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EMA/CHMP/233457/2018
Human Medicines Evaluation Division

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

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/001095/P46/036

Note

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

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1. Introduction

On 11 December 2017, the MAH submitted an addendum to a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated, with their submission in 2014, that V59_40 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Menveo has been developed for use in children and adults. The same formulation and dose is used across the full age range approved.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an addendum to the final clinical study report (CSR) dated 15/10/2013 for:

- V59_40 A Phase 4, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix) and Quadrivalent Human Papillomavirus [Types 06, 11, 16, 18] Recombinant Vaccine (Gardasil) in Healthy Adolescents when Administered with MenACWY Conjugate Vaccine;

The final CSR presented data for the first coprimary objective (non-inferiority of the immune response of Tdap vaccine given concomitantly with MenACWY vaccine and HPV vaccine compared to the response of Tdap vaccine given with placebo and HPV vaccine, measured at 1 month after 1 dose of Tdap vaccine), and the secondary immunogenicity descriptive endpoint not related to the assessment of immune response against HPV antigens and all safety objectives.

This CSR has been discussed and assessed in a previous Art 46 AR (dd 2014).

The immunogenicity analysis for the second coprimary objective (non-inferiority of the immune response of HPV vaccine given concomitantly with MenACWY and Tdap vaccines to the response of HPV vaccine given with placebo and Tdap vaccine, measured at 1 month after the third dose of HPV vaccine) and the secondary objective for the assessment of immune response against HPV antigens could not be performed as the serological results for HPV testing were not available for reporting in the final CSR. These results are now presented in this addendum to the final CSR dated 15 OCT 2013.

2.3.2. Clinical study

V59_40 A Phase 4, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix) and

Quadrivalent Human Papillomavirus [Types 06, 11, 16, 18] Recombinant Vaccine (Gardasil) in Healthy Adolescents when Administered with MenACWY Conjugate Vaccine

Description

This is a placebo controlled randomised study with the aim to evaluate the immune response and safety of Tdap vaccine and HPV vaccine in healthy adolescents aged 11-18 years when administered with MenACWY conjugate vaccine. The study was conducted in the US and Italy.

CHMP comments

The Methods of the study and the results for the first coprimary objective have been assessed in a previous Art 46 AR circulated on 28/08/2014, for which the procedure was concluded in September 2014. The MAH has now only submitted the results related to the second coprimary objective. Methods that are considered relevant to the present submission, i.e. to understand the context of the results, are repeated below. The objectives and methods relevant to this submission are highlighted yellow. The results are limited to those now submitted.

Methods

Objectives

Immunogenicity Objectives:

Coprimary:

1. To demonstrate that the immune response of Tdap given concomitantly with MenACWY and HPV is noninferior to the response of Tdap when given with placebo and HPV when measured at 1 month after 1 dose of Tdap.

2. To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is noninferior to the response when HPV is given with placebo and Tdap when measured at 1 month after the third dose of HPV vaccination.

Study design

This study was designed as a phase 4, placebo-controlled, randomized study to evaluate the immunogenicity and safety of a combined tetanus, reduced diphtheria toxoid, acellular pertussis vaccine and quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in healthy adolescents when administered with MenACWY.

Study population /Sample size

The study included healthy male/ (non-pregnant) female subjects with no history of meningococcal infection and/or vaccination or HPV vaccination, and with an up-to-date vaccination record for DTP. Approximately 800 subjects, 400 in group 1 and 400 in group 2 were to be enrolled in this study. The expected dropout rate was 10%.

Treatments

Subjects were randomized in a 1:1 allocation ratio within each study centre. Group 1 received Tdap, HPV and MenACWY concomitantly for the first vaccination. Group 2 received Tdap, HPV and placebo concomitantly for the first vaccination.

Outcomes/endpoints

Primary outcomes:

▫ Seroconversion rates for HPV types 6, 11, 16 and 18 at 1 month after 3 HPV vaccinations. Seroconversion was defined as a negative baseline sample for anti-HPV antibodies and anti-HPV antibody level greater than or equal to the HPV type-specific cutoff at 1 month after the third dose of HPV vaccine. The HPV type-specific seroconversion cutoffs were:

- Percentage of subjects with HPV 6 ≥ 20 mMU/mL;
- Percentage of subjects with HPV 11 ≥16 mMU/mL;
- Percentage of subjects with HPV 16 ≥20 mMU/mL; and
- Percentage of subjects with HPV 18 ≥24 mMU/mL.

General Endpoints and Statistics:

▫ GMT or GMC with associated 2-sided 95% CIs are displayed by visit and vaccine group. When baseline values were available, geometric mean ratios (GMRs) to baseline were also presented.

