European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR GARDASIL

International non-proprietary name: human papillomavirus vaccine [types 6, 11 16, 18] (recombinant, adsorbed)

Procedure No: EMEA/H/C/000703/II/0006

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

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I. SCIENTIFIC DISCUSSION

1.1 Introduction

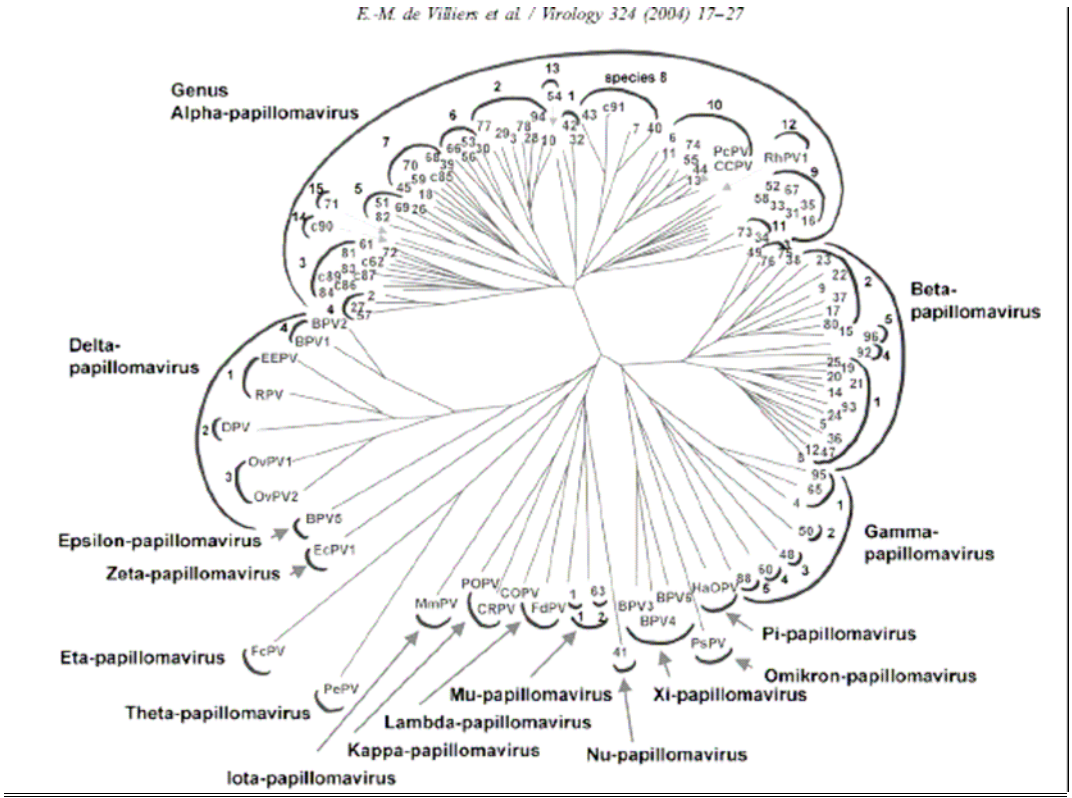
During the initial assessment of Gardasil the MAH committed to provide an efficacy analysis with respect to cross-protection against related non-vaccine HPV type disease and persistent infection (FUM 025). Protocols 012 and 013/015 (FUTURE studies) submitted in the Marketing Authorisation Application (MAA) were planned to fulfil this commitment. Based on the data on outcome of the cross-protection analysis, the MAH submitted this variation to extend the indication to include protection against HPV 31-, 33- 52- and 58-related low- and high-grade cervical dysplasia and cervical adenocarcinoma in situ (AIS) and to revise sections 4.1, 4.4 and 5.1 of the SPC.

Following CHMP request the MAH agreed to withdraw the request for an extension of indication to limit this application to the update of section 5.1 and this type II variation is thereby considered approvable.

1.2 Clinical aspects

The Papillomavirus family has been organised into genus and species groupings based on the major capsid protein, L1, sequence homologies (see figure 1). The L1 protein gene is the most conserved gene within the viral genome. Members of a papillomavirus genus share at least 60% L1 gene sequence homology. HPV species members share 70 to 75% L1 gene sequence homology on average, as well as a common pathophysiology. Individual types within a given HPV species may have up to 90% homology.

Figure 1



Forty (40) HPV types infect the genital tract. All of the known genital HPV types are members of Genus Alpha-papillomavirus. The 18 HPV types that have been classified as being oncogenic based on epidemiologic and/or phylogenetic evidence (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) are members of 5 species within the Alpha-papillomavirus genus (see table 1). HPV 16 is the prototype of the A9 species, and HPV 18 is the prototype of the A7 species.

Table 1: Taxonomy of oncogenic HPV types

Species	Types
A5	26, 51, 82
A6	53, 56, 66
A7	**18**, 39, 45, 59, 68
A9	**16,** 31, 33, 35, 52, 58
A11	73

HPV 16 and or HPV 18 cause most of HPV-related cancer cases (~70%). Non-vaccine members of the A9 and A7 species are responsible for up to 20% of all cervical cancers, and an even larger proportion of CIN lesions. The remaining 3 oncogenic HPV species (A5 [prototype HPV 51], A6 [prototype HPV 56] and A11 [prototype HPV 73]) include HPV types that rarely cause cancer, but commonly cause CIN. Table 2 summarises HPV types detected in cervical cancers.

Table 2: Distribution of HPV Types in Cervical Cancer (Munoz et al NEJM, 2003)

Species	HPV Type	Contribution
A9	HPV 16	58.7%
A7	HPV 18	12.2%
A7	HPV 45	4.7%
A9	HPV 31	3.8%
A9	HPV 33	2.3%
A9	HPV 52	,2.2%
A9	HPV 58	2.2%
A9	HPV 35	1.4%
A7	HPV 59	1.2%
A5	HPV 51	0.7%
A6	HPV 56	0.6%
A7	HPV 39	0.5%
A5, A6, A7, A11	HPV 26, 53, 66, 68, 73, 82	0.9%
Various	Intermediate and Low Risk Types	2.0%
--	Non-typable and infections with ≥3 types	7.2%
For calculations of HPV type contribution in the context of infection with 2 or more HPV types, a hierarchy based on the known pathogenicity of HPV types was used (HPV 16>18>31/45>52/58>33>all others).		

Given the homologies between HPV species members and the polyclonal nature of the immune responses generated by HPV vaccine it is biologically plausible that anti-HPV 16 and anti-HPV 18 generated by Gardasil may be able to neutralize virions for HPV types related to HPV 16 and/or HPV 18, thereby preventing infection and/or disease caused by these types, i.e. cross-protection. The highest degree of homologies in amino acid sequences are between HPV 18 and 45 (88%) followed by HPV 16 and 31 (83%) and HPV 16 and 33 (81%).

In the MAA, data were provided on cross-reactivity of Month 7 sera with non-vaccine HPV types from 10 vaccinated females in P007 in an antigen-binding assay. Cross-reactive antibodies were detected against HPV 31, 45, 52 and 58 virus-like particles (VLPs) and with similar kinetics as the vaccine types including persistence through 4 years postdose 3. Highest titers were observed for HPV 45 and HPV 31, as could be expected based on their high degree of homologies to HPV 18 and HPV 16, respectively. However, the total IgG titers were 1.5 to 2 logs lower than the anti-HPV 16 and 18 titers. The antibodies were shown by a pseudovirus (PsV) neutralization tests to cross-neutralise HPV

45 and HPV 31, although to a varying degree. These data demonstrated that cross-neutralisation antibodies to related HPV types are induced by Gardasil, although at a 1-2 log lower level than against vaccine types. To investigate whether these reduced antibody titers against related non-vaccine types translate to clinically-meaningful cross-protection, the current cross-protection efficacy analyses were performed.

An important objective of the clinical program for Gardasil was to determine whether the vaccine's prophylactic efficacy extends to HPV types whose L1 proteins share 80% homology (at the amino acid level) with HPV 16 or HPV 18 and are responsible for ≥2% of cervical cancers. The HPV types meeting these criteria are HPV types 31, 33, 45, 52, and 58. The impact of the vaccine on other oncogenic members of the A9 and A7 species, as well as members of the A5 and A6 species, was also to be evaluated. A11 species members were not evaluated since they very rarely cause cancer.

Two pre-specified analyses were prospectively planned to meet these objectives:

- Protocol 012 (Infection Cross-Protection)

Protocol 012 was a Phase III, randomised, double-blind, placebo-controlled study including 3578 16- to 24-year-old subjects who were randomised to receive Gardasil or placebo. This study was used to evaluate the vaccine efficacy with respect to the combined incidence of persistent infection or disease caused by HPV 31, 33, 45, 52 and 58. The vaccine efficacy with respect to infection and disease caused by other common HPV types was also evaluated.

