28 March 2019
EMA/147123/2019
Committee for Medicinal Products for Human Use (CHMP)

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/P46/040

Note

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

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1. Introduction

On 21 December 2018, the MAH submitted a completed paediatric study for Menveo in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitidis groups A, C, W135 and Y, to prevent invasive disease.

The use of this vaccine should be in accordance with official recommendations.

Menveo should be administered as a single dose (0.5 ml). To ensure optimal antibody levels against all vaccine serogroups, the primary vaccination schedule with Menveo should be completed one month prior to risk of exposure to Neisseria meningitides groups A, C, W135 and Y.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea, study V59_75, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study vaccine specific to this study was the MenACWY-CRM vaccine (Menveo, GSK Biologicals). There is no specific paediatric formulation. The meningococcal ACWY conjugate vaccine was to be reconstituted just before injection of the lyophilized MenA-CRM component with the MenCWY-CRM full liquid vaccine. The pharmaceutical form was a powder and solution for injection. Menveo was provided as vial/vial presentation. MenA lyophilised conjugate component (glass vial) and MenCWY liquid conjugate component (glass vial).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- V59_75: A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

In May 2014 the indication of Menveo was extended to infants 2 months of age to 55 years in South Korea and the current study was performed upon request ofthe Regulatory Authorities of the Republic of South Korea, (MFDS) as a post commitment of indication change, providing data on immunogenicity persistence in the Korean children who received 4 doses of Menveo at 2-4-6-12 months of age.Clinical study.

V59_75: A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

Description

This is a Phase IV multicenter open label, post marketing study to evaluate the persistence of antibody response in approximately 135 children 1 year after completion of series of Menveo vaccination at 2-4-6-12 month vaccination.

Methods

Objectives

Primary Immunogenicity Objective:

- To evaluate the persistence of the antibody response against *Neisseria meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4 dose infant vaccination series (2, 4, 6 and 12 months of age) of Meningococcal ACWY (MenACWY) vaccine as measured by human complement Serum Bactericidal Assay (hSBA) $\geq$ 8.
- To evaluate the persistence of the antibody response against N meningitidis serogroups A, C, W and Y at approximately 1 year after completion of a 4 dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rabbit complement Serum Bactericidal Assay (rSBA) $\geq$ 8 and $\geq$ 128.

Secondary Immunogenicity Objectives:

- To describe hSBA $\geq$ 8 and hSBA geometric mean titers (GMTs) against N meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2,4,6 and 12 months of age.
- To describe rSBA $\geq$ 8 and $\geq$ 128 and rSBA GMTs against N meningitidis serogroups A, C, W and Y 1 month after a full vaccination series at 2,4,6 and 12 months of age.
- To evaluate the persistence of the antibody response against N meningitidis serogroups A, C, W and Y at approximately 1 year after completion of a 4 dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.

Primary Safety Objectives:

- To assess the safety and tolerability of MenACWY administered at 2, 4, 6 and 12 months of age.

Study design

This is a Phase IV multicenter open label, post marketing study to evaluate the persistence of antibody response in approximately 135 children 1 year after completion of series of Menveo vaccination at 2-4-6-12 month vaccination. All participants will receive 4 doses of Menveo in an open label fashion. A total of two blood samples will be drawn from all subjects for immunogenicity evaluation at the following time points: 1 month after the fourth and last dose of Menveo vaccine, (Visit 5, 13 months of age) and one during the last clinical visit (Visit 6, 24 months of age). Safety data will be solicited for 7 days through a subject diary.

Table 3.1-1 Overview of the study design

N Subjects	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	2-Months	4-Months	6-Months	12-Months	13- Months	24- Months
135	Menveo®	Menveo®	Menveo®	Menveo®	Blood draw	Blood draw

Study population /Sample size

The study included healthy male and female infants aged between 55 and 89 days on the day of consent. Exclusion criteria common to vaccine studies applied, in addition subjects were not to have previously received MenACWY vaccine, previously had confirmed or suspected *N meningitidis,* or close contact with a case, or have any underlying (unstable, uncontrolled) clinical condition, immunosuppression, acute or chronic infection.

Assessor's comments

This study is in healthy infants of around 2 months of age, and therefore falls outside the current indication for Menveo.

Treatments

Subjects received Menveo at 2, 4, 6 and 12 months. No reference (control) vaccine was used in this study.

Outcomes/endpoints

Primary Immunogenicity Endpoints

One year after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), establish the persistence by:

- Percentage of subjects with hSBA ≥ 8 for each serogroup.
- The percentage of subjects with rSBA ≥ 8 and with rSBA ≥ 128 for each serogroup.

