17 March 2015
EMA/184046/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Gardasil/Silgard

Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)

Procedure No: EMEA/H/C/703 and EMEA/H/C/732

P46 056 / P46 055

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

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I. INTRODUCTION

On October 5, 2009, the MAH submitted two completed paediatric studies for Gardasil/Silgard in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Gardasil/Silgard and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study(ies)

In the study Gardasil/Silgard was administered using the currently approved formulation.

Note: Information on the pharmaceutical formulation used in the study(ies), the existence of a paediatric formulation, or conditions for extemporaneous formulations if applicable, should be mentioned here

Clinical aspects

1. Introduction

Note: If several studies are submitted, a list of all the clinical studies should be included with a brief description for each study.

The MAH submitted two final reports for:

- P029; Evaluation of Safety, Tolerability and Immunogenicity of Quadrivalent HPV vaccine in Healthy Females 9 to 15 years of age in India;
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- P035; An Open-Label, Single-Dose, Safety and Tolerability Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like particle (VLP) Vaccine in Chinese Female Subjects Aged 9 to 26 Years.

2. Clinical studies

Note: For each clinical study, the following structure is recommended

- **P029** Evaluation of Safety, Tolerability and Immunogenicity of Quadrivalent HPV vaccine in Healthy Females 9 to 15 years of age in India;
-

➢ **Description**

➢ **Methods**

- Objective(s)
  To observe the safety, tolerability and immunogenicity of a 3-dose regimen of quadrivalent HPV Vaccine in healthy females 9 to 15 years of age in India.

- Study design

This was an **o**pen-label, nonrandomized, multicenter immunogenicity and safety study in preadolescent and adolescent females aged 9 to 15 years old. For each subject enrolled, the duration of the study was approximately 7 months.

- Study population /Sample size

This study was planned to prove that rate of serious vaccine-related adverse experiences in Indian population would be <3.3% with 95% probability. 110 healthy female were enrolled in this study to achieve this objective

- Treatments

Participants received a total of 3 intramuscular injections of Gardasil/Silgard, the quadrivalent HPV VLP Vaccine (HPV types 6/11/16/18) which contained 20/40/40/20 mcg in a 0.5 mL dose. Vaccine was administered at time 0, Month 2 and Month 6.
Serological response using the competitive Luminex Immunoassay was measured at Month 7.

- Outcomes/endpoints

The main immunogenicity measurements used to address this objective were:

1. Among subjects who were baseline naïve to HPV 6, HPV 11, HPV 16, and/or HPV 18, the proportion who became seropositive to the relevant vaccine HPV type by Month 7.

2. Geometric mean anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 serum cLIA levels at Month 7.
The quadrivalent human papillomavirus (HPV) competitive Luminex immunoassay (cLIA) was used to detect antibody to HPV virus-like particles (VLPs), serotypes 6, 11, 16, 18 before and after vaccination with the HPV quadrivalent vaccine. The seropositivity cutoffs for the HPV 6, 11, 16, and 18 cLIAs are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL,and 24 mMU/mL, respectively.

Serum samples were to be collected from all subjects at Day 1 and Month 7.

Safety was assessed by injection site reactions, systemic adverse reactions (up to 14 days after each injection), and serious adverse events.

- Statistical Methods

Continuous variables were summarized using mean, standard deviation, median, minimum, and maximum, while categorical variables were summarized using proportions (counts and percentages).
Data on subject disposition (number of subjects enrolled, number of dropouts, and reasons for dropout), demographics (gender, age, weight, height and BMI), and other baseline characteristics were summarized.
The seroconversion rates and geometric mean titers (GMTs) to each of HPV type 6, 11, 16, and 18 were summarized by time-point with 95% confidence intervals. Exact 95% confidence intervals were provided for the seroconversion rates. For the GMTs, 95% confidence intervals were provided based on the asymptotic t-distribution.
Overall summary of safety of quadrivalent HPV Vaccine, for safety measures such as the proportion of subjects reporting: (1) any adverse experiences, (2) any injection-site adverse experiences, (3) any systemic adverse experiences, and (4) any vaccine-related adverse experiences that occurred throughout the study were summarized.

➢ Results

- Recruitment/ Number analysed

A total of 110 subjects were enrolled for participation at 7 investigative sites. One hundred and eight subjects who had follow-up data were included in the safety analyses. Two subjects did not complete the vaccination regimen. One subject had month 7 serum sample for Immunogenicity collected outside the acceptable day range and one subject received non-study vaccine (Tetanus toxoid) during the study. Hence 106 subjects were eligible for Immunogenicity analysis.