- Protocols 013/015 combined (Disease Cross-Protection)

Protocols 013/015 (Future I and II studies) involved an evaluation of the efficacy of Gardasil with respect to the combined incidence of HPV 31- or 45-related CIN (any grade) or AIS (primary) and the combined incidence of HPV 31-, 33-, 45-, 52-, or 58-related CIN (any grade) or AIS (secondary), as well as other oncogenic HPV types.

Since submission of the Variation in April 2007, Protocol 013 and Protocol 015 have been completed, and relevant information for the database that incorporates the additional follow-up of the cross-protective efficacy population was submitted. Analyses of the End-of-Study database including a mean follow-up duration of 3.59 years post enrolment were evaluated.

1.2.1 Clinical efficacy

1.2.1 Protocol 012 (Infection cross-protection analysis)

1.2.1.1 Description

This study, included in the MAA, was a substudy to P013 (Future I) that aimed at bridging anti-HPV 16 responses between the monovalent HPV 16 vaccine used in Protocol 005 and the quadrivalent vaccine. The study enrolled a total of 3882 16- to 24-year-old women from 13 countries (USA, EU, Latin America and the Pacific region). The subjects receiving the HPV 16 vaccine (n=304) completed the study at Month 7, whereas all subjects that received the quadrivalent vaccine or placebo (n=3588) continued in the efficacy part of the P013 study. According to the provided documentation 3578 subjects were included in the cross-protection study.

Of note is that P012 cross-infection analysis was not powered to evaluate efficacy against infection caused by individual HPV types. HPV type-specific analyses were only supportive and descriptive.

The description of the study is introduced in Table 3.

Table 3: Summary of study P012

No subjects age group (Randomised)	Study design	Objectives	End points	Methodology
3578 HPV Vaccine: 1784 Placebo: 1794 16- to 24-year-old Month 36 visit 83.4% Month 48 visit 16.8%	Phase III, randomised, double-blind (with in-house blinding), placebo-controlled study of HPV Vaccine 6, 11, 16, 18. Primary analysis population: MITT-4 Other analysis population: MITT-2, RMITT-2, MITT-3	**Primary Objective**: To demonstrate that administration of HPV Vaccine 6, 11, 16, 18 reduces the incidence of persistent infection or disease caused by HPV 31, 33, 45, 52, and 58, compared with placebo. **Other Objectives**: To demonstrate that administration of HPV Vaccine 6, 11, 16, 18 reduces the incidence of persistent infection or disease compared with placebo (1) caused by non-vaccine A9 species members; (2) caused by non-vaccine A7 species members. To evaluate the impact of administration of HPV Vaccine 6, 11, 16, 18 on the overall rates of infection caused by non-vaccine HPV Types	Persistent HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58 Infection.(4-month definition) Replacement Analysis Endpoint: Persistent infection due to HPV types not included in HPV 6, 11, 16, 18.	To address the primary hypothesis regarding the endpoint of HPV 31-, 33-, 45-, 52- and 58-related persistent infection, CIN (any grade) or AIS, or EGL, the statistical criterion for success corresponds to a lower bound of the 95% CI > 0%.

Study populations

Primary Analysis Population

➢**Modified Intention-to-Treat-4 (MITT-4)** (included all subjects who were PCR negative on all specimens collected from Day 1 through Month 3 for the relevant HPV types, had received at least 2 doses of vaccine/placebo and had follow-up following Month 3): This population approximates adolescent and young adult women who are naïve to relevant HPV types prior to receipt of a full regimen of Gardasil.

Supplemental Prophylactic Efficacy Analysis Populations

➢**Restricted MITT-2 (RMITT-2)** Population (included all subjects who were seronegative (4 vaccine types) and PCR negative to all 14 HPV types at Day 1, had a negative Pap test, received at least one dose of vaccine/placebo and had at least one follow-up visit post-Day 30): This population corresponds to the general population of adolescent girls prior to sexual debut and is the target population for mass vaccination.

➢**MITT-2 Population** (included all subjects who were naïve to the relevant HPV types (HPV 31, 33, 45, 52 and 58) at Day 1, received at least one dose of vaccine/placebo and had at least one follow-up visit post-Day 30): This population is the broadest efficacy population corresponding to the general population of adolescents prior to sexual debut and sexually active young women and corresponds to the primary target population in clinical practice.

General population

➢**MITT-3 Population** (included all subjects who received at least one dose of vaccine/placebo, regardless of HPV status at Day 1 and had at least one follow-up visit post-Day 30): This population included women infected with vaccine and/or non-vaccine HPV types at vaccination onset and provides a real world estimate of efficacy in the vaccinated population.

The vaccine and placebo groups were well-balanced with respect to key demographic, behavioural and sexually-transmitted screening parameters. The mean age of subjects was 20.2 years. Overall, 94% of the subjects were sexually active, 3.9% had sexual transmitted diseases (STD) and 11% had

Pap testing finding suggestive of HPV infection at baseline. Overall, 77.2% of the population was naïve to all 4 vaccine HPV types by PCR or serology.

Overall 70.6 % of the study population was PCR negative at Day 1 to all 14 HPV types and 28.6% were PCR positive to at least one HPV type. HPV 16 was most common (8.2%) followed by HPV 51 (5.9%), HPV 56 (5.2%) and HPV 39 (5.0%), whereas HPV 31 (3.9%) and HPV 45 (1.9%) were less common.

1.2.1.2 Results

As of the cut-off date for analysis of the clinical trials database, a total of 83.4% and 16.8% of the study subjects completed the scheduled Month 36 and Month 48 visits, respectively.

Primary efficacy analysis using the 4 month definition
Administration of Gardasil reduced the combined incidence of persistent infection (4 month definition) and disease related to HPV 31, 33, 45, 52 and 58 (vaccine efficacy (VE): 24.7%). Time to event analysis showed that vaccine efficacy increased over time from Month 7 until Month 36. By HPV type, reductions were largest for HPV 31 and 33 and smallest for HPV 52 and HPV 58. The majority of endpoints were persistent infections. VE was not significant against cervical disease and External Genital Lesions (EGL) endpoints (lower bound of 95% CIs <0%).

Efficacy estimates were comparable in the RMITT-2 and MITT-2 populations to those in the MITT-4. Vaccine efficacy was somewhat lower in the MITT-3 population that included also women with ongoing infections were included.

Post-hoc analysis: Efficacy with respect to the combined incidence of HPV 31 and HPV 45 infection and disease using the 4 month definition
HPV 31 and HPV 45 are the HPV types that share the closest homology with HPV 16 and HPV 18. It was therefore of interest to assess VE against these HPV types (post-hoc analysis). Also, it was of interest to provide a virological context for the cross-protection disease analysis. In MITT-4 population VE was 47.7% (CIs 29.4, 61.5). Consistent VE against persistent infection and disease was observed in all populations, although of lower magnitude in the MITT-3 population. VE was only significant for the HPV 31-related endpoint in all populations.

Secondary analysis: Cross-protection against persistent infection or disease by HPV species using the 4 month definition
Gardasil reduced the incidence of persistent infection/disease caused by non-HPV 16 A9 HPV species members (HPV 31, 33, 35, 52, 58) and by non-HPV 18 A7 HPV species members (HPV 45, 59) in similar magnitudes (around 20%). The non-HPV 16-A9-species members were most common.

Cross-protective efficacy against persistent infection or disease at end of study
The MAH in the response to the RSI submitted the analyses regarding persistent infection by diagnostic visits based on the End-of-Study cross-protection efficacy analysis, which extends the follow-up period of the study population to a mean of 3.59 years after enrollment. Results with respect to persistent infection were provided using the more established 6- and 12-month definitions (the same HPV type DNA detected in ≥1 sample obtained on ≥2 consecutive visits that were ≥6 or ≥12 months apart)

End of Study cross protection efficacy analyses regarding persistent infection using the 12 month definition
The MITT-4 population was the pre-defined primary efficacy population in the cross-protection persistent infection analysis. Significant results were observed for the primary endpoint, HPV 31/33/45/52/58-related persistent infection, using the 12-month definition. In all other study populations, only trends towards efficacy were observed since the lower bounds of the 95% CIs were

<0%. This was likely due to the lower number of endpoints detected using the 12 months persistence definition.

As for the primary analysis, significant results were observed in the MITT-4 population for the post-hoc endpoint, HPV 31/45-related persistent infection, using the 12-month definition. In all other study populations, only numerical reductions were observed (lower bounds of the 95% CIs <0%).

