17 March 2015
EMA/182964/2015
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 072.1 / P46 071.1

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. INTRODUCTION

On February 27, 2013 the MAH submitted a completed paediatric study for Gardasil in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The MAH stated that the submitted paediatric study does not influence the benefit risk for Gardasil and that there is not a consequential regulatory action.
However, in the Preliminary assessment report of this study the Rapporteur stated that the paediatric procedure was **not** fulfilled until a satisfactory clarification regarding the identified protocol violations was received. Additional clarifications were requested.

According to this request the MAH has now provided a clarification to the identified protocol violation.

In summary the following background data were discussed in the Preliminary assessment report.

II. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study
The same formulation as the commercial formulation was used in the study.

Clinical aspects
1. Introduction
The MAH had submitted a final report for:

- V501-046 Evaluation of Safety and Immunogenicity of GARDASIL™ in Healthy Females Between 9 and 26 Years of Age in Sub Saharan Africa;

2. Clinical study

V501-046 Evaluation of Safety and Immunogenicity of GARDASIL™ in Healthy Females Between 9 and 26 Years of Age in Sub Saharan Africa;(Phase A)

- **Description**

Methods

- *Objectives*
  Immunogenicity: To estimate the percentage of subjects who seroconvert to each of HPV 6, 11, 16, and 18 at Month 7 (4 weeks Postdose 3)
- Safety: To evaluate the safety and tolerability of GARDASIL in females 9- 26 years of age in Sub Saharan Africa

- *Study design*
  Protocol 046 was conducted in two phases.
- **Primary phase**: the base study of immunogenicity and safety
- **Vaccination of placebo subject**

- *Study population /Sample size*

Table 7-1 Study Populations by Age

Study Populations by Age	GARDASIL™	Placebo
9-12	80	20
13-15	30	-
16-26	120	-

- *Treatments*
  Subjects received one 0.5-mL intramuscular dose of GARDASIL or placebo at Day 1, Month 2, and Month 6.

➢ *Outcomes/endpoints*
Immunogenicity: The primary endpoint of interest in this study was the percentages of GARDASIL recipients who seroconvert to each of HPV 6, 11, 16, and 18 at Week 4 Postdose 3.
Safety: The primary safety objective was to demonstrate that GARDASIL was generally well tolerated when administered in a 3-dose regimen.

➢ *Statistical Methods*
Immunogenicity: The primary hypothesis was the percentage of subjects receiving GARDASIL who seroconvert to each of HPV 6, 11, 16, and 18 at week 4 Postdose 3 was acceptable.
Safety: Safety and tolerability were assessed by clinical review of all relevant parameters including adverse experiences (AEs).

➢ **Results**

➢ *Recruitment/ Number analysed*
A total of 257 subjects were screened for inclusion in this study and 250 subjects were randomized. The disposition of subjects from Day 1 to Month 7 by age strata is presented in Table 10-1. Among the 250 randomized subjects, a total of 27 subjects (10.8%) discontinued during the study period Day 1 through Month 7.

Among the 27 subjects discontinued subjects:
– Eighteen (18) randomized subjects were discontinued due to a protocol violation.
– Eight (8) subjects were lost to follow-up.
– One (1) subject withdrew consent.
– None of the subjects randomized were discontinued prior to their first vaccination.
– No subject discontinued due to an adverse event.

A total of 224 subjects (89.6%) completed the 3 study vaccinations regimen, including 207 subjects who received GARDASIL and 17 subjects who received placebo. Many subjects in the 9 to12 year old age group have unknown Protocol Milestone status because there was randomization to GARDASIL or placebo and enrollment to Phase B had not been initiated at the time of this database lock.

