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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Gardasil

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

Procedure no: EMEA/H/C/000703/P46/088

Note

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

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1. Introduction

On February 25, 2019, the MAH submitted a completed paediatric study for Gardasil/Silgard, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study P200 –A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine (V501) in 9- to 15 Year-Old Japanese Boys is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- P200 –A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine (V501) in 9- to 15Year-Old Japanese Boys;

The original study report was not provided. Instead the synopsis and Clinical overview were submitted.

2.3.2. Clinical study

P200 –A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine (V501) in 9- to 15 Year-Old Japanese Boys;

Description

Methods

Objectives

Primary objective:

1) To demonstrate that administration of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine (V501) induces high seroconversion rates for the vaccine HPV types (6, 11, 16 and 18) at 1 month post dose 3 in 9- to 15-year-old Japanese boys.

2) To demonstrate that a 3-dose regimen of V501 to 9- to 15year-old Japanese boys is well tolerated.

Exploratory objectives:

1) To demonstrate that administration of V501 induces noninferior geometric mean titers (GMTs) for serum anti-HPV 6, 11, 16 and 18 at 1 month post dose 3 in Japanese boys aged 9- to 15-year-old compared with those in Japanese men aged 16- to 26-year-old in Phase III study (PN122) for V501 at 1 month post dose 3.

2) To describe the persistence of the serum antibody titers for the vaccine HPV types 24 months following the third dose of V501.

3) To estimate the immune response for the vaccine HPV types (6, 11, 16 and 18) at 1 month post dose 3 using GMTs.

Study design

Multi-center, non-randomized, open-label, single-arm study. The trial was conducted at 4 trial centers in Japan.

Study population /Sample size

Inclusion criteria: Subjects who met the following criteria at Visit 1 (Day 1) were eligible for the study.

1) Be a healthy, Japanese male between the age of 9 years and 0 days and 15 years and 364 days on the day of the first study vaccination.

2) Have a legal representative who fully understands study procedures, alternative treatments available, the risks involved with the study, and provides written informed consent for the trial on the subject's behalf. The legal representative may also provide consent for Future Biomedical Research on the subject's behalf. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3) Have a legal representative who is able to read, understand, and complete the Vaccination Report Card.

4) Agree to provide the investigators, or study collaborator, with a priority telephone number and second priority telephone number/email address for follow-up purpose.

5) Show no temperature ≥37.5° C (oral) within 24 hours prior to vaccinations. If the subject does not meet this criterion, the Day 1 visit will be rescheduled for a time when this criterion can be met.

6) Must not yet have had sexual intercourse and does not plan on becoming sexually active from Day 1 through Month 7.

The number of subjects In the study was 100.

Treatments

HPV Type 6/11/16/18 vaccine contains L1 VLP 20/40/40/20 µg respectively in 0.5 mL per dose. A total of 3 vaccinations were given on Day 1, Month 2 and Month 6.

Outcomes/endpoints

Primary endpoint: immunogenicity, meaning seroconversion percentages for the vaccine HPV types (6, 11, 16 and 18) at 1 month post dose 3

Secondary endpoints: immunogenicity,
a) seroconversion percentages for the vaccine HPV types (6, 11, 16 and 18) at 12 months and 24 months post dose 3

b) geometric mean antibody titres (GMTs) measured using competitive Luminex Immunoassay (cLIA) for the vaccine HPV type (6, 11, 16 and 18) at 1, 12 months and 24 months post dose 3,
c) Comparison of GMTs at 1 month post dose 3 (9 to 15 years old Japanese boys vs. 16 to 26 years old Japanese men)

Safety and tolerability endpoint: Adverse events (AEs), vaccine related AEs, and new medical conditions were evaluated at each study vaccination. Specifically, injection-site AEs were recorded between days 1-5, systemic AEs days 1-15, serious AEs (SAEs) days 1 to 15 of each study vaccination and vaccine-related SAEs occurring any time during the study up to month 30.

Statistical Methods

Statistical analysis

All analyses for immunogenicity and safety were stated as performed in accordance with the statistical analysis plan provided in Section 8 of the protocol [16.1.1].

Assessor's comment: The full clinical study report was not submitted in this application, only the study report and a clinical overview. It is assumed that the original report was written in Japanese. Without a full report there are limitations in what can be assessed, i.e. the above statement can not be verified. However, considering the study results as presented and the overall study size, it is not considered necessary to provide a full clinical study report within this application.

The primary analysis population was the PPI population, which consists of subjects who received all the 3 vaccinations within acceptable day ranges, provided blood samples for serology testing within the acceptable day range, do not have any major protocol violations, and were seronegative at Day 1.

The analyses of serum data collected at Day 1, Month 7, Month 18 and Month 30 had were conducted. A brief summary of the statistical analyses for immunogenicity is provided below.

