17 August 2017
EMA/420632/2017
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/P46/085

Note

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

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1. Introduction

On May 15, 2017, 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 P110 – A phase IV open-label descriptive study to evaluate the safety and effectiveness on the incidence of HPV 6, 11, 16 and 18 related CIN2/3 or worse of the quadrivalent HPV (types 6,11, 16, 18) L1 virus-like particle (VLP) vaccine in 16-26year old 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:

- P110 A Phase IV Open-label, Descriptive Study to Evaluate the Safety and Effectiveness on the Incidence of HPV 6, 11, 16 and 18 Related CIN 2/3 or worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in 16- to 26-Year-Old Japanese Women;

The original study report was provided in Japanese, and the synopsis translated to English.

2.3.2. Clinical study

P110 A Phase IV Open-label, Descriptive Study to Evaluate the Safety and Effectiveness on the Incidence of HPV 6, 11, 16 and 18 Related CIN 2/3 or worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in 16- to 26-Year-Old Japanese Women;

Description

Methods

Objectives

Primary objective:

To investigate the incidences of CIN 2/3, AIS and/or cervical cancer related to HPV types 6, 11, 16 or 18 in Japanese women aged 16 to 26 years who had been vaccinated with the quadrivalent HPV L1 VLP vaccine, and were seronegative to relevant HPV type on Day 1 and polymerase chain reaction (PCR) negative from Day 1 through Month 7.

Exploratory objectives:

1) To investigate the incidence of external genital lesion (condyloma acuminata, VIN 1/2/3, VaIN 1/2/3, vulvar cancer and/or vaginal cancer) related to HPV types 6, 11, 16 or 18 in Japanese women aged 16 to 26 years who had been vaccinated with the quadrivalent HPV L1 VLP vaccine, and were seronegative to relevant HPV type on Day 1 and PCR negative from Day 1 through Month 7.

2) To evaluate safety and tolerability after 3-dose regimen of quadrivalent HPV L1 VLP vaccine.

Study design

Multi-center, open-label, single-arm study. The trial was conducted at 21 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) Healthy Japanese females aged 16 to 26 years.

2) Subjects (or, for minor subjects, parent/legal guardian and subject) fully understand study procedures, alternative treatments available, the risks involved with the study and voluntarily agree to participate by giving written informed consent.

3) No clinical evidence of gross purulent cervicitis (otherwise postpone until the completion of treatment or obtaining confirmation on examination that no further treatment is required).

4) Agree to refrain from douching/vaginal cleansing or using vaginal medication or preparation for 2 calendar days prior to any scheduled visit that includes pelvic examination.

5) Agree to refrain from sexual activity (including vaginal and anal penetration, and any genital contact) for 2 calendar days prior to any scheduled visit that includes a pelvic exam, in an attempt to avoid detection of viral DNA which has been deposited in the vagina or on the perineal/perianal area during sexual intercourse and is not the result of ongoing infection.

6) Not pregnant (as determined by human chorionic gonadotropin [hCG] urine pregnancy test with sensitivity ≥25 mIU/mL), and agree to use effective contraception through Month 7 of the study. Effective contraception includes oral contraceptives or injection contraception, intrauterine device (IUD), sterilization, abstinence, condom (male), diaphragm and cervical cap.

7) Individuals who have had sexual intercourse within 2 weeks prior to enrollment must have been using effective contraception as defined above. (Emergency contraception is not considered effective contraception for enrollment in the study.)

8) Individuals with a lifetime history of 0 to 4 male or female sexual partners. Women with 0 lifetime male or female sexual partners must be at least 18 years of age and plan to become sexually active within the first 3 months of the study.

9) Agree to provide the investigators or study collaborator with telephone numbers (priority and second priority numbers) for followup purposes.

10) No oral temperature ≥37.5°C within 24 hours prior to the first investigational vaccination.

The number of subjects In the study was 1030.

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 efficacy endpoint: Incidence of CIN 2/3, AIS and/or cervical cancer relative to HPV Type 6, 11, 16 or 18.

Exploratory efficacy endpoint: Incidence of external genital lesion (condyloma acuminatum, VIN 1/2/3, VaIN 1/2/3, vulvar cancer and/or vaginal cancer) relevant to HPV Type 6, 11, 16 or 18.

Other endpoints: - Incidence of CIN 1/2/3, AIS and/or cervical cancer relative to all HPV types.

- Incidence of external genital lesion relative to all HPV types.