▫ Percentage of subjects meeting response criteria. For the routine vaccine antigens, the cut-off levels indicated seroprotection/seroconversion rates. The 2-sided 95% CIs for all response rates were displayed for all available immunogenicity data by visit and vaccine group.

▫ Anti-HPV seroconversion was defined as a negative baseline sample for anti-HPV and an anti-HPV greater than or equal to the HPV type-specific cutoff at 1 month after the third dose of the vaccine.

▫ All primary and secondary objectives are embedded within the display of GMT/GMC/percentage response according to the respective visit and vaccine group of interest.

Statistical Methods

Definition of populations analysed:

All Enrolled Population: The enrolled population contained all subjects enrolled and randomized in the study.

Exposed Population: All subjects in the enrolled population who received a study vaccination.

MITT Population: The MITT population included all subjects in the enrolled population who received all the relevant doses of vaccine, and provided at least 1 evaluable serum sample after baseline.

Per Protocol (PP) Population: The PP population included all subjects in the MITT immunogenicity population who correctly received all the relevant doses of vaccine, provided evaluable serum samples at the relevant time points; and ▫ had no major protocol deviation as defined prior to study unblinding.

The PP populations were:

PP – Tdap Serology results at visit 2 within required windows for at least 1 Tdap antigen.

PP – HPV Serology results for at least 1 HPV type at both visit 1 and visit 5 within required window

PP – MenACWY Serology results for at least 1 serogroup at both visit 1 and visit 2 within the required window

Subjects were included in the PP population if they had no major deviations. A major deviation was defined as a protocol deviation that was considered to have a significant impact on the immunogenicity result of the subject.

Analysis for the primary immunogenicity objectives was based on the PP population as well as the MITT population. Analyses for secondary immunogenicity objectives and other immunogenicity endpoints were carried out in the PP population only.

Safety Population

All subjects who had received at least 1 study vaccine and had postbaseline safety data were included in the safety analysis. If an error in administration occurred where the actual vaccination that the subject received was different than the one to which they were randomly assigned (unless they received all doses in accordance with the incorrect schedule), the subject was included in the vaccination group for the vaccine they were randomized to receive. If the full series was provided incorrectly, the subject was analyzed as treated. Safety analyses were based on the safety population.

Subjects who only provided safety data at 30 minutes postvaccination were represented in summaries of safety at 30 minutes postvaccination and were excluded from all other summaries of safety.

Analysis of Immunogenicity criteria

The success criterion for this study was a composite based upon 2 coprimary objectives that involve 9 noninferiority hypotheses. The first coprimary objective was to demonstrate that the immune response of Tdap given concomitantly with MenACWY and HPV was noninferior to the response of Tdap when given with placebo and HPV when measured at 1 month after 1 dose of Tdap. The second coprimary objective was to demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap was noninferior to the response when HPV was given with placebo and Tdap when measured at 1 month after the third dose of HPV vaccination.

Second Coprimary Objective: To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is noninferior to the response when HPV was given with placebo and Tdap when measured at 1 month after the third dose of HPV.

The group 1 immune response to HPV will be considered noninferior to the group 2 immune response to HPV if the lower limit of the 2-sided 95% CI on the differences between the group 1 and group 2 HPV type 6, 11, 16, and 18 seroconversion rates are each greater than -5%. The 2-sided 95% CIs for the group 1 minus group 2 differences in HPV 6, HPV 11, HPV 16, and HPV 18 seroconversion rates will be constructed using the method of Miettinen and Nurminen. Titers below the limit of detection will be set to half the limit for the purpose of analysis.

Results

Recruitment / Number analysed

A total of 801 subjects who signed informed consent forms were enrolled in the study and were randomized; 402 subjects were included in the Men+Tdap+HPV group and 399 subjects in the Placebo+Tdap+HPV group.

Overall, 739 subjects (92%) were included in the HPV modified intention-to-treat (MITT) population and 634 (79%; 309 in the Men+Tdap+HPV group and 325 in Placebo+Tdap+HPV group) subjects were included in the HPV per protocol (PP) population. The main reasons for excluding subjects from the HPV PP population were blood draw/vaccination out of visit window, blood draw/vaccination not done and subject receiving prohibited vaccination.

Baseline data

The demographic parameters for the *enrolled population*, such as age, sex and race, were generally similar across the study groups. The average age of the subjects at study entry was 11.9 (±1.6) years and the majority of the subjects were male (60%). The percentage of female subjects was 42% in the Men+Tdap+HPV group and 39% in the Placebo+Tdap+HPV group.

In the HPV PP population, the demographic parameters, such as age, sex and race, were generally similar across the two study groups. The average age of the subjects at study entry was 11.9 (±1.56) years and the majority of the subjects were male (62%).