Statistically significant efficacy was observed against persistent infection caused by HPV 31 across prophylactic populations based on any duration of infection (with detection at ≥2 consecutive visits) and for duration of infection ≥12 months (the exception was the RMITT-2 population for infection with a duration of ≥12 months for which the 95% CI on the efficacy estimate was <0%). For all other individual non-vaccine HPV types analysed, there was no statistically significant efficacy against persistent infection using the definitions included in these analyses.

Efficacy against HPV 31/33/45/52/58-related persistent infection at end-of-study using the 6-month definition

By use of the 6-month definition of persistent infection statistically significant efficacy against the primary composite endpoints, HPV 31/33/45/52/58-related and HPV 31/45-related persistent infection was observed across all analysis populations, driven largely by efficacy against persistent infection caused by HPV 31 (Table 4).

Table 4: Vaccine efficacy against HPV 31/33/45/52/58 -related 6-month persistent infection (Protocol 012 at End-of-Study)

Endpoint	R-MITT-2			MITT-2			MITT-3		
	Vaccine cases	**Placebo cases**	**Observed efficacy (95% CI)**	**Vaccine cases**	**Placebo cases**	**Observed efficacy (95% CI)**	**Vaccine cases**	**Placebo cases**	**Observed efficacy (95% CI)**
Composite endpoints									
HPV 31/33/45/52/58	127	167	**25.0** (5.0, 41.0)	263	328	**21.8** (7.7, 33.8)	358	424	**18.1** (5,5, 29.0)
HPV 31/45	49	81	**40.3** (13.9, 59.0)	97	168	**43.6** (27.2, 56.6)	152	217	21.4 (-5.6, 41.7)
Individual HPV types									
HPV 31	31	57	**46.2** (15.3, 66.5)	62	119	**49.0** (30.0, 63.1)	107	158	**33.6** (14.6, 48.6)
HPV 33	15	21	28.7 (-41.5 65.8)	33	45	27.1 (-16.8, 54.9)	43	55	22.5 (-17.6,, 49.3)
HPV 45	24	26	7.8 (-67.0, 49.3)	44	54	19.9 (-21.5, 47.5)	59	73	20.1 (-14.2, 44.3)
HPV 52	50	61	18.4 (-20.6, 45.0)	113	114	0.9 (-29.7, 24.3)	158	161	2.3 (-22.4, 22.1)
HPV 58	35	37	5.5 (-54.3, 42.2)	70	77	9.9 (-26.2, 35.8)	90	103	13.8 (-15.4, 35.8)

Vaccine efficacy against 6-month persistent HPV 31-infection was almost 50% in the prophylactic study populations, MITT-2 and RMITT-2. It is of note that this is close to the efficacy estimate of 57% observed against HPV 31-related CIN 2/3 (if co-infected lesions were excluded).

Efficacy against vaccine types - HPV 16/18-related persistent infection - results at end-of-study using the 6-month and 12-month definition

Tables 5 and 6 present the end-of-study analyses of efficacy against persistent infection related to HPV 16 and 18 using the 6-month and 12-month definitions, respectively, based on the same study data. The analyses of efficacy against HPV 16/18-related persistent infection through the end-of-study timepoint demonstrate conclusively that the vaccine is efficacious against these endpoints for each HPV type and regardless of the duration of infection considered.

Table 5: Efficacy against HPV 16/18-related persistent infection - 6-month definition (End-of-Study Analysis (Protocol 012)

Study population	qHPV vaccine n=1783		Placebo n=1788		Observed efficacy (%)	95% CI
	n	Number of cases	n	Number of cases		
Per-protcol						
HPV 16/18-related	1457	2	1475	180	98.9	96.1, 99.9
HPV 16-related	1269	2	1245	141	98.7	95.1, 99.8
HPV 18-related	1405	0	1414	55	100.0	93.2, 100
MITT-2						
HPV 16/18-related	1685	18	1680	254	93.5	89.4, 96.2
HPV 16-related	1475	12	1467	196	94.3	89.8, 97.1
HPV 18-related	1632	7	1629	83	91.8	82.3, 96.8
MITT-3						
HPV 16/18-related	1730	127	1725	348	66.3	58.6, 72.7
HPV 16-related	1730	106	1725	275	63.7	54.4, 71.2
HPV 18-related	1730	27	1725	109	76.1	63.2, 84.9

Table 6: Efficacy against HPV 16/18-related persistent infection - 12-month definition (End-of-Study Analysis (Protocol 012)

Study population	qHPV vaccine n=1783		Placebo n=1788		Observed efficacy (%)	95% CI
	n	Number of cases	n	Number of cases		
Per-protcol						
HPV 16/18-related	1447	0	1465	79	100	95.3, 100
HPV 16-related	1269	0	1241	60	100	93.9, 100
HPV 18-related	1395	0	1403	20	100	79.9, 100
MITT-2						
HPV 16/18-related	1642	9	1637	124	93.1	86.4, 96.9
HPV 16-related	1447	6	1440	94	93.9	86.2, 97.8
HPV 18-related	1591	3	1585	33	91.1	71.5,98.2
MITT-3						
HPV 16/18-related	1695	72	1686	173	60.1	47.2, 70.2
HPV 16-related	1695	59	1685	133	57.1	41.3, 69.0
HPV 18-related	1685	16	1675	48	67.4	41.5, 82.7

1.2.1.3 Discussion

Data on the PCR test methodology for the non-vaccine HPV types provided by the MAH to ensure that these assays were validated and as sensitive, specific and robust as those for the vaccine HPV types were considered acceptable.

The criteria to include the HPV types chosen in the primary endpoint (HPV 31, 33, 45, 52 and 58), i.e. based on amino acid homology (>80%) with L1 proteins of HPV 16 and 18 and on prevalence in cervical cancer (>2%) are supported. However, the use of composite endpoints including several non-vaccine HPV types is somewhat troublesome, e.g. if no vaccine efficacy is shown for certain types. On the other hand, the study could hardly be powered to demonstrate efficacy against each of the non-vaccine HPV types, and therefore, a combined endpoint of the related HPV types could be used. The use of a composite endpoint requires specific statements in the SPC on the efficacy against individual components of the composite to make possible an appropriate interpretation of the results obtained.

Infection cross-protection analysis

In the infection cross-protection analysis (mean follow-up 3 years post enrolment), the success criterion for the primary hypothesis was met. Vaccine efficacy in the combined incidence of persistent HPV 31, 33, 45, 52 and 58 infection and HPV 31, 33, 45, 52, 58-related genital disease compared with placebo was modest, 24.7% in the primary efficacy population MITT-4. The magnitudes of efficacy for persistent infection, CIN, AIS and EGL were comparable, but statistically significant

results were only shown for persistent infection. The results in the MITT-2 and RMITT-2 populations supported those obtained in the MITT-4. In the MITT-3 population efficacy estimates were lower, but benefit was still demonstrated, also in the disease endpoint.
Cross-protective efficacy was not evaluated against EGL since most low-grade vulvar/vaginal lesions and genital warts are attributed to HPV 6 and 11. The role of non-vaccine HPV types in development of these lesions is relatively small. As regards high-grade vulvar and vaginal lesions and cancers the majority are related to oncogenic HPV types, in particular HPV 16. The limited number of cases with high-grade vulvar and vaginal lesions precluded any meaningful analyses with respect to cross-protection.

A post-hoc efficacy analysis with respect to the closest HPV 16/18-related types, HPV 31 and HPV 45, showed larger reductions in the combined incidence of persistent infection and CIN disease, VE 47.7% in the MITT-4 population. Efficacy estimates in the MITT-2 and RMITT-2 were of similar magnitude. However, analyses by HPV type showed that efficacy was driven by HPV 31 and significant efficacy was not demonstrated for HPV 45 in any study population.

With respect to individual non-vaccine HPV types, reductions in the combined incidence of persistent infection/CIN were largest for HPV 31 and 33. No relevant efficacy was seen for HPV 35, HPV 52 or HPV 58. When analysed by A9 and A7 species (non-vaccine HPV types), similar VE estimates around 20% were obtained.

This Infection Cross-Protection analysis was designed to provide a virologic context for the Disease Cross-Protection analysis, and to evaluate the vaccine efficacy against persistent infection. However, the 4-month definition of persistent infection is not endorsed and the results could therefore not be accepted as presented in the study report. The WHO consensus paper (Vaccine 2004) defines persistent HPV infection as detection of the same HPV DNA in follow-up visits 6-12 months apart in women naïve for the relevant type at baseline. Since the definition of persistent infection was questioned several re-analyses were performed using the more established 6- and 12-month persistent infection. Statistically significant efficacy against the primary composite using the 6-month definition was observed across all analysis population at end of study. It was 21.8% (95% CI: 7.7, 33.8) in the MITT-2 population. In the secondary *post-hoc* composite (HPV 31/45) endpoint, vaccine efficacy was 43.6% (95% CI: 27.2, 56.6) in the MITT-2 population. The efficacy was driven by HPV 16-related types, primarily HPV 31, whereas no significant efficacy was observed for HPV 18-related types (including HPV 45). When analysed by individual HPV type, statistically significant results were only reached for HPV 31; vaccine efficacy was 49% (95% CI: 30.0, 63.1) in the MITT-2 population.
An updated end-of-study analysis of HPV 16 and 18 persistent infection was also provided, demonstrating high vaccine efficacy; 99-100% in the per-protocol population and 92-94% in the MITT-2 population, regardless of the duration of infection considered (6 or 12 months). These data merit to be mentioned in section 5.1 of the SPC.