Safety endpoint: Vaccine-related serious adverse events, death, and new medical conditions occurred during the entire study period and adverse events (AEs) and serious adverse events (SAEs) occurred between Day 1 and Day 15 of each study vaccination

Statistical Methods

Statistical analysis plan

Efficacy

For the effectiveness analyses, if a subject had experienced one or more lesion (event) that comprise each endpoint, the event detected for the first time was included in the analyses. The event was counted only when the lesion that comprises each endpoint occurred in the subject. In each effectiveness analysis, 1 event at a maximum was counted for one subject. In individual analysis of each HPV type and each lesion that comprise the composite endpoint, the lesion that occurred was counted as 1 for each sub category. When a lesion occurred in more than one sub category, the lesion was counted as 1 in each sub category. Missing data were not imputed.

Safety and tolerability

AEs and SAEs between Day 1 and Day 15 of each study vaccination, and death, vaccine-related SAEs and new medical conditions during the entire study period were counted. Primary safety endpoint was the incidence of vaccine-related SAEs during the entire study period. In the interim analysis, efficacy and safety data through Month 24 were analyzed.

Analysis description (Efficacy)

For the effectiveness analyses, point estimates and exact 95% confidence interval (CI) for incidence of event was computed based on Poisson distribution. Wherever possible, incidence rate estimates from this study were visually compared to the corresponding rates observed in other studies of quadrivalent HPV L1 VLP vaccines and other relevant epidemiologic data in and outside Japan.

In the primary analysis in Per-protocol efficacy [PPE] population, follow-up period started after Month 7 visit. Therefore, follow-up period for each subject was obtained by calculating the number of days from her Month 7 visit to her final visit. For the subjects who experienced the event, "final visit" was the first day of visit at which lesion was detected to calculate person-day. This value was converted to

person-years by dividing by 365.25. The total follow-up period was the sum of person-years of all subjects. A subject treated with definitive therapy was not to be censored for the relevant effectiveness evaluations on and after the start of therapy. If biopsy specimen obtained before or during the definitive therapy met the definition of the event for the relevant endpoint, the subject was considered to have an event.

With respect to missing serology results for any HPV type on Day 1, the occurrence of the lesion event of the subject for the relevant type of HPV was not to be counted. With respect to missing PCR status of swab specimen, existence of missing data determined the counting of the event occurrence for each subject. It means that for swab specimen obtained on Day 1 or Month 7, if at least one PCR status to any HPV type contained in the investigational vaccine was missing, the occurrence of the lesion event of the relevant HPV type for the subject was not to be counted. For biopsy specimen obtained between Day 1 and Month 7 (inclusive), if any of PCR status of them was missing, the event of the relevant HPV type for the subject occurred after Month 7 visit was not to be counted when the biopsy result showed pathological abnormalities and to be counted when the biopsy result was normal. This rule was established because abnormal tissue is likely to be HPV PCR-positive.

Efficacy Analysis population

Four efficacy populations (PPE, HPV-naïve to the relevant type [HNRT], Full analysis set [FAS] and Generally-HPV naïve population [GHN]) are defined as follows.

- PPE Population: All subjects who received 3 doses of investigational vaccination within 1 year, and had 1 or more follow-up data after Month 7, did not have any general protocol violations that could affect the efficacy evaluation of the investigational vaccination, and were seronegative to the relevant HPV type on Day 1, and PCR swab tests and PCR in biopsy specimen were negative from Day 1 through Month 7.

- HNRT Population: All subjects who were seronegative and PCRnegative (on swabs and biopsies) to the relevant vaccine HPV type(s) on Day 1, who received at least 1 investigational vaccination, and who had at least 1 follow-up data after Day 1.

- FAS Population: All subjects who received at least 1 investigational vaccination and who had at least 1 follow-up data after Day 1, regardless of initial serology and PCR status on Day 1.

- GHN Population: All subjects who received at least 1 study vaccination, who were sero- and PCR-negative on Day 1 to all vaccine HPV types (6, 11, 16 and 18), who were PCR-negative on Day 1 to all non-vaccine HPV types with PCR assays available, who had a negative Day 1 Papanicolaou (Pap) test result and who had at least 1 follow-up data after Day 1.

The cut-offs for the HPV 6, 11, 16 and 18 are defined 20 milli Merck Units per milliliter (mMU/mL), 16 mMU/mL, 20 mMU/mL and 24 mMU/mL by competitive Luminex Immunoassay, respectively when a subject is considered seropositive or seronegative to HPV Type 6, 11, 16 and 18.