Table 10-1. Disposition of Subjects (All Randomized Subjects by Age Strata)

	GARDASIL™ 9 to 12 years old		GARDASIL™ 13 to 15 years old		GARDASIL™ 16 to 26 years old		Placebo 9 to 12 years old		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized									7	
Subjects in population	80		30		120		20		250	
Vaccinated at										
Vaccination 1	80	(100.0)	30	(100.0)	120	(100.0)	20	(100.0)	250	(100.0)
Vaccination 2	79	(98.8)	29	(96.7)	119	(99.2)	19	(95.0)	246	(98.4)
Vaccination 3	77	(96.3)	28	(93.3)	117	(97.5)	19	(95.0)	241	(96.4)
Study Disposition										
Completed	61	(76.3)	24	(80.0)	106	(88.3)	15	(75.0)	206	(82.4)
Discontinued	9	(11.3)	5	(16.7)	10	(8.3)	3	(15.0)	27	(10.8)
Lost To Follow-Up	0	(0.0)	1	(3.3)	7	(5.8)	0	(0.0)	8	(3.2)
Protocol Violation	9	(11.3)	4	(13.3)	2	(1.7)	3	(15.0)	18	(7.2)
Withdrawal By Subject	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.4)
Unknown	10	(12.5)	1	(3.3)	4	(3.3)	2	(10.0)	17	(6.8)
Study Medication Disposition										
Completed	67	(83.8)	27	(90.0)	113	(94.2)	17	(85.0)	224	(89.6)
Discontinued	3	(3.8)	2	(6.7)	3	(2.5)	1	(5.0)	9	(3.6)
Lost To Follow-Up	0	(0.0)	1	(3.3)	2	(1.7)	0	(0.0)	3	(1.2)
Protocol Violation	3	(3.8)	1	(3.3)	0	(0.0)	1	(5.0)	5	(2.0)
Withdrawal By Subject	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.4)
Unknown	10	(12.5)	1	(3.3)	4	(3.3)	2	(10.0)	17	(6.8)
Protocol Milestone										
Continuing Into Next Trial Segment	6	(7.5)	0	(0.0)	0	(0.0)	3	(15.0)	9	(3.6)
Not Continuing Into Next Trial Segment	0	(0.0)	24	(80.0)	106	(88.3)	0	(0.0)	130	(52.0)
Unknown	74	(92.5)	6	(20.0)	14	(11.7)	17	(85.0)	111	(44.4)

Each subject is counted once for Study Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

Assessor's comment: The protocol violations were explained in the CSR, and were due to either subject consented by legal guardian without legal guardianship documentation (N=18) or subjects not native to Sub Saharan Africa (N=7) (one subject had both protocol violations, i.e. 24 subjects were excluded). It is unclear why only 18+5=23 subjects are included in the table 10-1 as excluded due to protocol violations, and what the difference between Study Disposition and Study Medication Disposition is. The Applicant is asked to explain the discrepancy between Table 10-1 and the list of protocol violations in the CSR.

- *Immunogenicity results*

  Overall, 100% of the subjects seroconverted by Week 4 Postdose 3, in all populations (all age strata and the All Type-Specific Naïve subjects with serology population), for each of the 4 HPV types summarized. The results support the results in the per protocol immunogenicity population.

- *Safety results*

  The adverse events reported in this study are in agreement with data from previously reported studies and no new safety signal was raised in this study

3. Discussion on clinical aspects

The current study included healthy Sub Saharan girls and women 9-26 years. The study results were in agreement with results from previously assessed studies in the same age groups from other parts of the world. The immune responses are considered robust, and the safety profile did not raise further questions. The study is continuing into phase B, i.e. vaccination of the placebo group, and a report of that phase is expected when available as a separated article 46 procedure. However, a clarification is requested regarding the number of subjects excluded due to protocol violations in the study.

III. CLARIFICATION TO THE QUESTION POSED BY THE RAPPORTEUR IN THE PRELIMINARY ASSESSMENT REPORT

Based on the data submitted the MAH was requested to provide a response to the following question as part of this procedure P 46 072. The MAH has accordingly presented the requested clarification.

1 Rapporteur Additional Clarification requested:
The protocol violations were explained in the CSR, and were due to either subject consented by legal guardian without legal guardianship documentation (N=18) or subjects not native to Sub Saharan Africa (N=7) (one subject had both protocol violations, i.e. 24 subjects were excluded). It is unclear why only 18+5=23 subjects are included in the table 10-1 as excluded due to protocol violations, and what the difference between Study Disposition and Study Medication Disposition is. The Applicant is asked to explain the discrepancy between Table 10-1 and the list of protocol violations in the CSR.