1.2.2 Protocols 013 and 015 combined (Disease cross-protection analysis)

1.2.2.1 Description

The analysis of disease cross-protection was conducted in the combined database of P013 and P015. These phase III efficacy studies enrolled a total of 17,622 young women (P013 n=5,455 and P015 n=12,167). The populations in the 2 studies were generally comparable with regard to key enrollment parameters. Both studies limited enrollment to women 16 to 23 years old (P015 to 26 years in the Singapore site) with 4 or fewer life time sexual partners and excluded those with a history of genital warts and abnormal Pap test.

The description of studies is introduced in Table 7.

Table 7: Summary of study P013-P015

No subjects age group (Randomised)	Study design	Objectives	End points	Methodology
17622 *P013: 5455* *P015: 12167* HPV Vaccine: 8810 Placebo: 8812 16- to 26-year-old Month 36 visit: 88.7% Month 48 visit: 17.0%	Phase III, randomised, double-blind (with in-house blinding), placebo-controlled study of HPV Vaccine 6, 11, 16, 18]. Primary analysis population: MITT-2 Secondary analysis population MITT-3, RMITT-2	**Principal Cross-Protection Objectives**. Primary: To demonstrate that administration of a 3-dose regimen of HPV Vaccine 6, 11, 16, 18 reduces the incidence of CIN (any grade), AIS, or cervical cancer caused by HPV Types 31 and 45. Secondary: To demonstrate that administration of a 3-dose regimen of HPV Vaccine 6, 11, 16, 18 reduces the incidence of CIN (any grade), AIS, or cervical cancer caused by HPV Types 31, 33, 45, 52, and 58. **Other Cross-Protection Objectives**. To demonstrate that administration of a 3-dose regimen of HPV Vaccine 6, 11, 16, 18 to 16- to 26-year-old women reduces their risk of developing: (1) CIN (any grade), AIS, or cervical cancer caused by non-vaccine HPV type A9 species members (i.e., HPV 31, 33, 35, 52, 58); (2) CIN (any grade), AIS, or cervical cancer caused by non-vaccine HPV type A7 species members (i.e., HPV 39, 45, and 59); (3) CIN (any grade), AIS, or cervical cancer caused by HPV 56; (4) CIN (any grade), AIS, or cervical cancer caused by HPV 51. **HPV Replacement Objectives**. To evaluate the impact of prophylactic administration of a 3-dose regimen of HPV Vaccine 6, 11, 16, 18 to 16- to 26-year-old women on their risk for development of CIN (any grade), AIS, or cervical cancer caused by HPV types other than HPV 6, HPV 11, HPV 16, or HPV 18.	**Primary Cross-Protection Endpoint.** The primary endpoint was the composite endpoint of CIN (any grade), AIS, or cervical cancer caused by HPV 31 or 45 **Secondary Cross-Protection Endpoint.** The secondary endpoint was the composite endpoint of CIN (any grade), AIS, or cervical cancer caused by HPV 31, HPV 33, HPV 45, HPV 52, or HPV 58 **Other Cross-Protection Endpoints.** For each endpoint focusing on CIN (any grade), AIS, or cervical cancer caused by a specific subset of HPV types **HPV Replacement Endpoints.** The endpoints of interest for the replacement analyses are: CIN (any grade) or AIS, and CIN 2/3 or AIS, caused by HPV types other than HPV 6, 11, 16, or 18.	To address the primary hypothesis regarding the endpoint of HPV 31-, 45 CIN (any grade) or AIS and the secondary endpoint of HPV 31-, 33-, 45-, 52- and 58-related CIN (any grade) or AIS the statistical criterion for success corresponds to a lower bound of the CI95% > 0%.

Study Population

Primary Analysis Population: MITT-2 Population

included subjects who:

- were PCR negative to the relevant HPV type at Day 1,
- received at least one dose of vaccine/placebo
- had at least one follow-up visit post-Day 30

Case counting started at Day 31

Note: because P015 did not include cervicovaginal specimen collection at Month 3, it was not possible to conduct an analysis in the MITT-4 population in the Disease Cross-Protection Data Set. The MITT-2 population was chosen as a conservative approximation of this population.

Key Secondary Efficacy Analysis Population: RMITT-2 Population

General Population: MITT-3 Population

The criteria for inclusion into the RMITT-2 and MITT-3 are the same as for P012.

1.2.2.2 Results

As of the cut-off date for analysis, a total of 88.7% (P013 84% and P015 91%) and 17.0% of subjects completed the scheduled Month 36 and Month 48 visits, respectively.

The vaccine and placebo groups were well-balanced with respect to key demographic, behavioural and sexually-transmitted screening parameters. The mean age of subjects was 20.0 years.

Primary efficacy analyses
In the disease cross-protection analysis with respect to HPV 31/45-related CIN (any grade) or AIS (mean follow up duration of 3.0 years), the success criterion for the primary hypothesis was not met in the primary efficacy population (MITT-2) (VE was 25.1%, 95% CI: -3.5; 46.0). VE against CIN 2/3 was also non-significant (lower bound of 95% CI <0%). In the supporting analyses in the RMITT-2 population, higher VE was found against CIN (any grade) (VE: 45%, 95% CI: 6.4; 68.4) and importantly also against HPV 31/45-related CIN 2/3 (VE: 61.6%, 95% CI: 9.7, 85.3).

Of note is that there were differences between the studies, with much lower efficacy estimates in the P015 study than in P013. In all study populations in P015, the lower bound of the 95% CI was <0% and no reductions in disease endpoints were observed in the vaccines compared with placebo.

Analyses of End of Study database (mean follow up duration of 3.59 years)
In the primary composite endpoint, HPV 31/45-related CIN (any grade) or AIS, vaccine efficacy was statistically significant in all populations; 37% (95% CI: 17.0; 52.8) in the MITT-2 population (primary efficacy population), 44% (95% CI: 12.9; 64.1) in the RMITT-2 population and 23% (95% CI: 9.6; 31.3) in the MITT-3 population. With regard to the more relevant endpoint HPV 31/45-related CIN 2/3 the corresponding percentages were 43% (95% CI: 12.1; 63.9), 59% (95% CI: 14.1; 81.5) and 21% (95% CI: -5.6; 41.7). The updated efficacy estimates were higher in the MITT-2 and -3 populations compared with those in the original cross-protection analysis. In the MITT-2 analyses significant results were now observed (lower 95% CI bound >0%). The results in the RMITT-2 population were somewhat lower, but consistent with those in the original cross-protection efficacy analysis.

Secondary efficacy analyses
In the disease cross-protection analysis with respect to HPV 31/33/45/52/58-related CIN/AIS (mean follow up duration of 3.0 years), the success criterion for the secondary hypothesis was met. VE was 18.6% (95% CI: 1.0, 33.2) in the MITT-2 population. The analysis in the RMITT-2 and MITT-3 populations supported the results obtained in the primary population. However, the magnitude of VE was modest with wide 95% confidence intervals in all analyses. When evaluated by disease severity, VE against CIN 2/3 was 43.3% (95% CI: 7.3, 66.0) in the RMITT-2 population, but substantially lower in the MITT-2 (VE: 16%, ns) and MITT-3 (VE:9.8%, ns).

With regard to AIS, there were 6 placebo cases (HPV 45 (n=1), HPV 52 (n=4), HPV 58 (n=1)) and 1 vaccine case (HPV 52) who were diagnosed with AIS. There were no cases of cervical cancer.

As for the primary analysis, in P015, the lower bound of the 95%CI was <0% in all efficacy analyses and no reductions in disease endpoints were observed in the vaccinees compared with placebo.