Immunogenicity:

1) The primary endpoint HPV 6, 11, 16, 18 seroconversion percentages and GMTs at 1 month (Month 7), and secondary endpoints 12 months (Month 18) and 24 months (Month 30) post dose 3 were evaluated by computing point estimates and constructing 95% CI. A Calculation of the CI is based on the exact binomial method proposed by Clopper and Pearson (1934). Success of this study required that the point estimates of seroconversion percentage on the HPV types exceed 90%. Positive by serology was defined as having a titer at or above the serostatus cutoff [20 milli Merck Units/mL (mMU/mL), 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL for HPV 6, 11, 16 and 18 types, respectively]. Serostatus positive rate (= seropositivity rate) is the percentage of subjects who received vaccination and have a positive titer for the HPV types. In the PPI population, serostatus for the relevant vaccine HPV types at Day 1 is negative; which means that seropositivity rate is 0%. Seropositivity rates for the relevant vaccine HPV types at Month 7 mean seroconversion percentages.

2) The secondary endpoints HPV 6, 11, 16 and 18 GMTs post dose 3 (Month 7, 18 and 30) were evaluated by computing point estimates and constructing 95% CI. The values are log-transformed before analysis. As such, the CIs for the means are constructed on the natural log scale and reference the distribution. Exponentiating the means and lower and upper limits of these CIs yields estimates for the population GMT and CIs about the GMT on the original scale.

3) The secondary hypothesis that the immune response in 9- to 15-yearold boys is non-inferior to that in 16- to 26-year-old men (all men who were vaccinated by V501 and met the per-protocol immunogenicity criteria in PN122) was addressed by two-sided 95% CIs based on one

sided tests (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). The test was performed using an analysis of variance model with a response of log-transformed individual titers and a fixed effect for age group. The statistical criterion requires that the lower bound of two-sided 95% CI of GMT ratio (9- to 15-year-old boys divided by 16- to 26-year-old men) be greater than 0.5 for all 4 HPV types

Safety:

All subjects who received at least 1 dose of V501 and have follow up data were included in the safety analysis, and AE data are summarized.

Period 1 (up to 15 days after each vaccination): Safety and tolerability were assessed by clinical review of all relevant parameters (injection-site or systemic AEs and vaccine-related AEs [injection-site AEs: Days 1 to 5, systemic AEs: Days 1 to 15], SAEs [Days 1 to 15], vaccine-related SAEs, and death). - Incidence was defined as (number of subjects with the indicated endpoint / the total number of subjects with follow-up data over the relevant period) × 100%. - For the measured AEs of injection site erythema and injection site swelling, 0 to 1 inch is categorized as mild intensity, >1 inch to 2 inches is categorized as moderate intensity, and >2 inches is categorized as severe intensity. The specific events of interest in this study were injection-site AEs prompted for on the Vaccination Report Card, such as injection site pain/tenderness, injection site swelling and injection site erythema occurring from Day 1 to Day 5 following any vaccination, and elevated temperature (≥37.5° C), from Day 1 to Day 5 following any vaccination.

Period 2 (entire 30 months period): Safety and tolerability were assessed by vaccine-related SAEs and death.

Results

Recruitment/ Number analysed

Disposition of Subjects

Disposition of subjects are presented in the table below. Among 101 enrolled subjects, 100 subjects received at least one vaccination, and 1 subject did not receive any vaccinations because of withdrawal. The 100 subjects completed all 3 vaccinations and study visits from Day 1 to Month 30.

	V501	
	n	(%)
Subjects in population	101	
Vaccinated at		
Treatment 1	100	(99.0)
Treatment 2	100	(99.0)
Treatment 3	100	(99.0)
Trial Disposition		
Completed	100	(99.0)
Discontinued	1	(1.0)
Withdrawal By Subject	1	(1.0)
Subject Study Medication Disposition		
Completed	100	(99.0)
Discontinued	1	(1.0)
Withdrawal By Subject	1	(1.0)
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.		

Source: [P200V501: adam-adsl]

Baseline data

Baseline Characteristics

Baseline characteristics of vaccinated subjects are presented in the table below.

Subject Characteristics
(All Enrolled Subjects)

	V501	
	n	(%)
Subjects in population	101	
Gender		
Male	101	(100.0)
Age (Years)		
9 to 12	53	(52.5)
13 to 16†	48	(47.5)
Mean	12.2	
SD	2.0	
Median	12.0	
Range	9 to 16	
Race		
Asian	101	(100.0)
Ethnicity		
Not Hispanic Or Latino	101	(100.0)
Weight(kg)		
Subjects with data	101	
Mean	42.0	
SD	14.5	
Median	37.4	
Range	21.0 to 111.4	
BMI(kg/m^2)		
Subjects with data	101	
Mean	18.2	
SD	3.2	
Median	17.7	
Range	12.1 to 33.1	

Source: [P200V501: adam-adsl]

† All subjects met the inclusion criteria and then were enrolled under the age of 16. The age of subject was tabulated based on the birth month. On the other hand, the enrolled date of five subjects ([redacted]) were the same month as the birthday of the 16th years. Therefore, the age of these subjects was aggregated as the age of 16 notation.