For primary and exploratory endpoints, PPE was primary population, and HNRT, FAS and GHN were supplemental population. For other endpoints, HNRT, FAS and GHN were used as the analysis populations.

Analysis description (Safety)

All AEs occurred between Day 1 and Day 15 of each investigational vaccination were counted. Safety and tolerability were clinically assessed on all safety endpoints including AEs. As this study had only 1 treatment group, the following parameters were counted.

- Any AEs/vaccine-related AEs

- Injection site and non-injection site AEs/vaccine-related AEs

- AEs and vaccine-related AEs by severity

- SAEs

- Deaths (entire study period)

- Serious vaccine-related SAEs (entire study period)

- AEs/ vaccine-related AEs/ SAEs/ serious vaccine-related SAEs leading to discontinuation of vaccination

- Non-SAEs of special interest

- New medical conditions (new medical conditions not recorded as medical history or complication including autoimmune disease for entire study period)

Incidence (%) was defined as (subjects with the indicated endpoint divided by the number of safety analysis population) × 100.

Primary safety endpoint was the incidence of SAE related to investigational vaccine during the entire study period.

Safety Analysis Population

All subjects who received at least 1 investigational vaccine and had follow-up data were included.

Results

Recruitment/ Number analysed

Disposition of Subjects

Disposition of subjects are presented in the table below. 1036 subjects participated with written informed consents and screened. Among them, 6 subjects were not enrolled because of the results of screening.

	HPV		Total	
	n	(%)	n	(%)
Not Enrolled			6	
Subjects in population	1,030		1,030	
Vaccinated at				
Vaccination 1	1,030	(100.0)	1,030	(100.0)
Vaccination 2	1,026	(99.6)	1,026	(99.6)
Vaccination 3	1,019	(98.9)	1,019	(98.9)
Study Disposition				
COMPLETED	912	(88.5)	912	(88.5)
DISCONTINUED	118	(11.5)	118	(11.5)
ADVERSE EVENT	1	(0.1)	1	(0.1)
DEATH	1	(0.1)	1	(0.1)
LOST TO FOLLOW-UP	48	(4.7)	48	(4.7)
PHYSICIAN DECISION	15	(1.5)	15	(1.5)
PREGNANCY	1	(0.1)	1	(0.1)
WITHDRAWAL BY SUBJECT	52	(5.0)	52	(5.0)
Study Medication Disposition				
COMPLETED	1,019	(98.9)	1,019	(98.9)
DISCONTINUED	11	(1.1)	11	(1.1)
ADVERSE EVENT	1	(0.1)	1	(0.1)
LOST TO FOLLOW-UP	4	(0.4)	4	(0.4)
PREGNANCY	1	(0.1)	1	(0.1)
WITHDRAWAL BY SUBJECT	5	(0.5)	5	(0.5)
Each subject is counted once for Study Disposition, Study Medication Disposition based on the latest corresponding disposition record.				

Baseline data

Baseline Characteristics

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

Characteristic at Day 1 (qHPV)	Vaccination Group (N=1,030)
Gender - % (m)	
Female	100% (1,030)
Age (years)	
Mean	22.9
Standard Deviation	2.2
Median	23
Range	17 to 26
Race - % (m)	
Asian	100% (1,030)
Serostatus - % (m/n)	
Positive to HPV 6/11/16/18	9.8% (101/1,030)
Positive to HPV 6	4.3% (44/1,030)
Positive to HPV 11	0.7% (7/1,030)
Positive to HPV 16	4.7% (48/1,030)
Positive to HPV 18	2.1% (22/1,030)
PCR status - % (m/n)	
Positive to HPV 6/11/16/18	5.5% (56/1,023)
Positive to HPV 6	1.3% (13/1,023)
Positive to HPV 11	0.2% (2/1,023)
Positive to HPV 16	3.4% (35/1,022)
Positive to HPV 18	1.2% (12/1,023)
Day 1 (qHPV) is the day of injection of dose 1 of the qHPV vaccine. Unless otherwise indicated the percents shown were calculated as 100*(m/N). N = Number of subjects in the indicated vaccination group who received at least 1 dose of the qHPV vaccine. n = Number of subjects with non-missing Day 1 (qHPV) status corresponding to the indicated HPV type. m = Number of subjects belonging to the indicated category. qHPV = Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine.	

Efficacy results

Evaluation of the incidences of CIN 1/2/3, AIS, cervical cancer and external genital lesion following the quadrivalent HPV L1 VLP vaccination in 16 to 26 year-old Japanese women demonstrated the results as follows.