Analyses of End of Study database (mean follow up duration of 3.59 years)
In the secondary composite endpoint HPV 31/33/45/52/58-related CIN (any grade), VE was statistically significant in all populations; 26% (MITT-2 95% CI: 12.9; 37.8), 29% (RMITT-2 95% CI: 8.3; 45.5) and 20% (MITT-3 95% CI: 8.2; 29.6). VE against HPV 31/33/45/52/58-related CIN 2/3 or AIS was only significant in the MITT-2 population (26% 95% CI: 4.6; 42.5), whereas only numerical reductions were seen in the RMITT-2 (33% 95% CI: -0.3; 55.0) and MITT-3 (14% 95% CI: -3.3; 28.8). The updated efficacy estimates were somewhat higher (MITT-2 and -3) than those observed in the original cross-protection efficacy analysis. In the RMITT-2 analyses of efficacy against CIN 2/3, estimates were lower with the lower 95% CI bound <0%.

Analysis of vaccine efficacy against individual HPV types
The studies were not powered to assess efficacy against disease caused by individual types, HPV type-specific analyses were only supportive and descriptive.

Efficacy was primarily driven by reductions in the HPV 31-related endpoint (VE 38.4% for MITT-2 population and VE 59.8% for RMITT-2 population) (mean follow up duration of 3.0 years). No significant efficacy was observed for the other members of the HPV A9 species. In particular, no efficacy was observed relative to HPV 45 (A7 species member). To evaluate the impact of Gardasil on the primary and secondary endpoints *post-hoc analyses* excluding the HPV 45-related endpoints were also conducted.

Analyses of vaccine efficacy against HPV31/33/45/52/58-related CIN 2/3 by HPV type - End of Study database (mean follow up duration of 3.59 years)
Upon CHMP request the MAH submitted the analyses of vaccine efficacy with regard to CIN 2/3 or AIS caused by selected HPV types of the combined database of protocols 013/ 015 at End-of-Study. The results are presented in table 8 below. As regards individual HPV types, only for HPV 31 significant efficacy against CIN 2/3 was demonstrated, with VE 70% in the RMITT-2 population and VE 56% in the MITT-2 population.

Table 8: Vaccine efficacy with regard to CIN 2/3 or AIS caused by selected HPV types (Combined Database of Protocols 013/ 015 at End-of-Study)

	R-MITT-2			MITT-2			MITT-3		
	Vaccine cases	Placebo cases	Observed efficacy (95% CI)	Vaccine cases	Placebo cases	Observed efficacy (95% CI)	Vaccine cases	Placebo cases	Observed efficacy (95% CI)
Composite endpoints									
HPV 31/33/45/52/58	44	66	32.5 (-0.3. 55.0)	111	150	25.8 (4.6, 42.5)	216	252	14.2 (-3.3, 28.8)
HPV 31/45	11	27	58.7 (14.1, 81.5)	34	60	43.2 (12.1, 63.9)	84	107	21.4 (-5.6, 41.7)
HPV 31/33/52/58	41	66	37.1 (5.7, 58.5)	100	146	31.4 (10.9, 47.3)	205	246	16.6 (-0.8, 31.3)
A9 species (not HPV 16)	27	52	47.5 (15.0, 68.3)	111	157	29.1 (9.1, 44.9)	221	262	15.6 (-1.3, 29.8)
A7 species(not HPV 18)	11	21	47.0 (-14.9, 76.9)	34	46	25.9 (-17.9, 53.9)	55	66	16.6 (-21.1, 42.8)
Individual HPV types									
HPV 31	8	27	70.0 (31.9, 88.3)	23	52	55.6 (26.0, 74.1)	67	92	27.1 (-1.1, 47.7)
HPV 33	12	16	24.0 (-71.7, 67.3)	29	36	19.1 (-36.0, 52.3)	49	59	16.8 (-23.8, 44.4)
HPV 35	4	4	-1.5% (-449, 81)	13	15	13.0 (-96.6, 62.2)	21	23	8.6 (-73.1, 52.0)
HPV 39	4	10	59.6 (-40.8, 90.8)	15	24	37.5 (-24.5, 69.6)	28	33	15.1 (-42.5, 50.7)
HPV 45	3	2	-51.9 (-1738, 83)	11	11	0.0 (-155, 60.9)	18	19	5.2 (-91.4, 53.2)
HPV 51	16	15	-8.1 (-136, 50.1)	34	41	16.3 (-35.5, 48.6)	53	64	17.1 (-21.4, 43.6)
HPV 52	17	23	25.2 (-46.8, 62.6)	44	52	14.7 (-30.2, 44.3)	78	87	10.3 (-23.3, 34.9)
HPV 56	12	16	24.1 (-71.6, 67.3)	34	30	-13.7 (-92.8, 32.6)	48	44	-9.2 (-68.6, 29.1)
HPV 58	16	20	18.9 (-65.2, 60.8)	24	35	31.5 (-18.8, 61.1)	41	59	30.5 (-5.5, 54.6)
HPV 59	5	9	43.8 (-87.7, 85.3)	9	15	39.9 (-47.0, 76.9)	11	19	42.1 (-28.5, 75.2)

Post-hoc analyses: Exclusion of HPV 45-related endpoints
Analyses of End of Study database (mean follow up duration of 3.59 years) showed significant results against CIN (any grade) and CIN 2/3 in both prophylactic populations (VE: 31% (MITT-2) and VE: 37% (RMITT-2)), but not in the MITT-3 population. VE as regards CIN (any grade) was 30% (MITT-2) and 34% (RMITT-2).

Cross-protective efficacy against CIN 2/3 or AIS due to any HPV type
End of study results (mean follow up duration of 3.59 years)
End of study results showed that administration of Gardasil reduced the overall incidence of CIN 2/3 or AIS due to any HPV type by 42.7% in the RMITT-2 population, 33.8% in the MITT-2 population and by 18.4% in the MITT-3 population.

With regard to all non-vaccine types Gardasil resulted in a non-significant reduction in the incidence of CIN 2/3 or AIS for all studied populations, 23.6% in RMITT-2 population, 16.2% in MITT population and 9.0% in MITT -3 population.
The negative findings with respect to efficacy against other non-vaccine HPV types (not tested for) could be explained due to the masking effect, rather than to a HPV type replacement phenomenon.

HPV type replacement analysis
The question whether there would be an upsurge of persistent infection and disease caused by non-vaccine HPV types was investigated by using the P012 and the combined P013/P015 infection and disease cross-protection databases, respectively. The analyses focused on the RMITT-2 and MITT-3 populations.

For the infection cross-protection analyses, the rates of persistent infection, CIN, AIS or EGL caused by non-vaccine type individually and as a composite were compared by vaccination groups.

For the disease cross-protection analyses, the rates of CIN (any grade) or AIS or, of CIN 2/3 or AIS, overall, caused by vaccine HPV types and caused by non-vaccine HPV types were compared between vaccination groups.

Results on HPV type replacement analysis - Protocol 012
In the RMITT-2 population the incidence of persistent infection and CIN (any grade) or AIS caused by non-vaccine types (HPV 31, 33, 35, 45, 52, 58, 59) was reduced by 19.7% (-0.3 to 35.8%) in the vaccine group compared with placebo. Reductions were observed for all HPV types within the composite endpoint with the exception of HPV 58 (30 cases in the vaccine group vs. 29 cases in the placebo group).

In the MITT-3 population the rate of persistent infection and CIN (any grade) or AIS caused by non-vaccine types was reduced by 15.1% (2.8 to 17.2%) compared with placebo. Reductions were observed for all HPV types within the composite endpoint.

These data do not suggest HPV type replacement; rather there was some evidence of cross-protection against non-vaccine HPV types for which testing was performed.

Results on HPV type replacement analysis - Protocol 013/015
In the RMITT-2 population the incidence of CIN (any grade)/AIS or CIN 2/3/AIS caused by non-vaccine types was reduced by 18% (0.3 to 32.7%) and 25.3% % (-8.7 to 48.9%) respectively, in the vaccine group compared with placebo. The strongest reduction was observed for HPV 31 (76.1%) whereas for HPV 35 and HPV 45 no efficacy was seen.

In the MITT-3 population the incidence of CIN (any grade)/AIS or CIN 2/3/AIS caused by non-vaccine types was reduced by 8.2% (-1.6 to 17.2%) and 4.5% (-12.9 to 19.2%) respectively, in the vaccine group compared with placebo. For HPV 45 and HPV 56 no efficacy was seen.

It was noted that with respect to “other HPV type-related” CIN i.e. CIN due to a HPV type for which testing was not done and “other HPV type-related” CIN 2/3 i.e. CIN 2/3 due to a HPV type for which testing was not done, there were more cases in the vaccine group than placebo. For CIN (any grade) there were 74 vs. 71 cases in the vaccine and placebo group, respectively, in the RMITT-2 population and 161 vs. 140 cases in the MITT-2 population. For CIN 2/3 there were similar findings with 20 vs. 9 cases in the RMITT-2 and 70 vs. 59 cases in the MITT-3. The negative findings with respect to efficacy against “other HPV type-related” (not tested for) could be explained due to the masking effect, rather than to a HPV type replacement phenomenon.