Table 11.2-4: Summary of Demography – HPV PP Population

	Men+Tdap+HPV N=309	Placebo+Tdap+HPV N=325	Total N=634
Age (Years):	11.9±1.63	11.8±1.48	11.9±1.56
Sex:			
Male	185 (60%)	209 (64%)	394 (62%)
Female	124 (40%)	116 (36%)	240 (38%)
Race:			
Asian	3 (1%)	6 (2%)	9 (1%)
Black or African	25 (8%)	26 (8%)	51 (8%)
White	253 (82%)	260 (80%)	513 (81%)
American Indian or Alaska Native	1 (<1%)	1 (<1%)	2 (<1%)
Pacific/Hawaii	0	2 (1%)	2 (<1%)
Other	27 (9%)	30 (9%)	57 (9%)
Weight (kg):	50.22±14.812	49.92±15.08	50.07±14.939
Height (cm):	153.1±11.72	153.3±11.09	153.2±11.39
Body Mass Index (kg/m^2):	21.2±4.68	21±4.82	21.1±4.75
Pregnancy Test:			
Negative	123 (40%)	113 (35%)	236 (37%)
Not Done	1 (<1%)	3 (1%)	4 (1%)
Child Bearing Potential:			
No	70 (23%)	69 (21%)	139 (22%)
Yes	54 (17%)	47 (14%)	101 (16%)

Source: Table 14.1.1.3.4.

Abbreviations: HPV, human papilloma virus vaccine; Men, meningococcal ACWY vaccine; Tdap, tetanus diphtheria acellular pertussis vaccine.

Categorical parameters: N (%), non-categorical parameters: Mean±Standard deviation.

Efficacy results

Second Co-Primary Objective:

The second coprimary objective was to demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap vaccines was non-inferior to the response to HPV vaccine given concomitantly with placebo and Tdap vaccine, when measured at 1 month after the third dose of HPV vaccine. The immune response to HPV vaccine, given concomitantly with MenACWY and Tdap vaccines, was to be considered non-inferior to the immune response to HPV vaccine given concomitantly with placebo and Tdap vaccines if the lower limits of the 2-sided 95% CI on the differences between the Men+Tdap+HPV group and Placebo+Tdap+HPV group seroconversion rates for HPV types 06, 11, 16, and 18 were each greater than -5%.

Percentage of subjects with seroconversion for HPV types 06, 11, 16, 18:

At one month after the third dose of HPV vaccine, the percentages of subjects with seroconversion against the HPV types tested were ranging from 98% (HPV 06 type) to 99.7% (HPV 11 and HPV 18 types) in Men+Tdap+HPV group, and from 99% (HPV 11 and HPV 16 types) to 99.7% (HPV 06 and HPV 18 types) in Placebo+Tdap+HPV group (Table 11.4.1-1A). The lower limits of 2-sided 95% CI on the differences between the Men+Tdap+HPV group and Placebo+Tdap+HPV group were greater than -5% against each of the HPV types tested. Thus, the immune response of HPV vaccine given concomitantly with MenACWY and Tdap vaccines was non-inferior to the immune response when HPV vaccine as given with placebo and Tdap vaccine.

Table 11.4.1-1A Percentages of Subjects with Seroconversion for HPV types, and Vaccine Group Differences, 1 Month After Third HPV Vaccination– HPV PP Population

		Number (%) of Subjects (95% CI)		Vaccine Group Difference 95% CI[a]
HPV Strain	Antibody Cutoff Level	Men+Tdap+HPV N=309	Placebo+Tdap+HPV N=325	
HPV 06	≥20 mMU/mL	304 (98%) (96.3%-99.5%)	324 (99.7%) (98.3%-99.99%)	-1% (-3.5%-0.3%)
HPV 11	≥16 mMU/mL	308 (99.7%) (98.2%-99.99%)	323 (99%) (97.8%-99.93%)	0.3% (-1.2%-1.9%)
HPV 16	≥20 mMU/mL	307 (99%) (97.7%-99.92%)	321 (99%) (96.9%-99.66%)	1% (-1.2%-2.6%)
HPV 18	≥24 mMU/mL	308 (99.7%) (98.2%-99.99%)	324 (99.7%) (98.3%-99.99%)	0% (-1.5%-1.4%)

Source: Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6.
Abbreviations: CI, confidence interval; HPV, human papilloma virus vaccine; Men, meningococcal ACWY vaccine; PP, per protocol; Tdap, tetanus diphtheria acellular pertussis vaccine.
[a] Non-inferiority criterion: The lower limits of the 2-sided 95% CIs on the inter-group differences for HPV types 06, 11, 16, and 18 seroconversion rates were to be each greater than -5%.
Note: Bold values indicate that non-inferiority criteria were met.