Primary endpoint:

- As a result of evaluation of incidences of CIN 2/3, AIS and/or cervical cancer relative to HPV types 6, 11, 16 or 18 in the primary population (PPE), no event was reported and the incidence of the event (/100 person-years) was 0.0 (95%CI: 0.0, 0.1).

- As a result of evaluation of incidences of CIN 2/3, AIS and/or cervical cancer relative to HPV types 6, 11, 16 or 18 in the supplemental populations (HNRT, FAS and GHN), 14 events were reported only in FAS, and the incidence of the event (/100 person-years) in HNRT, FAS and GHN were 0.0 (95%CI: 0.0, 0.1), 0.4 (95%CI: 0.2, 0.6) and 0.0 (95%CI: 0.0, 0.1), respectively.

Exploratory endpoints:

- As a result of evaluation of incidences of external genital lesion (condyloma acuminata, VIN 1/2/3, VaIN 1/2/3, vulvar cancer and/or vaginal cancer) relative to HPV types 6, 11, 16 or 18 in the primary

population (PPE), no event was reported and the incidence (/100 person-years) of the event was 0.0 (95%CI: 0.0, 0.1).

- As a result of evaluation of external genital lesion relative to HPV types 6, 11, 16 or 18 in the supplemental populations (HNRT, FAS and GHN), no events were reported in any of populations, and the incidences (/100 person-years) of the event were all 0.0 (95%CI: 0.0, 0.1).

Other endpoints:

- As a result of evaluation of incidences of CIN 1/2/3, AIS and/or cervical cancer relative to all HPV types, 73 events were reported only in FAS, and the incidences (/100 personyears) of the event in HNRT, FAS and GHN were 0.0 (95%CI: 0.0, 0.1), 2.0 (95%CI: 1.6, 2.5) and 0.0 (95%CI: 0.0, 0.1), respectively. Of the events reported in FAS, 27 events were severe graded as CIN 2 or worse (incidence: 0.7/100 personyears, 95%CI: 0.5, 1.1).

- As a result of evaluation of incidence of external genital lesions (condyloma acuminata, VIN 1/2/3, VaIN 1/2/3, vulvar cancer and/or vaginal cancer) relative to all HPV types, one event was reported in HNRT, FAS and GHN, respectively. Incidences (/100 person-years) of the event in HNRT, FAS and GHN were 0.0 (95%CI: 0.0, 0.1), 0.0 (95%CI: 0.0, 0.1) and 0.0 (95%CI: 0.0, 0.2), respectively.

Safety results

Evaluation of the safety and tolerability after 3-dose regimen of quadrivalent HPV L1 VLP vaccination in 16 to 26 year-old Japanese women demonstrated the results as follows.

- The incidence of injection site AEs reported from Day 1 to Day 15 of each investigational vaccination was 14.5% (149/1,029 subjects). All of these events were AEs considered to be related to the investigational vaccine except for one event. All of them were mild except for one moderate of injection site pain. Most events resolved within 15 days after the occurrence.

- The incidence of non-injection site AEs and vaccine-related AEs reported from Day 1 to Day 15 of each investigational vaccination were 23.5% (242/1,029 subjects) and 8.6% (89/1,029 subjects), respectively.

- Incidence of SAEs reported during the entire study period was 0.8% (8/1,029 subjects: Abortion induced in 4 subjects, abortion spontaneous, peritonsillitis, subarachnoid haemorrhage and foetal malpresentation in 1 subject each). All of these events were considered not related to the investigational vaccine by the investigators. One adverse event leading to death (subarachnoid haemorrhage, described above) was reported.

- One subject discontinued investigational vaccine due to mild urticaria occurring 2 days after the first investigational vaccination, and recovered 2 days after the occurrence of AE.

- Three dose regimen of quadrivalent HPV L1 VLP vaccine was generally safe and well tolerated.

2.3.3. Discussion on clinical aspects

In the PPE population there were no cases of CIN 2/3, AIS and/or cervical cancer relative to HPV types 6, 11, 16 or 18 at 48 months after the first vaccination. In the FAS population there were 14 events reported of the above endpoints. Likewise there were no cases of external genital lesion (condyloma acuminata, VIN 1/2/3, VaIN 1/2/3, vulvar cancer and/or vaginal cancer) relative to HPV types 6, 11, 16 or 18 in the PPE as well as the supplemental populations. It is not reported what the background incidence in the population is. The study was descriptive and no comparisons were made. The results

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

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.