Contributions of oncogenic HPV types to CIN lesions and AIS
The contributions of oncogenic HPV types to CIN 1, CIN 2, and CIN 3 vary. It is of note that non-HPV 16/18 oncogenic HPV types are much more commonly detected in CIN 1, 2, and 3 lesions than

in cervical cancer cases. Also, detection of more than one HPV type in a given CIN biopsy specimen is common. HPV 16 is unique in that the proportions of lesions that are HPV 16-positive increase with histopathologic grade severity.

The cumulative incidence (through end of study) of CIN 2/3 or AIS lesions by HPV type in the placebo group within the RMITT-2 population of the Combined Protocol 013/015 is shown in Figure 1-1. The incidence of HPV 16-related CIN 2/3 was the highest, followed by CIN 2/3 caused by other Species A9 members and HPV 18.

Figure 1-1: Cumulative incidence of CIN 2/3 or AIS lesions by HPV types through End-of-Study (Placebo Group, RMITT-2 population, Combined Protocol 013/Protocol 015)

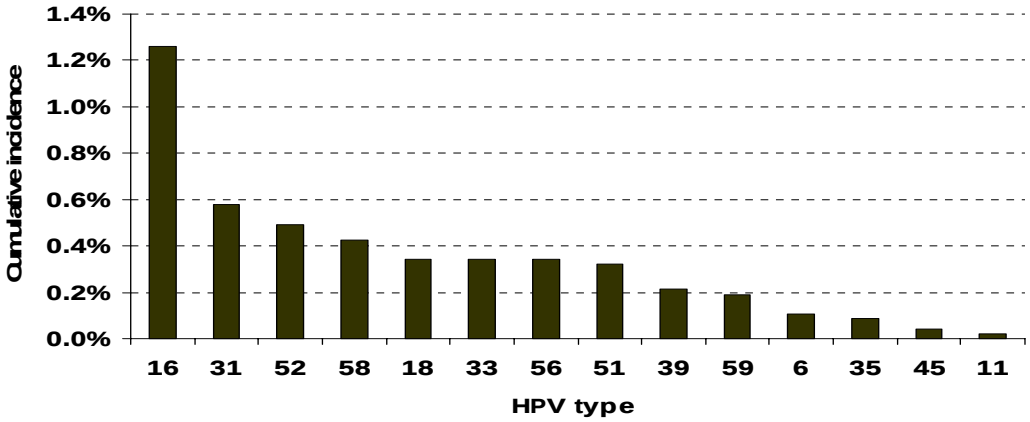


Table 9 summarises the proportion of lesions in which co-infection occurred by categories of HPV types. CIN 1, CIN 2, and CIN 3 lesions that contained vaccine and non-vaccine HPV types were common.

Table 9: Categories of co-Infection in tissue specimens with of CIN 2/3 or AIS (RMITT-2 Population in the Combined Protocol 013/015 End-of-Study Database)

	CIN 1	CIN 2	CIN 3 or AIS
Proportion of HPV 16-positive lesions that were also positive for non-vaccine A7/A9 HPV types	27.0%	22.6%	17.9%
Proportion HPV 18-positive lesions whose lesion that were also positive for non-vaccine A7/A9 HPV types	44.0%	50.0%	14.3%
Proportion of HPV 31, 33, 52, or 58-positive lesions[†] that were also positive for a vaccine HPV type	31.4%	25.6%	32.1%
[†] Types for which mention in Section 4.1 is being sought.			

The HPV types differ substantially by malignant potential with HPV 16 and HPV 18 being the most oncogenic HPV types. For non-HPV 16/18 types, CIN 2/3 rarely progress to cervical cancer. The spectrum of disease is thus different, and the use of CIN 2/3 related to oncogenic non-vaccine HPV types as a surrogate marker for cervical cancer could be discussed. However, all over the world, the detection of CIN 2/3 regardless of HPV type leads to excision of the lesion and therefore the clinical impact of CIN 2/3 caused by oncogenic non-vaccine HPV types will be the same as for HPV 16/18.

It is noteworthy that the contribution of non-HPV 16 A9 species types to CIN 2/3 or AIS is considerably larger than that for HPV 18. Data were only given for the most restricted population. Upon CHMP request the MAH provided data for the MITT-3 population, which were consistent with the findings in the RMITT-2 population, The cumulative incidence of CIN 2/3 related to HPV 31 and HPV 52 was higher than that of HPV 18, whereas HPV 58 and HPV 33 were as common as HPV 18.

Therefore, the prevalence of non-vaccine HPV types in CIN 2/3 is not as rare as perceived. However, it is applicable to HPV 45, which was the least frequent oncogenic non-vaccine HPV type observed in the studies.

Quantification of the clinical benefit of the cross-protective efficacy
The calculations at the end of study demonstrated that, when accounting for co-infection, 0.9 HPV 32/33/52/58-related CIN 2/3 cases per 1000 subjects vaccinated were prevented in the RMITT-2 population and 0.7 cases in the MITT-2 population. This translates to a net benefit of 4 and 6 additional cases prevented. For HPV 16/18-related CIN 2/3 (regardless of presence of HPV 31/33/52/58), there were 17.7 prevented cases per 1000 subjects vaccinated in the RMITT-2 population and 15.6 cases in the MITT-2.

1.2.2.3 Discussion

The disease cross-protection analysis was performed in the combined phase III efficacy trials including 17,599 16 -to 26 year-old women. An analysis of the combined study data, instead of studies 013 and 015 separately, would give adequate power for demonstration of cross-protection and would improve the precision of vaccine efficacy. Nevertheless, this type of combined analysis was already accepted for the marketing authorisation application and is therefore considered appropriate. The follow-up was for 3 years from start of enrolment, but was updated in the MAH response to the RSI with the End-of-Study results at 3.59 years. As was shown in the efficacy time-to-event analyses, cross-protective efficacy was only evident after 12 months following start of immunisation and increased over time. However, this repeated testing of data raises a multiplicity concern.

The cross-protection endpoints should have focused on high-grade CIN lesions (CIN 2/3) rather than CIN (any grade) or AIS. The vaccine has only been approved for the prevention of HPV 16- and HPV 18-related CIN 2/3, which should also apply for an indication with respect to related non-vaccine oncogenic HPV types. As the analyses for cross-protective efficacy against CIN 2/3 due to non-vaccine types were also provided, this concern is resolved. Low-grade cervical dyplasia is not considered a relevant disease endpoint and the proposed text for section 4.1 of the SPC is not acceptable. Adenocarcinoma in situ (AIS) has also not been accepted in the indication for vaccine HPV types. The data provided on AIS (altogether 7 cases) in the cross-protection analysis are insufficient to support an indication. However, since AIS has been included as part of high-grade cervical lesion endpoint (CIN 2/3 or AIS) in all efficacy trials, it is appropriate to mention this disease category in the SPC section 5.1

The use of composite efficacy endpoints, including pre-specified combinations of non-vaccine HPV types, could be questioned. The non-vaccine types are not uncommon causes of CIN lesions, but due to the anticipated lower vaccine efficacy against non-HPV 16/18 types more endpoints would be necessary to obtain statistical significance. The MAH´s justification with respect to this aspect including the biology-based selection of HPV types could be accepted, as long as the analyses of individual components support the overall conclusion given by the composite. However, composite endpoints make interpretation of data difficult, since the vaccine might not be efficacious against all of the types evaluated, as was also seen in the combined dataset. No significant efficacy could be demonstrated for HPV 45, which was used in the primary efficacy endpoint in combination with HPV 31 and in the secondary efficacy endpoint in combination with HPV 31, 33, 52 and 58. The pre-specified composite endpoints should be mentioned in the SPC, but require specific statements on the efficacy against individual components of the composite to facilitate an appropriate interpretation of the results. Since HPV type-specific analyses were defined as descriptive and supportive, the lack of adjustment of multiplicity is considered acceptable.

The high frequency of baseline PCR positivity to vaccine (14.8%) and related non-vaccine HPV types (14.8%) is noted. In the response to the RSI, the MAH addressed the geographical distribution of HPV types in the combined P013/P015 database and showed that HPV prevalence was in accordance with the data described in the literature. It was clarified that HPV prevalence and HPV type

distribution depend heavily on study populations (age, sexual characteristics) and associated HPV-related lesions and could therefore differ between epidemiological studies. HPV 16 has been consistently found to be the most prevalent HPV type worldwide, which was also observed in the 013/015 studies. The high prevalence of some of the non-vaccine HPV types, such as HPV 51 and HPV 56, is an expected finding since there types cause a substantial number of CIN 1 lesions, but rarely cause CIN 3 or result in cervical cancer The causal role of any of the HPV types identified in CIN 2/3 lesions will be ascribed the most oncogenic HPV type, i.e. HPV 16 and 18.