Efficacy results

Primary endpoint:

-For the primary endpoint, at 1 month post dose 3 (Month 7), the seroconversion percentages (with 95% confidence intervals [CIs]) for anti-HPV 6, 11, 16 and 18 were 94.9% (88.5%, 98.3%), 99.0% (94.4%, 100%), 99.0% (94.5%, 100%), and 99.0% (94.4%, 100%), respectively. The point estimates for the seroconversion percentages were >90%for each HPV type; therefore, the primary objective of the study was met.

Exploratory endpoints:

-For the secondary endpoint, at 12 months (Month 18) and 24months (Month 30) post dose 3, the anti-HPV 6, 11, 16 and 18 seroconversion percentages (95% CIs) were maintained at >90% for each HPV type. Marked HPV 6, 11, 16 and 18 antibody responses were observed for the entire duration of the study.

-The GMTsfor anti-HPV 6, 11, 16 and 18 at 1 month post dose 3 (Month 7), as assessed by cLIA, were 482.9 mMU/mL, 1,052.8 mMU/mL, 3,878.3 mMU/mL, and 1,114.5mMU/mL, respectively.The GMTs for all HPV types declined after Month 7.The GMTs at Month 18 and Month 30 were 222.0 and 177.5 mMU/mL for HPV 6;259.9 and 181.5 mMU/mL for HPV 11;1,154.1 and 831.3 mMU/mL for HPV 16; and212.1and 144.2mMU/mL for HPV 18.

Other endpoints:

-Comparison of immune response (9-to 15-year-old Japanese boys [Protocol V501-200]/16to 26-year-old Japanese men [Protocol V501-122]) at Month 7 indicated that the GMT ratios [boys/men] and associated 95% Cis were 1.25 (95% CI: 1.00, 1.57), 2.30 (95% CI: 1.89, 2.78), 1.69 (95% CI: 1.35, 2.11), and 3.05 (95% CI: 2.33, 3.99) for HPV types 6, 11, 16, and 18, respectively. The lower bound of 95% CI for GMT ratio was greater than 0.5 for all HPV types. The results demonstrated non-inferiority of the serum antibody response generated by the qHPV vaccinein 9-to 15-year-old Japanese boys (Protocol V501-200) to that in 16-to 26-year-old Japanese men (Protocol V501-122).

Assessor's comment: The applicant wrote that results demonstrated non-inferiority of the serum antibody response generated by the qHPV vaccine in 9-to 15-year-old Japanese boys (Protocol V501-200) to that in 16-to 26-year-old Japanese men (Protocol V501-122). In fact younger age-group demonstrated statistically significant higher antibody titer, especially in case of HPV 18. These results are in agreement with earlier observations, which have been demonstrated higher antibody titers among younger individuals in comparison to older ones in case of Gardasil.

Safety results

Evaluation of the safety and tolerability after 3-dose regimen of quadrivalent HPV L1 VLP vaccination in 9 to 15 year-old Japanese boys demonstrated the results as follows.

-From Day 1 through Month 7 (Period I); the proportion of AEs reported from Day 1 to Day 15 following any vaccination in the 3-dose series was 70.0%.

-The proportion of injection-site AEs and systemic AEs were 64.0% and 21.0%, respectively.

-The most common injection-site AE was injection site pain (57.0%), followed by injection site swelling (34.0%), and injection site erythema (31.0%). A severe injection-site AE was reported only in 1 subject who experienced injection site pain, which resolved on the third day after onset.

-Systemic vaccine-related AEs were reported in 3 subjects (3.0%); all of these were pyrexia of mild intensity which resolved within 2 days after onset.

-No subjects reported vaccine-related SAEs, death or AEs leading to study discontinuation during Period I and Period II.

-Overall, during the entire study period, administration of the 3-dose regimen of the qHPV vaccine to 9-to 15-year-old Japanese boys was generally well tolerated.

Assessor's comment: As the study size was small (N=100), chance for rare AEs and SAEs to happen was low. Anyhow, described AEs are well known and are previously described for Gardasil.

Rapporteurs discussion on clinical aspects

Administration of the 3-dose regimen of the qHPV vaccine to 9-to 15-year-old Japanese boys demonstrated high seroconversion percentages for the HPV types (6, 11, 16 and 18) at 1month post dose 3 and induced strong immune responses for the HPV types. Generated anti-HPV 6, 11, 16 and 18 GMTs at 1month post dose 3 that were non-inferior (actually superior) to those in 16-to 26-year-old Japanese men (Protocol V501-122). The immune response for the HPV types (6, 11, 16 and 18) persisted up to 24 months post dose 3.

The results are in agreement with previously reported studies. No concern regarding lacking efficacy is raised from this study.

The study population was relatively small (N=100) and therefore the chance to detect rare AEs and SAEs is low. The safety results are also in agreement with previously reported studies. No new safety concern is raised from this study.

3. Rapporteur's CHMP overall conclusion and recommendation

The results of this study indicate no new efficacy or safety concern. The P46 procedure is considered fulfilled.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

None.