- Out of the 106 subjects eligible for immunogenicity analysis at baseline, the number of subjects evaluable for Immunogenicity per protocol for each HPV type was as follows:

Table 1: Per-protocol data set

HPV Type	N
HPV-6	99
HPV-11	105
HPV-16	105
HPV-18	105

- Baseline data

Table 2: Number of subjects enrolled and eligible for the analyses and reasons for exclusion

	n (%)
Number of subjects enrolled	110
Safety cohort	108 (98.18)
Reasons for exclusion from safety cohort	
Lack of safety follow-up	2 (1.82)
Eligible for Immunogenicity	106 (96.36)
Reasons for exclusion from Immunogenicity analysis	
Discontinued from study	2 (1.82)
Subject [redacted] was not compliant with blood sampling schedule *(14 to 49 days after the third dose)*	1 (0.91)
Subject [redacted] received Non – study Non – Replicating (Inactive) Vaccine through 14 days after study vaccination	1 (0.91)

- Immunogenicity results

Table 3 presents a summary of the percentages of subjects who seroconverted for each vaccine HPV type at 4 weeks postdose 3, in different age groups, in the per-protocol immunogenicity group. Estimated seroconversion rates and associated 95% confidence intervals are shown for each vaccine HPV type. Overall, >96% of subjects seroconverted by Week 4 Postdose 3, for each of the 4 HPV types summarized in the per-protocol immunogenicity group. Therefore, GARDASIL® induced acceptable anti-HPV 6, 11, 16, 18 responses in females 9 to 15 years of age in India.

Table 4 presents a summary of anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs measured 4 weeks Postdose 3 in the per-protocol immunogenicity group. Analysis per age group revealed that GMTs in younger subjects (9 to 12 years of age) were more robust than those in older subjects (13 to 15 years of age).

Table 3: Summary of Month 7 HPV cLIA Seroconversion Rates by Age Group Among Subjects Who Received Quadrivalent HPV (Types 6, 11, 16, 18) L 1 VLP Vaccine (Per-Protocol Immunogenicity Population)

	Quadrivalent HPV (Types 6, 11, 16, 18) L 1 VLP Vaccine							
	9 to 12 Years of Age N=76				13 to 15 Years of Age N=30			
		Seroconversion				Seroconversion		
Assay (cLIA)	n†	m	Percent	95 % CI	n†	m	Percent	95 % CI
Anti-HPV 6	71	69	97.18	(93.33,101.03)	28	27	96.43	(89.55, 103.30)
Anti-HPV 11	75	74	98.67	(96.07, 101.26)	30	30	100	-
Anti-HPV 16	75	74	98.67	(96.07, 101.26)	30	30	100	-
Anti-HPV 18	75	74	98.67	(96.07, 101.26)	30	30	100	-

† The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

Seropositive is defined as anti-HPV serum cLIA levels ≥ 20, 16, 20, or 24 mMU/mL for HPV types 6, 11, 16, and 18, respectively.

N = Number of subjects in the respective demographic cohort who received at least 1 injection.

n = Number of subjects evaluable for Immunogenicity (per-protocol) for individual HPV Types

m = Number of seropositive subjects at month 7.

CI = Confidence interval;

cLIA = Competitive Luminex immunoassay;

HPV = Human papillomavirus;

mMU = Milli Merck units.

VLP = Virus-like particles.

Table 4: Summary of HPV cLIA Geometric Mean Titers by Age Group Among

I. Subjects Who Received Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine (Per-Protocol Immunogenicity Population)

Assay (cLIA)	Time Point	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine					
		9 to 12 Years of Age N=76			13 to 15 Years of Age N=30		
		n†	GMT (mMU/mL)	95% CI	n†	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	71	6.40	(6.11, 6.70)	28	6.00	(6.00, 6.00)
	Month 7		459.23	(312.61, 674.61)		304.21	(168.74, 548.44)
Anti-HPV 11	Day 1	75	7.14	(6.98, 7.31)	30	7.13	(6.87, 7.39)
	Month 7		980.50	(747.10, 1286.81)		849.43	(607.06, 1188.58)
Anti-HPV 16	Day 1	75	10	(10.00, 10.00)	30	10	(10.00, 10.00)
	Month 7		3295.25	(2377.97, 4566.36)		2050.59	(1321.74, 3181.35)
Anti-HPV 18	Day 1	75	9.06	(8.94, 9.19)	30	9.00	(9.00, 9.00)
	Month 7		965.79	(692.83, 1346.28)		757.08	(474.96, 1206.78)

† The Number of subjects contributing to the analysis includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range..