2 MAH Response:
The MAH would first like to provide clarification about the data in the subject disposition table including: explaining the difference between Study Disposition and Study Medication Disposition and clarifying that 18 subjects (not 23) had discontinued the study by Month 7 due to protocol violations. (Of note, Month 7 is the final visit for this CSR, the study continued after Month 7.) The MAH would then like to clarify the difference between protocol violators on the subject disposition table and those on the protocol violator list.

Subject Disposition Table Clarifications
The subject disposition table includes two related sections: Study Disposition and Study Medication Disposition. The Study Disposition section includes subjects who discontinued from the study prior to the final scheduled visit (i.e., subjects who discontinued at or before the Month 7, the final scheduled visit for this CSR). These subjects may or may not have completed vaccination per protocol. The Study Medication Disposition section includes subjects who discontinued study medication early (i.e., reported as not completing all 3 doses of vaccine). (Typically subjects who discontinue study medication early are a subset of subjects who discontinue from the study early). The 5 subjects who appear as discontinuing study medication due to protocol violation are a subset of the 18 subjects who discontinued the study due to a protocol violation, i.e., only 18 subjects (not 23) are listed as discontinuing the study due to protocol violation at the time point for this CSR (Month 7). These 18 subjects are the subjects with the protocol violation of 'legal guardianship documentation.'

Subject Disposition Table vs. Protocol Violator List
The MAH would like to clarify that the Subject Disposition table (Table 10-1, enclosed) only specifies the number of subjects (18) who, by Month 7, reported discontinuing the study/study medication due to a protocol violation. This table does not provide a comprehensive accounting of subjects who were excluded from the primary analysis due to protocol violation. Twenty-four (24) subjects were excluded from the primary analysis due to protocol violation (see Table 14-2 enclosed).

The reason there is an apparent discrepancy in number of subjects between Table 10-1 (18) and the list of protocol violations (24) is that 6 subjects continued to be followed for safety after Month 7. These are the 6 subjects who only had protocol violation of 'not native to Sub Saharan Africa.' Thus, they appear on Protocol Violators table (as they were excluded from immunogenicity analysis) but do not appear as discontinued due to protocol violation on Table 10-1 (as they continued in the study and were followed for safety).

See Figure 1 for graphic representation of the above.

Figure 1 Protocol Violator Subject Accounting

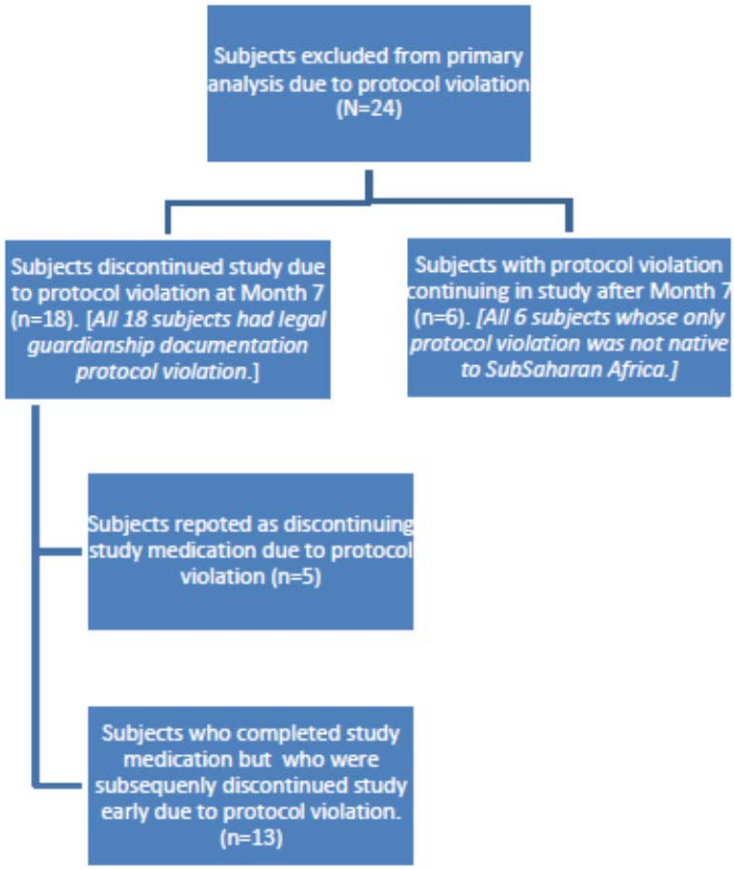

Table 10-1
Disposition of Subjects
(All Randomized Subjects by Age Strata)

