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EMA/632425/2012
Committee for Medicinal Products for Human Use (CHMP)

Gardasil

(human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed))

Procedure No. EMEA/H/C/000703/P45/047

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Rapporteur's Final Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

P45 FUM 047/FUM 047

An immunogenicity and safety study in females 9-23 years of age in Korea, Protocol 023

Gardasil/Silgard (Human papillomavirus vaccine, types 6, 11, 16, 18)

EMEA/H/C/703
EMEA/H/C/732

Marketing Authorisation Holder: Sanofi Pasteur MSD

Rapporteur:	Tomas Salmonson
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I. INTRODUCTION

On December 8, 2008 the MAH submitted one completed paediatric study for Gardasil/Silgard, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study

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

II.2 Clinical aspects

1. Introduction

The MAH submitted a report for:

V501: An Immunogenicity and Safety Study of GARDASIL (Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine) in females 9 to 23 years of age in Korea.

2. Clinical study

V501: An Immunogenicity and Safety Study of GARDASIL (Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine) in females 9 to 23 years of age in Korea.

Description

- **Methods**

  - Objective(s)
    Primary: To evaluate the vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses following administration of a 3-dose regimen of GARDASIL in females 9 to 23 years of age in Korea.
    Secondary: To demonstrate that a 3-dose regimen of GARDASIL is generally well tolerated in females 9 to 23 years of age in Korea.

  - Study design
    This was a randomized, double-blind, placebo-controlled, multicenter, immunogenicity and safety study in preadolescent and adolescent females aged 9 to 23 years old. For each subject enrolled, the duration of the study was approximately 7 months.

  - Study population /Sample size
    Approximately 171 subjects were to be randomized in a 2:1 ratio to receive either quadrivalent HPV vaccine or adjuvant containing placebo.

  - Treatments
    Participants received a total of 3 intramuscular injections of GARDASIL or placebo at Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks).

  - Outcomes/endpoints

For immunogenicity, the main endpoints of interest were:

- Percentage of subjects who seroconverted for each HPV Type 6, 11, 16, 18 by Week 4 Postdose 3
- Anti-HPV 6, 11, 16, 18 GMTs Week 4 Postdose 3

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.

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

- Statistical Methods
  An exact binomial 95% confidence interval proportion of subjects who seroconvert to each of HPV 6, 11, 16, 18 at Week 4 Postdose 3 was calculated and the response for each HPV type was considered acceptable if the lower bound of the 95% exact binomial confidence interval on the seroconversion rate was at least 90%. It was assumed that the true seroconversion rate for each HPV type was 98.5%. A separate test was performed for all 4 HPV types. Success was required for all 4 tests.
  The primary hypothesis test was performed on the per-protocol population to determine the success of the study and on the All Type-Specific HPV Naïve Subjects with Serology Data Population1 as a secondary approach. The GMTs to each of HPV 6, 11, 16, 18 were summarized and 95% confidence intervals for the GMTs were calculated.

➢ Results

- Recruitment/ Number analysed
  A total of 176 subjects were screened for participation at 10 investigative sites. A total of 176 subjects (100%) were randomized to 1 of 2 vaccination groups and received at least one injection of GARDASIL or placebo. Of the 176 subjects, 175 subjects (99.4%) received all 3 vaccinations.

- Immunogenicity results
  Table 1 presents a summary of the percentages of subjects who seroconverted for each vaccine HPV type by Week 4 Postdose 3 in the per-protocol immunogenicity group. Estimated seroconversion rates and associated 95% confidence intervals are shown for each vaccine HPV type. The statistical criterion for primary hypothesis was met: the lower bound of the 95% exact binomial confidence interval on the seroconversion rate was at least 90% for each vaccine HPV type. Overall, >98% 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 23 years of age in Korea.

  The results from the All Type-Specific HPV-Naïve Subjects With Serology Data population support the results in the per-protocol immunogenicity group (data not shown in this AR).

  Table 2 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. A analysis per age group revealed that GMTs in younger subjects (9 to 17 years of age) were more robust than those in older subjects (18 to 23 years of age).

Table 1. Summary of Month 7 HPV cLIA Seroconversion Rates (Per-Protocol Immunogenicity Population†)

	GARDASIL® (N = 117)				Placebo (N = 59)			
Assay (cLIA)	n	m	Percent	95% CI	n	m	Percent	95% CI
Anti-HPV 6	111	109	98.2	(93.6%, 99.8%)	58	0	0.0	(0.0%, 6.2%)
Anti-HPV 11	112	112	100	(96.8%, 100%)	58	1	1.7	(0.0%, 9.2%)
Anti-HPV 16	113	112	99.1	(95.2%, 100%)	58	0	0.0	(0.0%, 6.2%)
Anti-HPV 18	110	109	99.1	(95.0%, 100%)	58	0	0.0	(0.0%, 6.2%)

† 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, 24 mMU/mL for HPV Types 6,11,16, and 18, respectively.
N = Number of subjects randomized; n = Number of subjects contributing to the analysis; m = Number of seropositive subjects.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; mMU = Milli Merck units.

Table 2. Summary of HPV cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population†)

		GARDASIL® (N = 117)			Placebo (N = 59)		
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	112	<8	(<8, <8)	58	<8	(<8, <8)
	Month 7	111	565.2	(439.8, 726.4)	58	<8	(<8, <8)
Anti-HPV 11	Day 1	112	<8	(<8, <8)	58	<8	(<8, <8)
	Month 7	112	1,004.6	(817.3, 1,234.7)	58	<8	(<8, <8)
Anti-HPV 16	Day 1	113	<12	(<12, <12)	58	<12	(<12, <12)
	Month 7	113	5,180.5	(4,005.5, 6,700.1)	58	<12	(<12, <12)
Anti-HPV 18	Day 1	112	<8	(<8, <8)	58	<8	(<8, <8)
	Month 7	110	886.2	(687.4, 1,142.5)	58	<8	(<8, <8)

† 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.
N = Number of subjects randomized; n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

- Safety results
  Overall, 78% of subjects who received GARDASIL and 71% of subjects who received placebo reported a clinical adverse experience. Compared with subjects who received placebo, more subjects who received GARDASIL reported injection-site adverse experiences (73% vs. 56%). On the other hand, fewer subjects who received GARDASIL reported systemic adverse experiences (32% vs. 44%). The incidence of serious adverse experiences, deaths, and discontinuations due to adverse experiences were comparable between the 2 vaccination groups.

3. Discussion on clinical aspects

Among healthy subjects between the ages of 9 years and 23 years in Korea 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 23 year old female induces over 98% 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 to 23 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 23 year old female 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.

- **Overall conclusion**

- **Recommendation**

X Fulfilled –

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.