N = Number of subjects in the respective demographic cohort who were eligible for Immunogenicity analysis

n = Number of subjects evaluable for Immunogenicity (per-protocol) for individual HPV Types

CI = Confidence interval;

cLIA = Competitive Luminex immunoassay;

GMT = Geometric mean titer;

HPV = Human papillomavirus;

mMU = Milli Merck units.

VLP = Virus-like particles.

- Safety results

Overall, 63(58%) subjects who received GARDASIL® reported at least one adverse experience. The most frequent adverse experience was injection site adverse experience, which was reported for 50 (46%) subjects.

There were 35 (32%) subjects with systemic adverse experiences. Pyrexia was the most common systemic adverse experience observed in 25 (23%) subjects. The next common systemic AE was nasopharyngitis reported by 8 (7%) subjects. Two subjects (2%) had severe systemic adverse experience (diarrhoea and vomiting).

A summary of clinical adverse experience, day 1 to 15 post-vaccination are given in table 5.There were no deaths or serious adverse experiences reported during this study. None of the study subjects discontinued study participation due to any adverse experience.

Table5: Clinical Adverse experience summary (Days 1 to 15 Post-vaccination) after any Vaccination Visit

PARTICULARS	N=110	
	n	(%)
Number of subjects	110	100
Subjects without follow-up	2	1.82
Subjects with follow-up	108	98.18
Number (%) of subjects:		
with no adverse experience	45	41.67
with atleast one adverse experiences	63	58.33
injection-site adverse experiences	50	46.30
systemic adverse experiences	35	32.41
with vaccine-related† adverse experiences	45	41.67
injection-site adverse experiences	37	34.26
systemic adverse experiences	26	24.07
with serious adverse experiences	0	0
with serious vaccine-related adverse experiences*	0	0
who died	0	0
discontinued‡ due to an adverse experience	0	0
discontinued due to a vaccine-related adverse experience	0	0
discontinued due to a serious adverse experience	0	0
discontinued due to a serious vaccine-related adverse experience	0	0

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Subjects discontinued from study.
Percentages are calculated based on the number of subjects with follow-up.
Adverse experience terms are from MedDRA Version 10.1
N = Number of subjects vaccinated in each group.
n = Number of subjects in each category.

Injection site pain was the most common injection site adverse experience observed followed by injection site tenderness. All subjects reported injection-site adverse experiences as non-serious in nature. The subjects with injection site adverse experiences within 15 days after any vaccination are shown in table 6. Most of the reported injection site adverse experiences were mild to moderate in intensity.

Table 6: Number (%) of Subjects with Injection Site Adverse Experiences (Incidence ≥ 1% in days 1 to 15 after any Vaccination visit)

Vaccination Group: HPV	Intensity							
Number of Subjects: N=110	Mild		Moderate		Severe		Total	
Number of Subjects With Follow-up: 108	n	(%)	N	(%)	n	(%)	n	(%)
Injection Site Pain	37	34.26	7	6.48	2	1.85	46	42.59
Injection Site Tenderness	19	17.59	6	5.56	-	-	25	23.15
Injection Site Erythema (Redness)	NA						13	12.04
Injection Site Swelling	NA						10	9.26

Percentages are calculated based on the number of subjects with follow-up.
A given adverse experience assigned multiple intensity ratings is reported only once under the highest associated intensity rating.
Adverse experience terms are from MedDRA Version 10.1
The VRC prompted the subject to record injection site pain or tenderness (which mapped to pain), swelling, and redness (which mapped to erythema).
N = Number of subjects vaccinated
n = Number of subjects with safety follow-up.
NA = Redness and Swelling were not reported as mild, moderate and severe. Details are presented in supplementary table 2

Most of the injection site adverse experiences were reported after the first dose of vaccine. These injection site adverse experiences decreased after the second and third vaccination doses.

3. Discussion on clinical aspects

Among healthy subjects between the ages of 9 years and 15 years in India who received GARDASIL®, the following conclusions can be drawn:

1. The administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9 to 15 year old female induces over 96% seroconversion rate for anti-HPV 6, anti- HPV 11, anti-HPV 16, and anti-HPV 18.
2. The administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9 to15 year old female induces robust geometric titers for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18.
3. The administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9 to 15 year old female is generally well tolerated.

- **P035**; An Open-Label, Single-Dose, Safety and Tolerability Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like particle (VLP) Vaccine in Chinese Female Subjects Aged 9 to 26 Years.

➢ **Description**

➢ **Methods**

Objective(s)
To observe the safety and tolerability of quadrivalent HPV Vaccine in healthy females 9 to 26 years of age in China.