GMTs and GMRs for anti-HPV antibodies:

At baseline (day 1) before HPV vaccination, the GMTs against the 4 HPV types were ranging from 4.03 to 5.82 across the study groups. At 1 month post the third HPV vaccination, the GMTs in the Men+Tdap+HPV group versus the Placebo+Tdap+HPV group were: 1012.60 and 1084.13 against HPV Type 06, 1052.35 and 1167.94 against HPV Type 11, 6293.21 and 7221.71 against HPV Type 16, 1124.26 and 1335.71 against HPV Type 18, respectively with all 95% CIs of GMTs overlapping between the two study groups, when analyzed by HPV type. At 1 month post third HPV vaccination, the 30 days post last HPV vaccination/ baseline geometric mean ratios (GMRs) in the Men+Tdap+HPV and in the Placebo+Tdap+HPV groups were as follows: 173.85 and 191.15 against HPV Type 06, 260.92 and 288.03 against HPV Type 11, 1111.67 and 1277.5 against HPV Type 16, 220.33 and 261.41 against HPV Type 18, respectively (Table 11.4.1-6).

In general, GMTs were comparable between the two groups at baseline. The GMTs and the GMRs were high at 30 days post the last HPV vaccination against all HPV strains. In all cases, 95% CIs of GMTs and GMRs were overlapping between the two study groups, when analyzed by HPV type (Table 11.4.1-6).

Table 11.4.1-6 Geometric Mean Titers and Ratios against HPV Types 06, 11, 16 and 18, 1 Month After Third HPV Vaccination – HPV PP Population

HPV Strain		HPV GMT/GMR 95% CI	
		Men+Tdap+HPV N=309	Placebo+Tdap+HPV N=325
HPV 06	Day 1 (Baseline)	5.82 (5.64-6.02)	5.67 (5.49-5.86)
	30 days post last vaccination	1012.60 (899-1141)	1084.13 (965-1218)
	30 days post last vaccination/Day 1	173.85 (154-196)	191.15 (170-215)
HPV 11	Day 1 (Baseline)	4.03 (3.96-4.1)	4.05 (3.99-4.12)
	30 days post last vaccination	1052.35 (945-1171)	1167.94 (1052-1296)
	30 days post last vaccination/Day 1	260.92 (234-291)	288.03 (259-320)
HPV 16	Day 1 (Baseline)	5.66 (5.47-5.85)	5.65 (5.47-5.84)
	30 days post last vaccination	6293.21 (5574-7105)	7221.71 (6417-8128)
	30 days post last vaccination/Day 1	1111.67 (981-1259)	1277.5 (1132-1442)
HPV 18	Day 1 (Baseline)	5.1 (5.01-5.2)	5.11 (5.02-5.2)
	30 days post last vaccination	1124.26 (967-1307)	1335.71 (1153-1547)
	30 days post last vaccination/Day 1	220.33 (189-256)	261.41 (225-303)

Source: Table 14.2.1.12.
Abbreviations: CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titer; HPV, human papilloma virus vaccine; Men, meningococcal ACWY vaccine; PP, per protocol; Tdap, tetanus diphtheria acellular pertussis vaccine.

CHMP comments

The results for the second coprimary endpoint show that there is no evidence of immune interference when HPV vaccine is given concomitantly with Menveo. The seroresponse rates in both groups are very similar and non-inferiority is demonstrated. Although GMTs are slightly lower when HPV vaccine is given together with Menveo, the difference is small – not statistically significant and unlikely of clinical relevance.

Safety results

No new safety results were presented.

2.3.3. Discussion on clinical aspects

The submitted data provide no evidence to suggest that there is immune interference when quadrivalent HPV vaccine (Gardasil) is given concomitantly with Menveo, as non-inferiority of the immune response to HPV at one month after the third HPV vaccination in terms of the percentages of subjects achieving seroconversion against each of the four HPV vaccine antigens (type 06, 11, 16, and 18),when given concomitantly with Menveo and Tdap vaccine has been demonstrated to HPV given with placebo and Tdap vaccine.

The possible interaction between Gardasil and Menveo and Tdap/Boostrix and Menveo was also studied in V59P18 (submitted and assessed in context of the MAA for Menveo), which has resulted in the following statement in section 4.5 of the SmPC:

In adolescents (11 to 18 years of age), Menveo has been evaluated in two co-administration studies with either Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine, Adsorbed (Tdap) alone or Tdap and Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (HPV), both of which support the co-administration of the vaccines.

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines in either study. Antibody responses to Menveo and the diphtheria, tetanus or HPV vaccine components were not negatively affected by co-administration.

The now submitted results for study V59_40 are in line with this information. No changes to the SmPC are therefore warranted.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.