The subjects with multiple HPV types were characterised by sexual demographics and disease severity. It was shown that subjects who were positive to multiple HPV types Day 1 were more sexually experienced. As regards CIN 2/3, more cases with multiple HPV types in the lesions were seen in the placebo group (~40%) than in the vaccine group (~30%). Very few subjects had co-infection with more than 3 types. This high prevalence of co-infections with several HPV types makes the assessment of vaccine efficacy for cross-protection difficult. The most common 2-type combination involved HPV 16 in combination with other HPV types such as HPV 18, HPV 51 and HPV 52.

A major concern in the initial assessment was that in the combined analysis of the pivotal phase III trials evidence of cross-protective efficacy was not convincingly demonstrated in the largest and most important P015 trial. With the provision of the end-of-study results including an extended follow-up to a mean of 3.59 years with more endpoints accrued, consistency between the two studies with respect to improved cross-protective efficacy was shown. The sources of variability were satisfactorily addressed by the MAH. The homogeneity test did not detect differences in the protocols for various endpoints.

Cross-protective efficacy results

In the updated end-of-study analyses, the primary endpoint of the cross-protection analysis, HPV 31/45-related CIN (any grade), met the success criterion in all study populations with vaccine efficacy of 37% in the primary MITT-2 population, 44% in the RMITT-2 and 23% in the MITT-3 population. In the analyses of efficacy against CIN 2/3, significant results were obtained in the MITT-2 (VE: 43%) and RMITT-2 (VE: 59%), whereas in the MITT-3 (VE: 21%) the lower bound of the 95% CI was <0 %. However, the results were driven by reductions in HPV 31-related endpoints, whereas no efficacy could be confirmed for HPV 45.

With respect to the secondary endpoint, the combined incidence of HPV 31/33/45/52/58-related CIN (any grade), the success criterion was fulfilled in all study populations. However, VE was modest in the primary population (VE: 26%) and also in the RMITT-2 (VE: 29%) and MITT-3 populations (VE: 20%). In the more important CIN 2/3 endpoint vaccine efficacy was 26% (95% CI: 5, 43) in the primary population, whereas statistically significant results were not obtained in the RMITT-2 population (VE: 33% (95% CI: 0, 55).
With respect to HPV species, the results give evidence of some cross-protective efficacy against the composite of non-vaccine A9 HPV species members including HPV types related to HPV 16. Vaccine efficacy against HPV 31/33/52/58-related CIN 2/3 was 31% (MITT-2) and 37% (RMITT-2). However, no statistically significant efficacy was demonstrated for the HPV 18-related non-vaccine types (A7 HPV species) individually or combined.

With respect to individual HPV types, only for HPV 31 cross-protective efficacy was confirmed. This HPV type has the closest structural relatedness to HPV 16. In the primary MITT-2 population, statistically significant results were obtained against HPV 31-related CIN 2/3 with VE of 56% (95% CI: 26, 74) and in the RMITT-2 population it was 70% (95% CI: 32, 88). In the MITT-3 population only numerical reductions were observed (VE: 27% (95% CI -1.1, 48). For all other individual HPV types no statistically significant efficacy against CIN 2/3 was demonstrated. Since the studies were not powered to assess efficacy against disease caused by individual types, HPV type-specific analyses were only supportive and descriptive.

In general, larger magnitude of cross-protection was observed for high-grade CIN lesions (CIN 2/3) than for low-grade cervical lesions.

The non-significant efficacy results observed with respect to HPV 45-related endpoints was unexpected in view of the MAH´s data demonstrating that Gardasil induced a cross-neutralization immune response to HPV 18, as reported in the MAA. In these laboratory experiments it was shown that anti-HPV responses induced by Gardasil prevented cell uptake of HPV 31 and HPV 45 VLPs, but 2 log higher antibody titres were required for cross-neutralization. The reasons for the negative outcome in the cross-protection analyses remain unknown.

In conclusion, the updated cross-protective efficacy results obtained in the end-of study analyses met the success criterion in all study populations and for the defined composite endpoints. Vaccine efficacy was modest in the primary HPV 31/45-related CIN endpoint and was only driven by reductions in HPV 31-related endpoints. No efficacy could be confirmed for any of the other individual HPV types included in the composite endpoint. There is, however, evidence that the vaccine exerts some cross-protection against certain HPV-16 related non-vaccine HPV types. No statistically significant efficacy was demonstrated for the HPV 18-related non-vaccine types individually or combined. The clinical relevance of the modest efficacy observed was satisfactorily addressed by the MAH. However, with regard to the non-vaccine types, the oncogenic potential differs profoundly from that of the vaccine HPV 16/18 types with the non-vaccine HPV types being commonly detected in CIN 1, CIN 2 and CIN 3 lesions, but rarely in cervical cancers. Hence, the type-specific spectrum of diseases differs by grades of histopathological severity. HPV 16 is unique in that the proportions of positive lesions increase with severity. The correlation of CIN 2/3 (surrogate endpoint for cervical cancer) with cancer is, thus, substantially lower for the oncogenic non-vaccine types. For this reason and given the modest efficacy against CIN 2/3 observed for non-vaccine HPV types cross-protection is to be regarded as an added benefit only to be mention in section 5.1 of the SPC. The MAH agreed to withdraw the request for an extension of indication to limit this application to the update of section 5.1 and this type II variation is thereby considered approvable.

Cross-protective efficacy against CIN 2/3 or AIS due to any HPV type

Overall Gardasil reduced the incidence of CIN 2/3 due to any HPV type by 42.7% in the RMITT-2 population, by 33.8 % in the MITT-2 population and by 18.4 % in the MITT-3 population during the extended 3.6-year follow-up. This magnitude of efficacy is clinically relevant in the RMITT-2 population, but seems low, based on the attributed burden of CIN 2/3 disease of vaccine (70%) + non-vaccine (24-39%) HPV types. The RMITT-2 population is the population most resembling sexually naïve subjects (target population for general vaccination programmes), but there are no means to exclude baseline HPV infections/diseases not tested for (6 oncogenic HPV types) even by Pap testing. The overall efficacy in the MITT-3 population was very low due to the fact that these subjects were included regardless of HPV status with ongoing infection/disease at the start of vaccination. Time event curves have shown that efficacy increased by time.

With regard to all non-vaccine HPV types, included those not tested for, Gardasil resulted in non-significant reductions of related CIN2/3 in all study populations.

The MAH provided a literature overview and update the SPC with respect to proportion of CIN 2/3 related to different oncogenic HPV types.

HPV type replacement analysis

The HPV type replacement issue is an important commitment for the MAH to pursue in the post-marketing period, which requires long-term population based evaluations. The current data at 3.59 years of follow-up in the pivotal efficacy studies 012/015, do not suggest the occurrence of HPV type replacement by the 10 non-vaccine types for which testing was performed. However, there was an increased number of cases with CIN 2/3 caused by other HPV types (not tested for) in the vaccine group compared to placebo. This might be artefactual and explained by a masking effect of the vaccine rather than a replacement phenomenon. HPV type replacement is an ongoing important commitment that requires long-term surveillance to give reliable results and will be the subject of future assessment.

1.3 Pharmacovigilance system

1.3.1 Risk Management Plan

The CHMP considers that this extension of therapeutic indication does not require revised Risk Management Plan.

1.4 Overall discussion and Benefit/Risk assessment

The aim of this variation application was to evaluate whether administration of Gardasil impacts on the incidences of infection and cervical disease caused by non-vaccine types. The HPV types to be assessed were selected for cross-protective efficacy evaluations based on the known homology of their L1 proteins with those of HPV 16 and HPV 18 (≥80% homology) and the relative contribution of each vaccine type to cervical cancer (responsible for ≥2% of cervical cancers). The HPV types meeting these criteria are HPV types 31, 33, 45, 52, and 58. Of these, HPV 31 and HPV 45, share the highest level of homology with vaccine HPV types 16 and 18. The selection criteria of HPV types are considered relevant.

Evaluations were conducted with respect to clinical disease endpoints (cervical intraepithelial neoplasia (CIN, any grade), adenocarcinoma in situ (AIS)) in the combined study of Protocol 013/015 and virological endpoints (persistent infection) in Protocol 012 (substudy to P013). With respect to disease endpoints high-grade CIN (CIN 2/3) lesions should have been the primary endpoint. Data on CIN 2/3 were, however, provided for all analyses, and should constitute the basis for approval. With respect to persistent infection, an unacceptable definition was used in study 012 (4-month definition) but upon request data on the more established 6-month and 12-month persistent infection were provided.
Vaccine efficacy was evaluated with respect to combined endpoints, i.e. HPV 31/33/45/52/58-related persistent infection and CIN/AIS and HPV 31/45-related CIN/AIS. Data were also provided by A7/A9 species and on each HPV type. The CHMP considers that the use of composite endpoints could be acceptable since it is based on defined biological and epidemiologic principles. However, the difficulty in using such endpoints was clearly illustrated by the results obtained in the clinical trials, with only one HPV type (HPV 31-related CIN 2/3) attaining statistical significant results. It is also of note that the MAH in the proposed indication excluded HPV 45 type from the pre-defined composite endpoint.