Study design

This was an open-label, single-dose, one-centre safety study, devided in two stages, in preadolescent and adolescent females aged 9 to 26 years old.
The two strata included 2 periods: 20 females aged 18-26 years receive test vaccine and adverse events and serious adverse events at injection site and systemic adverse events and serious adverse events were observed. Based on no serious side reaction was observed after vaccinations in stage I, another 20 cases of healthy females aged 9-17 years were selected, and a dose of test vaccine was intramuscularly administrated. Local and systemic reactions

during this observation period were recorded on diary cards. For each subject enrolled, the duration of the study was approximately 14 days.

- Study population /Sample size
  This study was planned to prove that rate of serious vaccine-related adverse experiences in Chinese population. Forty healthy female subjects were enrolled in this study, in two strata, twenty 9-17 years old and twenty 18-26 years old.

- Treatments
  Participants received one intramuscular injections of Gardasil/Silgard, the quadrivalent HPV VLP Vaccine (HPV types 6/11/16/18) which contained 20/40/40/20 mcg in a 0.5 mL dose. Vaccine was administered at time 0.

- Outcomes/endpoints
  Safety was assessed by injection site reactions, systemic adverse reactions (up to 14 days after each injection), and serious adverse events.

- Statistical Methods
  Only descriptive statistics for safety results were given for this phase I study.
  Overall summary of safety of quadrivalent HPV Vaccine, for safety measures such as the proportion of subjects reporting: (1) any adverse experiences, (2) any injection-site adverse experiences, (3) any systemic adverse experiences, and (4) any vaccine-related adverse experiences that occurred throughout the study were summarized.

➢ **Results**

- Recruitment/ Number analysed
  All 40 subjects were included in the safety set. Generally, during the whole observation period (14-day follow up), 21 subjects occurred at least 1 monitored adverse experience (local and/or systemic), 10 subjects in Group 1 (50%), 11 subjects in Group 2 (55%).

- Safety results
  During 14 days follow up, the rate of observed local and systemic adverse reaction was 52.50%, and the rate of adverse events related to vaccine was 40.00%. All adverse events were expected common reactions, mild in intensity, and medical treatments were not required.
  No serious adverse experiences or vaccine-related adverse experiences occurred during study period, none of severe local or systemic adverse experiences was observed. No acute allergic was observed within 30 minutes after first dosage in two groups. In one subject in group aged 9-17, occurred mild fever, there was no reaction in other subjects. The systemic adverse experiences incidence rate was 43%, the incidence rate of all systemic adverse experiences related to vaccination was 18%. Generally all systemic adverse experiences were mild. Table 1 presents a summary of adverse experience.

Table1. Overview of adverse experience (SS)

AEs	Group I(18-26)			Group II(9-17)			Total		
	n subj	n events	% subj.	n subj	n events	% subj.	n subj	n events	% subj.
Any AE	10	13	50.00	11	29	55.00	21	42	52.50
Vaccine-related AE*	7	9	35.00	9	11	45.00	16	20	40.00
Discontinued due to AE**	0	0	0.00	0	0	0.00	0	0	0.00
SAE	0	0	0.00	0	0	0.00	0	0	0.00
Injection-site AE	4	4	20.00	7	7	35.00	11	11	27.50
Vaccine-related injection-site AE*	4	4	20.00	7	7	35.00	11	11	27.50
Systemic AE	7	9	35.00	10	22	50.00	17	31	42.50
Vaccine-related systemic AE*	3	5	15.00	4	4	20.00	7	9	17.50

* Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
** Did not complete the study

The subjects with injection site adverse experiences within 15 days after the vaccination are shown in table 2. The injection site adverse experiences were mild in intensity.

Table 2: Frequency of injection-site AE by Intensity by age group (SS)

Symptom	Group I(18-26)			Group II(9-17)		
	n subj.	n events	% subj.	n subj.	n events	% subj.
Pain	4	4	20.00	7	7	35.00
Mild	4	4	20.00	7	7	35.00

Note: all the injection-site adverse experiences were related to vaccine.

3. Discussion on clinical aspects

Among healthy subjects between the ages of 9 years and 26 years in China who received GARDASIL®, the following conclusions can be drawn:
The administration of one dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9 to 26 year old females is generally well tolerated.

III.RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The MAH's conclusions of the study are endorsed. The results of this clinical study are well in line with previously reported results from other clinical studies. Therefore, the submitted data does not necessitate any changes to the current SPC, and no type II variation will be needed.

*Note: Please ensure that the **final** conclusion does not contain references to individual CHMP Members or Member States*

- **Overall conclusion**

- **Recommendation** *Note: please tick the appropriate box*

☒ **Fulfilled –**

No further action required

IV.ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable