <10)	263	< 10	(<10, <10)
Month 07	243	1,207.3	(1,053.5, 1,383.6)	252	1,702.6	(1,489.3, 1,946.3)	264	661.4	(580.4, 753.8)
Month 18	96	136.9	(106.1, 176.6)	99	236.2	(183.8, 303.6)	95	73.6	(57.0, 95.1)
Month 24	195	131.9	(109.1, 159.6)	187	266.7	(219.6, 323.9)	202	91.5	(75.9, 110.3)
Month 36	86	104.0	(76.6, 141.2)	83	239.1	(175.1, 326.6)	96	71.3	(53.4, 95.3)

†The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Table 4. Statistical Summary and Comparison of Month 7- HPV cLIA Geometric Titers (HPV-Types 6, 11, 16, 18) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population†)

		Comparison Group			Reference Group			Estimated Fold Difference
Assay (cLIA)	Comparison Group vs. Reference Group	N	n	Estimated GMT (mMU/mL)	N	n	Estimated GMT (mMU/mL)	Comp Grp / Ref Grp (95% CI)
Anti-HPV 6	2 Dose Girls vs. 3 Dose Girls	259	241	2,186.1	261	248	1,856.1	1.18 (0.93, 1.50)
	2 Dose Girls vs. 3 Dose Women	259	241	2,186.1	310	256	938.3	2.33 (1.83, 2.96)
	3 Dose Girls vs. 3 Dose Women	261	248	1,856.1	310	256	938.3	1.98 (1.58, 2.48)
Anti-HPV 11	2 Dose Girls vs. 3 Dose Girls	259	243	2,348.1	261	251	2,095.7	1.12 (0.95, 1.32)
	2 Dose Girls vs. 3 Dose Women	259	243	2,348.1	310	269	1,277.5	1.84 (1.56, 2.16)
	3 Dose Girls vs. 3 Dose Women	261	251	2,095.7	310	269	1,277.5	1.64 (1.40, 1.92)
Anti-HPV 16	2 Dose Girls vs. 3 Dose Girls	259	243	7,456.6	261	251	7,639.8	0.98 (0.77, 1.23)
	2 Dose Girls vs. 3 Dose Women	259	243	7,456.6	310	246	3,574.5	2.09 (1.68, 2.60)
	3 Dose Girls vs. 3 Dose Women	261	251	7,639.8	310	246	3,574.5	2.14 (1.75, 2.61)
Anti-HPV 18	2 Dose Girls vs. 3 Dose Girls	259	243	1,207.3	261	252	1,702.6	0.71 (0.59, 0.86)
	2 Dose Girls vs. 3 Dose Women	259	243	1,207.3	310	264	661.4	1.83 (1.52, 2.19)
	3 Dose Girls vs. 3 Dose Women	261	252	1,702.6	310	264	661.4	2.57 (2.12, 3.12)

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
‡ The estimated GMT, fold difference, and associated confidence intervals are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Table 5. Statistical Summary and Comparison of Month 18-HPV cLIA Geometric Titers (HPV-Types 6, 11, 16, 18) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population†)

		Comparison Group			Reference Group			Estimated Fold Difference
Assay (cLIA)	Comparison Group vs. Reference Group	N	n	Estimated GMT (mMU/mL)	N	n	Estimated GMT (mMU/mL)	Comp Grp / Ref Grp (95% CI)
Anti-HPV 6	2 Dose Girls vs. 3 Dose Girls	259	96	347.3	261	97	350.6	0.99 (0.76, 1.29)
	2 Dose Girls vs. 3 Dose Women	259	96	347.3	310	93	200.5	1.73 (1.34, 2.23)
	3 Dose Girls vs. 3 Dose Women	261	97	350.6	310	93	200.5	1.75 (1.39, 2.20)
Anti-HPV 11	2 Dose Girls vs. 3 Dose Girls	259	96	450.7	261	99	424.2	1.06 (0.83, 1.36)
	2 Dose Girls vs. 3 Dose Women	259	96	450.7	310	98	281.3	1.60 (1.27, 2.03)
	3 Dose Girls vs. 3 Dose Women	261	99	424.2	310	98	281.3	1.51 (1.19, 1.92)
Anti-HPV 16	2 Dose Girls vs. 3 Dose Girls	259	96	1,598.1	261	98	1,804.4	0.89 (0.68, 1.16)
	2 Dose Girls vs. 3 Dose Women	259	96	1,598.1	310	92	837.1	1.91 (1.46, 2.49)
	3 Dose Girls vs. 3 Dose Women	261	98	1,804.4	310	92	837.1	2.16 (1.70, 2.73)
Anti-HPV 18	2 Dose Girls vs. 3 Dose Girls	259	96	136.9	261	99	236.2	0.58 (0.41, 0.83)
	2 Dose Girls vs. 3 Dose Women	259	96	136.9	310	95	73.6	1.86 (1.30, 2.66)
	3 Dose Girls vs. 3 Dose Women	261	99	236.2	310	95	73.6	3.21 (2.23, 4.63)