The efficacy results were generally comparable between P012 infection cross-protection analysis and the combined Protocol 013/015 Disease Cross-Protection data set.

The updated cross-protective efficacy results obtained in the end-of study analyses (after a mean follow-up of 3.59 years) met the success criterion in all study populations and for the defined composite endpoints. Vaccine efficacy was very modest in the primary HPV 31/45-related CIN endpoint and was only driven by reductions in HPV 31-related endpoints. Against HPV 31, the type most structurally related to HPV 16, vaccine efficacy was 70% against related CIN 2/3 in the RMITT-2 population and 56% in the broader MITT-2 population. No efficacy could be confirmed for any of the other individual HPV types included in the composite endpoint. There is, however, definite evidence that the vaccine exerts some cross-protection against HPV-16 related non-vaccine HPV types (A9 species), whereas no statistically significant efficacy was demonstrated for the HPV 18-related (A7 species) non-vaccine types individually or combined,The clinical relevance of the modest efficacy observed was satisfactorily addressed by the MAH. The calculations at the end of study demonstrated that, when accounting for co-infection, 0.9 HPV 32/33/52/58-related CIN 2/3 cases per 1000 subjects vaccinated were prevented in the RMITT-2 population and 0.7 cases in the MITT-2 population. This translates to a net benefit of 4 and 6 additional cases prevented. For HPV 16/18-related CIN 2/3 (regardless of presence of HPV 31/33/52/58), there were 17.7 prevented cases per 1000 subjects vaccinated in the RMITT-2 population and 15.6 cases in the MITT-2. However, with

regard to the non-vaccine types, the oncogenic potential differs profoundly from that of the vaccine HPV 16/18 types with the non-vaccine HPV types being commonly detected in CIN 1, CIN 2 and CIN 3 lesions, but rarely result in cervical cancers. Hence, the type-specific spectrum of diseases differs by grades of histopathological severity. HPV 16 is unique in that the proportions of positive lesions increase with severity. The correlation of CIN 2/3 (surrogate endpoint for cervical cancer) with cancer is, thus, substantially lower for the oncogenic non-vaccine types. Cross-protective efficacy must therefore be evaluated differently with regard to cervical cancer than efficacy for vaccine HPV types. The cross-protective efficacy was also very modest compared with that against vaccine HPV types. Moreover, case ascertainment in disease endpoints was confounded by frequent occurrence of co-infections with vaccine and vaccine HPV types. For this reason, and since only modest efficacy was demonstrated, the CHMP considers that cross-protection should not be included in the indication. It is an added benefit that should be mentioned in section 5.1 of the SPC. Moreover, the inclusion of low-grade lesions and AIS in the proposed indication as well as the use of a *post-hoc* composite endpoint is not acceptable. Following CHMP request the MAH agreed to withdraw the request for an extension of indication to limit this application to the update of section 5.1 and this type II variation is thereby considered approvable.

1.5 Changes to the product information

Further to the assessment of the different proposals of the MAH to amend the Product Information and in the light of the assessment of the submitted data, the Product Information was revised as follows:

SPC

Section 4.1 "Therapeutic indication"

The MAH's initially proposed to extend the approved indication to include protection against HPV 31-, 33- 52- and 58-related low- and high-grade cervical dysplasia and cervical adenocarcinoma in situ (AIS) based on submission of supplementary data on non-vaccine types.
The claims for the requested indication were not accepted by the CHMP and were withdrawn by the MAH. This section remains unchanged.

Section 4.4 "Special warnings and precautions for use"

The warning concerning Gardasil protection against diseases caused by HPV types 6, 11, 16 and 18 was revised to include protection against diseases caused by certain related HPV types. A cross reference to section 5.1 was included.

"Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18 and to a limited extent against diseases caused by certain related HPV types (See section 5.1)."

Section 5.1 "Pharmacodynamic properties"

The paragraph on data on persistent infection caused by vaccine HPV types from protocols 005 and 007 was replaced by results from protocol 012 as follows:

"In Protocol 012, the efficacy of Gardasil against the 6 month definition of persistent infection [samples positive on two or more consecutive visits 6 months apart (±1 month) or longer] related to HPV 16 was 98.7 % (95% CI: 95.1, 99.8) and 100.0% (95% CI: 93.2, 100.0) for HPV 18 respectively, after a follow-up of up to 4 years (mean of 3.6 years). For the 12 month definition of persistent infection, efficacy against HPV 16 was 100.0 % (95% CI: 93.9, 100.0) and 100.0 % (95% CI: 79.9, 100.0) for HPV 18 respectively."

Results on cross-protective efficacy were included as follows:

"Cross-protective efficacy

The efficacy of Gardasil against CIN (any grade) and CIN 2/3 or AIS caused by 10 non-vaccine HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) structurally related to HPV 16 or HPV 18 was evaluated in the combined Phase III efficacy database (N = 17,599) after a mean follow-up of 3.0 years and 3.6 years (at end of study). Efficacy against disease endpoints caused by pre-specified combinations of non-vaccine HPV types was measured. The studies were not powered to assess efficacy against disease caused by individual HPV types.

The primary analysis was done in type-specific populations that required women to be negative for the type being analyzed, but who could be positive for other HPV types (96% of the overall population). The primary time point analysis after 3 years did not reach statistical significance for all pre-specified endpoints. The final end-of-study results for the combined incidence of CIN 2/3 or AIS in this population after a follow-up of up to 4 years (mean of 3.6 years) are shown in Table 3. For composite endpoints, statistically significant efficacy against disease was demonstrated against HPV types phylogenetically related to HPV 16 (primarily HPV 31) whereas no statistically significant efficacy was observed for HPV types phylogenetically related to HPV 18 (including HPV 45). For the 10 individual HPV types, statistical significance was only reached for HPV 31."

Table 3: Results for CIN 2/3 or AIS in Type-Specific HPV-Naïve Subjects† (end of study results)

Naïve to ≥ 1 HPV Type				
Composite Endpoint	Gardasil ® cases	Placebo cases	% Efficacy	95% CI
(HPV 31/45) ‡	34	60	43.2%	12.1, 63.9
(HPV 31/33/45/52/58) §	111	150	25.8%	4.6, 42.5
10 non-vaccine HPV Types‖	162	211	23.0%	5.1, 37.7
HPV-16 related types (A9 species)	111	157	29.1%	9.1, 44.9
HPV 31	23	52	55.6%	26.2, 74.1†
HPV 33	29	36	19.1%	<0, 52.1†
HPV 35	13	15	13.0%	<0, 61.9†
HPV 52	44	52	14.7%	<0, 44.2†
HPV 58	24	35	31.5%	<0, 61.0†
HPV-18 related types (A7 species)	34	46	25.9%	<0, 53.9
HPV 39	15	24	37.5%	<0, 69.5†
HPV 45	11	11	0.0%	<0, 60.7†
HPV 59	9	15	39.9%	<0, 76.8†
A5 species (HPV 51)	34	41	16.3%	<0, 48.5†
A6 species (HPV 56)	34	30	-13.7%	<0, 32.5†

† The studies were not powered to assess efficacy against disease caused by individual HPV types.
‡ Efficacy was based on reductions in HPV 31-related CIN 2/3 or AIS
§ Efficacy was based on reductions in HPV 31-, 33-, 52-, and 58-related CIN 2/3 or AIS
‖ Includes assay-identified non-vaccine HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

PL
The PL was updated with minor linguistic changes.

The MAH has agreed with the changes as proposed by the CHMP.

II. CONCLUSION

On 26 June 2007 the CHMP considered this Type II variation and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

III. GLOSSARY

1. AIS – adenocarcinoma in situ
2. CHMP – committee for medical products for human use
3. CIN – cervical intraepithelial neoplasia
4. EGL – external genital lesions
5. EMEA – European Medicines Agency
6. FUM – follow up measure
7. HPV – Human Papilloma virus
8. MAA – marketing authorisation application
9. MAH – marketing authorisation holder
10. PCR – polymerase chain reaction
11. SPC – summary of product characteristics
12. STD – sexual transmitted diseases
13. VaIN – vaginal intraepithelial neoplasia
14. VE – vaccine efficacy
15. VIN – vulvar intraepithelial neoplasia
16. VLP – virus-like particles
17. WHO – World Health Organisation