Secondary Immunogenicity Endpoints

One month after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), evaluate:

- Percentage of subjects with hSBA ≥ 8 for each serogroup.
- The percentage of subjects with rSBA ≥ 8 and with rSBA ≥ 128 for each serogroup.

One year after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), establish the persistence by:

- hSBA GMT for each serogroup,
- rSBA GMT for each serogroup.

One month after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), evaluate:

- hSBA GMT for each serogroup,
- rSBA GMT for each serogroup.

Assessor's comments

The immunogenicity endpoints do not take into account potential baseline immunogenicity, however considering the age of the study population natural exposure would be very low therefore this is acceptable.

Statistical Methods

There was no statistical hypothesis associated with the immunogenicity objective. All analyses were to be run descriptively.

Persistence was to be summarized as the percentage of subjects with a titer ≥ 8 (hSBA) or with a titer ≥ 8 and ≥ 128 (rSBA) along with associated 2-sided 95% Clopper-Pearson confidence intervals (CIs).

The antibody titers were to be summarized using GMTs with 2-sided 95% CIs constructed by exponentiation (base 10) of the means and confidence limits of the logarithmically transformed (base 10) antibody titer. Moreover, the geometric mean ratios (GMR) between visit 6 (1 year after full vaccination) and visit 5 (1 month after full vaccination) were to be provided along with the 2-sided 95% CIs.

Approximately 135 subjects were to be enrolled in this study providing approximately 100 evaluable subjects, assuming a 25% drop-out. The sample size was based on the number of subjects requested and agreed with South Korean Health Authorities for this persistence study.

With 100 evaluable subjects, the 95% confidence limits of the observed percentages of subjects with hSBA ≥ 8 or rSBA ≥ 8 or ≥ 128 were to be as presented in the following table:

Table 1 Calculated 95% Confidence Interval, Associated With Different Observed Percentages of Subjects

Observed percentage	95% confidence interval (MenACWY N = 100)
50%	40%- 60%
60%	50%-70%
70%	61%-79%
80%	72%-88%
90%	84%-96%

Source: Table 4 Protocol version 3 dated: 26 Feb 16.

Results

Recruitment/ Number analysed

This study was conducted at six study centres in South Korea. The first subject was enrolled on 13 July 2015, the last visit completed on 28 December 2017.

In total, 128 subjects were enrolled and all (100%) received the MenACWY vaccine. A total of 117 (91%) subjects completed the study. Reason for premature withdrawal of 11 subjects were: lost to follow-up (8), withdrawal by the subject (2), and protocol deviation/ violation (1).

For the primary objective, up to 114 (89%) subjects were included in hSBA FAS and up to 108 (84%) subjects were included in rSBA FAS. For the secondary objective, up to 122 (95%) subjects were included in hSBA FAS and up to 116 (91%) subjects were included in rSBA FAS. The main reason for exclusion from various analysis sets was, serological results not available post-vaccination.

Study conduct

Out of total 128 enrolled subjects, 42 (33%) subjects had protocol deviations. Main reason for protocol deviations was key study procedures missed or performed out of time window (30%) that included subject not complying with study vaccination schedule (18%) or blood draw schedule (5%) and serological results not available post-vaccination (11%).

Baseline data

The mean age of subjects at enrolment was 71.7 days, mean height was 59.5 cm, and mean body weight was 6.1 kg. 54% subjects were males and 46% subjects were females. All subjects, except for 1 subject ('Other'), were of 'Asian' race.

Efficacy results

Primary immunogenicity objective: persistence with hSBA ≥8 and rSBA titers ≥ 8 and ≥ 128

One year after the 4-dose infant vaccination series, the percentage of subjects with hSBA titers ≥ 8 ranged between 39% (MenA) and 89% (MenY).

Table 11.4.1-1 Number (%) of Subjects (95% CI) with hSBA Titer ≥ 8 Against Serogroups A, C, W and Y, 1 Year After Completion of the 4-dose MenACWY Vaccination Series – FAS hSBA 1 Year

Serogroup	MenACWY N = 128
A	45 (39%) (30.4%, 49.1%) N = 114
C	67 (61%) (51.1%, 70.1%) N = 110
W	99 (88%) (80.1%, 93.1%) N = 113
Y	101 (89%) (81.3%, 93.8%) N = 114

Source: Table 14.2.1.1.
Abbreviations: FAS, full analysis set; hSBA, Human complement serum bactericidal assay.

One year after completion of the 4-dose infant vaccination series, the percentage of subjects with rSBA titers ≥ 8 ranged between 54% (MenC) and 99% (MenA).

When using 128 as cut-off titer, the percentages of subjects with rSBA titers ≥ 128, one year after completion the 4-dose infant vaccination series, ranged between 30% (MenC) and 98% (MenA).

Table 11.4.1-2 **Number (%) of Subjects (95% CI) with rSBA Titer ≥ 8 and ≥ 128 Against Serogroups A, C, W and Y, 1 Year After Completion of the 4-dose MenACWY Vaccination Series – FAS rSBA 1 Year**

Serogroup	MenACWY	
	rSBA Titer ≥ 8	rSBA Titer ≥ 128
A	**N = 108**	**N = 108**
	107 (99%) (94.9%, 99.98 %)	106 (98%) (93.5%, 99.77%)
C	**N = 108**	**N = 108**
	58 (54%) (43.8%, 63.3%)	32 (30%) (21.2%, 39.2%)
W	**N = 108**	**N = 108**
	75 (69%) (59.8%, 77.9%)	67 (62%) (52.2%, 71.2%)
Y	**N = 107**	**N = 107**
	96 (90%) (82.3%, 94.8%)	86 (80%) (71.6%, 87.4%)

Source: Table 14.2.1.1.4; Table 14.2.1.1.8.

Abbreviations: FAS, full analysis set; rSBA, rabbit complement serum bactericidal assay.

Assessor's comments

There is poor correlation between the rSBA and hSBA response, which is also seen in other studies. Poor persistence is seen for MenA when considering the hSBA but not when considering the rSBA. For the rSBA, persistence seems to be poor for MenC; this is not seen with the hSBA.

Secondary Objectives

hSBA and rSBA one month after vaccination

One month after completion of the 4-dose infant MenACWY vaccination series the percentage of subjects with hSBA titer ≥ 8 ranged between 94% (MenA,) and 100% (MenW and MenY) and the hSBA GMTs ranged between 107.90 (MenA) and 426.74 (MenW).

One month after completion of the 4-dose infant MenACWY vaccination series, almost all subjects had rSBA titer ≥ 8 and the percentage of subjects with rSBA titer ≥ 128 raged between 92% (Men C) and 100% (MenA). The rSBA GMTs ranged between 735.07 (Men C) and 7394.18 (Men A).

Antibody persistence as hSBA GMTs and rSBA GMTs.

One year after completion of the 4-dose MenACWY vaccination series hSBA GMTs ranged between 6.80 (MenA) and 53.56 (MenW), while rSBA GMTs ranged between 17.17 (MenC) and 2269.48 (MenA).

Safety results

Exposure

Table 12.1-1 Number (%) of Subjects in the Safety Sets

Analysis Set	MenACWY N = 128
Exposed Set	128 (100%)
Solicited Safety Set	
First Vaccination (6 hours-Day 7)	128 (100%)
Second Vaccination (6 hours-Day 7)	128 (100%)
Third Vaccination (6 hours-Day 7)	127 (99%)
Fourth Vaccination (6 hours-Day 7)	124 (97%)
Unsolicited Safety Set	
Day 1-Day 61	128 (100%)
Day 61-Day 121	128 (100%)
Day 121-Day 301	126 (98%)
Day 301-Day 661	124 (97%)
Day 1-Day 661 (Study Termination)	128 (100%)
Overall Safety Set	
Day 1-End of the study	128 (100%)

Source: Table 14.1.1.1.

Adverse Events

Solicited AEs:

Overall, the percentage of subjects with any solicited AEs reported was 66% after the first vaccination, 51% after the second vaccination, 46% after the third vaccination, and 52% after the fourth vaccination.

- The most common solicited local AE was tenderness, reported in 13%, 16%, 11%, 16% subjects after each of the 4 vaccinations, with severe tenderness reported in 0%-2% subjects across vaccinations.
- Irritability (45%, 38%, 37%, 36% after each of the 4 vaccinations) and sleepiness (41%, 24%, 22%, 16% after each of the 4 vaccinations) were the most common solicited systemic AEs reported, with severe irritability in 2%-4% subjects and severe sleepiness in 0%-3% subjects.
- Most of the reported solicited local and systemic AEs were mild to moderate in intensity with onset from 6 hours to day 3 after vaccination and most of them resolved within 7 days.