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
‡ The estimated GMT, fold difference, and associated confidence intervals are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Table 6. Statistical Summary and Comparison of Month 24- HPV cLIA Geometric Titers (HPV-Types 6, 11, 16, 18) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population†)

		Comparison Group			Reference Group			Estimated Fold Difference
Assay (cLIA)	Comparison Group vs. Reference Group	N	n	Estimated GMT (mMU/mL)	N	n	Estimated GMT (mMU/mL)	Comp Grp / Ref Grp (95% CI)
Anti-HPV 6	2 Dose Girls vs. 3 Dose Girls	259	193	275.6	261	186	359.1	0.77 (0.63, 0.93)
	2 Dose Girls vs. 3 Dose Women	259	193	275.6	310	195	196.9	1.40 (1.17, 1.68)
	3 Dose Girls vs. 3 Dose Women	261	186	359.1	310	195	196.9	1.82 (1.53, 2.17)
Anti-HPV 11	2 Dose Girls vs. 3 Dose Girls	259	195	368.5	261	186	422.0	0.87 (0.72, 1.05)
	2 Dose Girls vs. 3 Dose Women	259	195	368.5	310	206	266.6	1.38 (1.15, 1.66)
	3 Dose Girls vs. 3 Dose Women	261	186	422.0	310	206	266.6	1.58 (1.32, 1.90)
Anti-HPV 16	2 Dose Girls vs. 3 Dose Girls	259	195	1,413.7	261	186	1,739.3	0.81 (0.67, 0.99)
	2 Dose Girls vs. 3 Dose Women	259	195	1,413.7	310	189	813.3	1.74 (1.43, 2.11)
	3 Dose Girls vs. 3 Dose Women	261	186	1,739.3	310	189	813.3	2.14 (1.78, 2.58)
Anti-HPV 18	2 Dose Girls vs. 3 Dose Girls	259	195	131.9	261	187	266.7	0.49 (0.38, 0.65)
	2 Dose Girls vs. 3 Dose Women	259	195	131.9	310	202	91.5	1.44 (1.10, 1.88)
	3 Dose Girls vs. 3 Dose Women	261	187	266.7	310	202	91.5	2.92 (2.22, 3.83)

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrolment and women were PCR negative at enrolment for the relevant HPV type(s), and had a Month 7 serum sample.
‡ The estimated GMT, fold difference, and associated confidence intervals are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

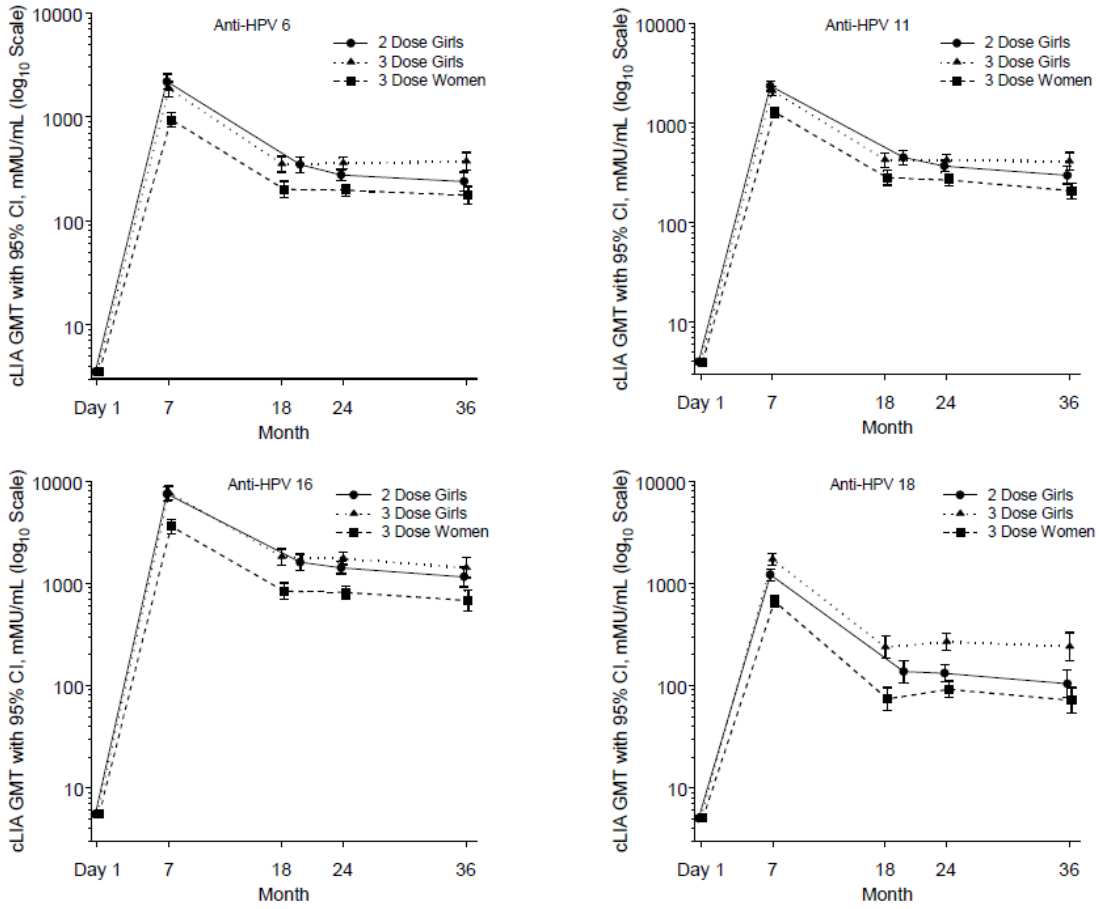
Table 7. Statistical Summary and Comparison of Month 36- HPV cLIA Geometric Titers (HPV-Types 6, 11, 16, 18) Between Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population†)

		Comparison Group			Reference Group			Estimated Fold Difference
Assay (cLIA)	Comparison Group vs. Reference Group	N	n	Estimated GMT (mMU/mL)	N	n	Estimated GMT (mMU/mL)	Comp Grp / Ref Grp (95% CI)
Anti-HPV 6	2 Dose Girls vs. 3 Dose Girls	259	84	239.0	261	83	372.1	0.64 (0.48, 0.86)
	2 Dose Girls vs. 3 Dose Women	259	84	239.0	310	92	175.7	1.36 (1.02, 1.81)
	3 Dose Girls vs. 3 Dose Women	261	83	372.1	310	92	175.7	2.12 (1.61, 2.79)
Anti-HPV 11	2 Dose Girls vs. 3 Dose Girls	259	86	297.9	261	82	410.2	0.73 (0.55, 0.96)
	2 Dose Girls vs. 3 Dose Women	259	86	297.9	310	97	207.7	1.43 (1.09, 1.89)
	3 Dose Girls vs. 3 Dose Women	261	82	410.2	310	97	207.7	1.97 (1.49, 2.62)
Anti-HPV 16	2 Dose Girls vs. 3 Dose Girls	259	86	1,151.1	261	83	1,413.4	0.81 (0.58, 1.14)
	2 Dose Girls vs. 3 Dose Women	259	86	1,151.1	310	86	677.8	1.70 (1.24, 2.33)
	3 Dose Girls vs. 3 Dose Women	261	83	1,413.4	310	86	677.8	2.09 (1.51, 2.87)
Anti-HPV 18	2 Dose Girls vs. 3 Dose Girls	259	86	104.0	261	83	239.1	0.43 (0.29, 0.66)
	2 Dose Girls vs. 3 Dose Women	259	86	104.0	310	96	71.3	1.46 (0.95, 2.24)
	3 Dose Girls vs. 3 Dose Women	261	83	239.1	310	96	71.3	3.35 (2.17, 5.18)

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all vaccinations, were seronegative at enrollment and women were PCR negative at enrollment for the relevant HPV type(s), and had a Month 7 serum sample.
‡ The estimated GMT, fold difference, and associated confidence intervals are based on a statistical analysis model that only includes treatment.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay.

Longitudinal plots are presented in Figure 1. Results are similar for the HPV Naive to the Relevant Type (HNRT) population. The same analysis was performed using the IgG assay for the per-protocol immunogenicity population and HNRT populations.

Figure 1. Longitudinal Anti-HPV 6, 11, 16, and 18 cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population)



2.2.3. Discussion

The current variation intended to investigate the possibility to use a two-dose vaccination schedule in children aged from9 to 13 years of age instead of the current 3-dose schedule.

The scientific basis consist of a comparison of immune responses in terms of cLIA titers between girls 9-13 years of age receiving 2 doses a 0, 6 months to women 16-26 years receiving 3 doses. The comparison is in principle the same as the basis for using a 3-dose schedule in girls 9-15 years, since efficacy studies are not considered feasible in the younger population. The immune responses at month 7 are clearly non-inferior in both younger study groups (i.e. 2-dose and 3-dose) compared to women, which support the possibility to use a 2-dose schedule among girls 9-13 years of age. The duration of immune responses were studied up to 36 months after dose 1. The decline of antibody titers was possibly slightly more rapid in 2-dose recipients compared to 3-dose recipients of the same age, but the clinical relevance of these relatively small differences is unknown. The numerical values were consistently higher in 2-dose girls compared to 3-dose women for all genotypes at all time-points. In contrast, the 0, 12 months schedule has not been compared within the same study to adult women, or 3-dose recipients of the same age.

The immunogenicity follow-up in girls receiving 2 doses of qHPV vaccine is ongoing as part of the presented study, however clarifications were requested regarding the plans for immunogenicity follow-up. The follow-up studies of the cohort of girls who received a 2 dose (0, 6 months) in the “Randomized Clinical Trial to Assess the Immunogenicity of a 2-Dose schedule of the qHPV in Younger Adolescents compared to a

3-Dose Schedule in Young Women" are in progress. Young girls who were vaccinated with 2 doses of Gardasil in the original non-inferiority immunogenicity study will be contacted and asked to provide 5-year follow-up and serological samples for antibody testing. The MAH, in collaboration with the Principal Investigator commits to submitting a descriptive summary of these serology data when available, expected in June 2016. Further serological testing at Year 10 in this cohort of girls is expected, but will be highly dependent on the degree of loss to follow-up that occurs and future local HPV vaccine recommendations for this age group.

Based on the available data, the CHMP endorsed the introduction of a 2-dose schedule (0, 6 months) in individuals 9 to and including 13 years of age. The CHMP recommended that the posology description (section 4.2 of the SmPC) should be done by age group with the 2-dose schedule presented first and the 3-dose schedule presented as an alternative for the age group 9-13 years.

During the assessment the CHMP highlighted the importance of a careful follow-up of girls receiving 2 doses of Gardasil and requested the MAH to provide the follow-up plans in the population that received the 2 dose scheduled. The MAH has been exploring options to assess the effectiveness of a 2-dose Gardasil schedule in girls 9 -13 years of age (the expected age indication for 2 doses in the EU) through observational vaccine effectiveness or vaccine impact studies.

The MAH proposed to identify a country or region where these conditions could be met, with a preference for a European country. If a true vaccine effectiveness study (directly comparing the incidence of genital disease outcomes in vaccinated and unvaccinated girls) cannot be performed, for example because high vaccine uptake prevents having a valid concurrent unvaccinated comparison group, then an impact study, assessing the effectiveness of a 2-dose vaccine program on cervical disease outcomes at the population level, will be proposed. Regardless of whether a vaccine effectiveness or impact study will be conducted, priority will be given to using vaccination and outcome data that can be linked at an individual level. It is also important to note that countries/regions meeting the conditions for a 2-dose schedule assessment in girls may have started their HPV program with a 3-dose schedule in this age group, which may affect the baseline level of HPV disease burden at the time of implementation of a 2-dose schedule, as well as HPV disease transmission at the population level.