	GARDASIL™ 9 to 12 years old		GARDASIL™ 13 to 15 years old		GARDASIL™ 16 to 26 years old		Placebo 9 to 12 years old		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized									7	
Subjects in population	80		30		120		20		250	
Vaccinated at										
Vaccination 1	80	(100.0)	30	(100.0)	120	(100.0)	20	(100.0)	250	(100.0)
Vaccination 2	79	(98.8)	29	(96.7)	119	(99.2)	19	(95.0)	246	(98.4)
Vaccination 3	77	(96.3)	28	(93.3)	117	(97.5)	19	(95.0)	241	(96.4)
Study Disposition										
Completed	61	(76.3)	24	(80.0)	106	(88.3)	15	(75.0)	206	(82.4)
Discontinued	9	(11.3)	5	(16.7)	10	(8.3)	3	(15.0)	27	(10.8)
Lost To Follow-Up	0	(0.0)	1	(3.3)	7	(5.8)	0	(0.0)	8	(3.2)
Protocol Violation	9	(11.3)	4	(13.3)	2	(1.7)	3	(15.0)	18	(7.2)
Withdrawal By Subject	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.4)
Unknown	10	(12.5)	1	(3.3)	4	(3.3)	2	(10.0)	17	(6.8)
Study Medication Disposition										
Completed	67	(83.8)	27	(90.0)	113	(94.2)	17	(85.0)	224	(89.6)

Disposition of Subjects
(All Randomized Subjects by Age Strata) (Cont.)

	GARDASIL™ 9 to 12 years old		GARDASIL™ 13 to 15 years old		GARDASIL™ 16 to 26 years old		Placebo 9 to 12 years old		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Study Medication Disposition										
Discontinued	3	(3.8)	2	(6.7)	3	(2.5)	1	(5.0)	9	(3.6)
Lost To Follow-Up	0	(0.0)	1	(3.3)	2	(1.7)	0	(0.0)	3	(1.2)
Protocol Violation	3	(3.8)	1	(3.3)	0	(0.0)	1	(5.0)	5†	(2.0)
Withdrawal By Subject	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.4)
Unknown	10	(12.5)	1	(3.3)	4	(3.3)	2	(10.0)	17	(6.8)
Protocol Milestone										
Continuing Into Next Trial Segment	6	(7.5)	0	(0.0)	0	(0.0)	3	(15.0)	9	(3.6)
Not Continuing Into Next Trial Segment	0	(0.0)	24	(80.0)	106	(88.3)	0	(0.0)	130	(52.0)
Unknown	74	(92.5)	6	(20.0)	14	(11.7)	17	(85.0)	111	(44.4)

Each subject is counted once for Study Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

† These 5 subjects, listed as discontinued due to protocol violations within the Study Medication Disposition section, are a sub-set of the 18 subjects listed as discontinuing study due to protocol violation within the Study Disposition section.

Table 14-1

Protocol Violations

Description of Violation	Site Number	Allocation Number	How Subjects Data are Treated in the Per-Protocol Analyses
Subject not native to SubSaharan Africa	[redacted]		Excluded
Swabs not frozen within 30 minutes of collection			Included†
Subject consented by legal guardian without legal guardianship documentation			Excluded
Subject had sexual intercourse within 48 hour of a scheduled visit on or before Month 7			Included†
GYN samples and exams not done to sexually active subject prior to vaccination1 (menses)			Included†
Subject were not administered 4 weeks following resolution of pregnancy as stipulated in the protocol			Included†
Subject were not administered 4 weeks following resolution of pregnancy as stipulated in the protocol			Included†

† Subjects will not be excluded for this violation category. A subject in this category will be excluded if the subject is also in a violation category in this table for which data will be excluded, or if other exclusion categories apply (such as Day 1 positivity to one or more vaccine HPV types) as discussed in the text of this memo.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH has satisfactorily explained how to interpret the information regarding the protocol violations. The subject disposition and the protocol violation are accepted.
The provided explanation, such as the graphic representation would, however, have been helpful already in the original presentation.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

1.