The CHMP considered the proposed Post-Authorization Efficacy Study (PAES) acceptable; however it does not seem to be possible to predict a country that will continue to use qHPV vaccine for the entire study period. There may be periods when e.g. other HPV vaccine will be used depending on the national policies. It is expected that a 2-dose Gardasil schedule will be implemented. The vaccination registries should include the dates of vaccination so that number and timing of doses is available.

In addition, if possible, a secondary objective could be the effectiveness against condyloma, as this is likely to be feasible to study at an earlier time point. The proposed primary outcome, CIN2+, is considered appropriate. A full assessment of the study synopsis will be made when the updated RMP is submitted.

The MAH commits to regularly update the CHMP with the feasibility assessment of options for such a PAES within 6 months after EU approval of the 2-dose schedule variation in adolescents and then annually. The MAH will provide a preliminary synopsis of a proposed 2-dose PAES in an updated RMP at the time of the next PSUR submission. The full synopsis will be provided once a country/region is identified where such a PAES is confirmed to be feasible.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

All subjects enrolled in Protocol 167 were to have received the full dose formulation of the qHPV vaccine administered at Day 1 and Month 6 or at Day 1, Month 2, and Month 6. All subjects were to be followed for

serious adverse experiences that occurred within 30 days of each vaccination. This information was to be collected at the next visit or if the subject called with concerns.

2.3.2. Results

Brief Summary of Adverse Experiences

No SAEs have been reported in the context of the study.

New Medical History

Table 11 displays the number and percentage of subject who reported new medical conditions with an incidence of ≥1% in one or more vaccination groups. The most common new medical conditions reported were eczema, asthma, and nearsighted vision.

Table 8. Subject Medical History Conditions (Incidence ≥1% in One or More Vaccination Groups)

	2 Dose girls		3 Dose girls		3 Dose Women	
	N	%	N	%	N	%
Subjects in population	259		261		310	
With one or more conditions	136	(52.5)	149	(57.1)	220	(71.0)
With no conditions	123	(47.5)	112	(42.9)	90	(29.0)
Blood and Lymphatic disorders	**4**	**(1.5)**	**1**	**(0.4)**	**6**	**(1.9)**
Cardiac Disorders	**6**	**(2.3)**	**5**	**(1.9)**	**9**	**(2.9)**
Congenital, familial and genetic disorders	**1**	**(0.4)**	**2**	**(0.8)**	**3**	**(1.0)**
Ear and labyrinth disorders	**8**	**(3.1)**	**5**	**(1.9)**	**4**	**(1.3)**
Endocrine disorders	**3**	**(1.2)**	**2**	**(0.8)**	**8**	**(2.6)**
Eye disorders	**23**	**(8.9)**	**31**	**(11.9)**	**48**	**(15.5)**
Astigmatism	0	(0.0)	1	(0.4)	4	(1.3)
Farsighted	3	(1.2)	4	(1.5)	5	(1.6)
Myopia	3	(1.2)	7	(2.7)	9	(2.9)
Nearsighted	9	(3.5)	13	(5.0)	23	(7.4)
Gastrointestinal disorders	**9**	(3.5)	**9**	**(3.4)**	**20**	**(6.5)**
Irritable bowel syndrome	0	(0.00	0	(0.0)	5	(1.6)
Reflux	0	(0.0)	0	(0.0)	3	(1.0)
Immune system disorders	**61**	**(23.6)**	**42**	**(16.1)**	**55**	**(17.7)**
Allergy to penicillin	2	(0.8)	5	(1.9)	5	(1.6)
Allergy to Sulpha drugs	3	(1.2)	4	(1.50	0	(0.0)
Environmental allergies	4	(1.5)	3	(1.1)	1	(0.3)
Penicillin allergy	3	(1.2)	1	(0.40	2	(0.6)
Seasonal allergies	6	(2.3)	7	(2.7)	7	(2.3)
Infections and infestations	**0**	**(0.0)**	**2**	**(0.8)**	**6**	**(1.9)**
Investigations	**0**	**(0.0)**	**3**	**(1.1)**	**3**	**(1.0)**
Metabolism and nutrition disorders	**1**	**(0.4)**	**1**	**(0.4)**	**3**	**(1.0)**
Musculoskeletal and connective tissue disorders	**7**	**(2.7)**	**15**	**(5.7)**	**21**	**(6.8)**
Scoliosis	0	(0.0)	0	(0.0)	4	(1.3)
Nervous system disorders	**23**	**(8.9)**	**26**	**(10.0)**	**25**	**(8.1)**
Attention deficit disorder	5	(1.9)	6	(2.3)	4	(1.3)
Fainting episodes	1	(0.4)	3	(1.1)	1	(0.3)
Headaches	3	(1.2)	1	(0.4)	2	(0.6)
Migraines	4	(1.5)	3	(1.1)	3	(1.00
Occasional migraines	0	(0.0)	1	(0.4)	3	(1.0)
Psychiatric disorders	**3**	**(1.2)**	**3**	**(1.1)**	**18**	**(5.8)**
Anxiety	0	(0.0)	0	(0.0)	3	(1.0)
Depression	0	(0.0)	0	(0.0)	8	(2.6)
Renal and urinary disorders	**5**	**(1.9)**	**6**	**(2.3)**	**22**	**(7.1)**
Dysmenorrhoea	1	(0.4)	2	(0.8)	14	(4.5)
Reproductive system and breast disorders	**0**	**(0.0)**	**0**	**(0.0)**	**9**	**(2.9)**
Respiratory and mediastinal disorders	**33**	**(12.7)**	**23**	**(8.8)**	**55**	**(17.7)**
Asthma	15	(5.8)	14	(5.4)	25	(8.1)
Nasal congestion	3	(1.2)	0	(0.0)	1	(0.3)
Respiratory allergy	3	(1.2)	1	(0.4)	16	(5.2)
Skin and subcutaneous tissue disorders	**48**	**(18.5)**	**53**	**(20.3)**	**70**	**(22.6)**
Acne	5	(1.9)	1	(0.4)	14	(4.5)
Acne –intermittent	0	(0.0)	0	(0.0)	3	(1.0)
Allergy (penicillium)	1	(0.4)	3	(1.1)	3	(1.0)

	2 Dose girls		3 Dose girls		3 Dose Women	
	N	%	N	%	N	%
Eczema	14	(5.4)	15	(5.7)	20	(6.5)
Facial Acne	2	(0.8)	2	(0.8)	3	(1.0)
Psoriasis	2	(0.8)	1	(0.4)	3	(1.0)
Surgical and medical procedures	**6**	**(2.3)**	**10**	**(3.8)**	**9**	**(2.9)**
Tonsillectomy and adenoidectomy	1	(0.40	3	(1.1)	0	(0.0)

Every subject is counted a single time for each applicable specific condition. A subject with multiple conditions within a system organ class is counted a single time for that system organ class.
A system organ class or specific condition appears only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

2.4. Risk management plan

The MAH did not submit an updated Risk Management Plan within this variation procedure and this was deemed acceptable.

2.5. Changes to the Product Information

Changes to the Product Information are presented as new text underlined and deleted text marked as strikethrough.

During the procedure, the CHMP requested further amendments to the PI as described in section 2.2.3:

4.2 Posology and method of administration

Posology

Individuals 9 to and including 13 years of age

Gardasil can be administered according to a 2-dose schedule (0.5 ml at 0, 6 months) (see section 5.1).

If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered.

Alternatively, Gardasil can be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule.

The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Individuals 14 years of age and older

Gardasil should be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule.

The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

The use of Gardasil should be in accordance with official recommendations.

Paediatric population

The safety and efficacy of Gardasil in children below 9 years of age have not been established. No data are available (see section 5.1).

It is recommended that individuals who receive a first dose of Gardasil complete the vaccination course with Gardasil (see section 4.4).

The need for a booster dose has not been established.

5.1 Pharmacodynamic properties

Clinical studies

Immune Responses to Gardasil using a 2-dose schedule in individuals 9-13 years of age

A clinical trial showed that among girls who received 2 doses of HPV vaccine 6 months apart, antibody responses to the 4 HPV types, one month after the last dose were non-inferior to those among young women who received 3 doses of the vaccine within 6 months.

At Month 7, in the Per Protocol population, the immune response in girls aged 9-13 years (n=241) who received 2 doses of Gardasil (at 0, 6 months) was non-inferior and numerically higher to the immune response in women aged 16-26 years (n=246) who received 3 doses of Gardasil (at 0, 2, 6 months).

At 36 month follow-up, the GMT in girls (2 doses, n=86) remained non-inferior to the GMT in women (3 doses, n=86) for all 4 HPV types.

In the same study, in girls aged 9-13 years, the immune response after a 2-dose schedule was numerically lower than after a 3-dose schedule (n=248 at Month 7; n=82 at Month 36). The clinical relevance of these findings is unknown.

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

Package Leaflet

3. ~~HOW GARDASIL IS GIVEN~~ How to use Gardasil

Gardasil is given as an injection by your doctor. Gardasil is intended for adolescents and adults from 9 years of age onwards. ~~The person to be vaccinated will receive three doses of the vaccine.~~

If you are from 9 to and including 13 years of age
Gardasil can be administered according to a 2-dose schedule:
- *First injection: at chosen date*
- *Second injection: 6 months after first injection*

If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered.

Alternatively, Gardasil can be administered according to a 3-dose schedule:
- *First injection: at chosen date*
- *Second injection: i~~deally~~ 2 months after first injection*
- *Third injection: i~~deally~~ 6 months after first injection*

~~If an alternate vaccination schedule is necessary,~~ The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period. Please speak to your doctor for more information.

If you are from 14 years of age
Gardasil should be administered according to a 3-dose schedule:
- *First injection: at chosen date*
- *Second injection: 2 months after first injection*
- *Third injection: 6 months after first injection*

The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period. Please speak to your doctor for more information.

It is recommended that individuals who receive a first dose of Gardasil complete the vaccination course with Gardasil.
~~The person to be vaccinated should complete the three-dose vaccination course; otherwise the person to b vaccinated may not be fully protected.~~
Gardasil will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

The vaccine should not be mixed in the same syringe with any other vaccines and solutions.

If you forget one dose of ~~to take~~ Gardasil:

If you miss a scheduled injection, your doctor will decide when to give the missed dose.
It is important that you follow the instructions of your doctor or nurse regarding return visits for the follow-up doses. If you forget or are not able to go back to your doctor at the scheduled time, ask your doctor for advice. When Gardasil is given as your first dose, the completion of the ~~following two doses to complete the 3-dose~~ vaccination course should ~~also~~ be done with Gardasil, and not with another HPV vaccine.
If you have any further questions on the use of this medicine~~product~~, ask your doctor or pharmacist.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP. Minor linguistic changes were also endorsed.

In addition, it was accepted to express the quantity of aluminium salt in milligrams instead of micrograms in order to harmonise with the bivalent HPV vaccines in section 2 of the SmPC, PL and Labelling.

3. Overall conclusion and impact on the benefit/risk balance

In the current variation the possibility to use a two-dose vaccination schedule in children aged from 9 to 13 years of age instead of the current 3-dose schedule was evaluated. The scientific basis for the change consists of a comparison of immune responses in terms of cLIA titers between girls 9-13 years of age receiving 2 doses a 0, 6 months vs. women 16-26 years receiving 3 doses. The data presented indicate that the immune responses to 2 doses of Gardasil given to girls 9-13 years of age are at least as good as those in women 16-26 years old who were given 3 doses, which is the populations in which efficacy has been demonstrated. The importance of a stringent and careful follow-up of girls receiving 2 doses of Gardasil has been emphasised and is to be carried out in accordance with the follow-up for the 3-dose schedule in the same age group. In response to this CHMP request the MAH proposed a preliminary protocol synopsis for a PAES, which was considered acceptable. The MAH commits to update the CHMP with the feasibility assessment of options for such a PAES within 6 months after EU approval of the 2-dose schedule variation in adolescents and then each year after that. The full synopsis shall be provided once a country/region is identified where such a PAES is confirmed to be feasible. An updated RMP shall be submitted at the time of the next PSUR submission.

Based on the available data, the CHMP endorsed the introduction of a 2-dose schedule (0, 6 months) in individuals 9 to and including 13 years of age. The benefit-risk balance for qHPV vaccines remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) to include an alternative 2-dose vaccination schedule in children aged from 9 to 13 years. The Package leaflet is updated accordingly.

In addition, the MAH took the opportunity to express the quantity of aluminium salt in milligrams instead of micrograms in order to harmonise with the bivalent HPV vaccine in section 2 of the SmPC, PL and Labelling.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and minor linguistic changes were implemented.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.