Table 2 Number (%) of Subjects with Solicited Local AEs and Solicited Systemic AEs and Other Indicators from 6 Hours Through Day 7 After Each Vaccination – Solicited Safety Set

			Number (%) of Subjects			
Vaccination			First	Second	Third	Fourth
	AE	Grade				
Local AEs	Erythema (mm)[a]		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	4 (3%)	6 (5%)	1 (1%)	6 (5%)
		Severe	0	0	1 (1%)	2 (2%)
	Induration (mm)[a]		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	4 (3%)	9 (7%)	3 (2%)	6 (5%)
		Severe	0	0	0	2 (2%)
	Tenderness[b]		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	17 (13%)	21 (16%)	14 (11%)	20 (16%)
		Severe	0	0	3 (2%)	2 (2%)

			Number (%) of Subjects			
Vaccination			First	Second	Third	Fourth
	AE	Grade				
Systemic AEs	Change in eating habits		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	29 (23%)	21 (16%)	21 (17%)	24 (19%)
		Severe	2 (2%)	0	0	3 (2%)
	Sleepiness		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	52 (41%)	31 (24%)	28 (22%)	20 (16%)
		Severe	2 (2%)	0	0	4 (3%)
	Irritability		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	58 (45%)	49 (38%)	47 (37%)	45 (36%)
		Severe	2 (2%)	3 (2%)	4 (3%)	5 (4%)
	Vomiting		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	26 (20%)	20 (16%)	15 (12%)	5 (4%)
		Severe	0	1 (1%)	0	1 (1%)
	Diarrhea		**N = 128**	**N = 128**	**N = 127**	**N = 124**
		Any	15 (12%)	13 (10%)	15 (12%)	17 (14%)
		Severe	0	1 (1%)	0	0
	Fever (≥ 38°C)		**N = 128**	**N = 128**	**N = 127**	**N = 124**
			4 (3%)	10 (8%)	6 (5%)	15 (12%)

Unsolicited AEs (medically attended):

A total of 66% subjects experienced an unsolicited AE, with 1 subject having at least possibly related AE (diarrhoea).

The most commonly reported unsolicited AEs were classified under the MedDRA SOC of 'infections and infestations' (59%). The most commonly reported unsolicited AEs, by Preferred Term, were: upper respiratory tract infection (27%), bronchiolitis (12%), and nasopharyngitis (12%). Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Table 3 Number (%) of Subjects with All and At Least Possibly Related Unsolicited Medically Attended Adverse Events from Day 1 to Study Termination Presented by System Organ Class – Unsolicited Safety Set

System Organ Class	MenACWY	
	All	At Least Possibly Related
	N = 128	N = 128
Any AE	85 (66%)	1 (1%)
Congenital, familial and genetic disorders	1 (1%)	0 (0%)
Ear and labyrinth disorders	1 (1%)	0 (0%)
Eye disorders	3 (2%)	0 (0%)
Gastrointestinal disorders	15 (12%)	1 (1%)
General disorders and administration site conditions	11 (9%)	0 (0%)
Immune system disorders	2 (2%)	0 (0%)
Infections and infestations	76 (59%)	0 (0%)
Injury, poisoning and procedural complications	14 (11%)	0 (0%)
Metabolism and nutrition disorders	2 (2%)	0 (0%)
Musculoskeletal and connective tissue disorders	1 (1%)	0 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1%)	0 (0%)
Nervous system disorders	1 (1%)	0 (0%)
Renal and urinary disorders	1 (1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	8 (6%)	0 (0%)
Skin and subcutaneous tissue disorders	16 (13%)	0 (0%)

Source: Table 14.3.1.13; Table 14.3.1.16.

Abbreviations: AE, adverse event.

Deaths, SAEs and other significant AEs

No death was reported in the study.

Twenty-six (20%) subjects were reported with SAEs and none of them that was considered by the investigator as related to the study vaccine. The most common MedDRA SOC reported for SAEs was 'infections and infestations' in 22 (17%) subjects.

No subject had unsolicited AEs leading to premature withdrawal.

2.3.2. Discussion on clinical aspects

This phase 4 uncontrolled open label study was designed to meet a regulatory requirement surrounding the licensure of Menveo in infants from 2 months of age in South Korean. The study population is not included in the indication of Menveo as licensed in Europe.

In total, 128 infants with a mean age of 71.7 days were enrolled and received Menveo according to a 2,4,6 and 12 months schedule. The primary objective was to describe the persistence of antibodies as measured by hSBA and rSBA one year after completing the vaccination schedule, and to determine the reactogenicity and safety of Menveo in this population.

At one year from schedule completion, percentages of subjects with hSBA titers $\geq$ 8 were 39% against MenA, 61% against MenC, 88% against MenW and 89% against MenY serogroups, respectively. When analyzed using a rSBA, at one year following completion of the vaccination series, the percentages of subjects with titers $\geq$ 8 were 99% against MenA, 54% against Men C, 69% against MenW and 90% against Men Y.

The 4-dose MenACWY infant schedule was well tolerated in the study population. Most of the AEs were mild to moderate in intensity, and resolved within study termination. One subject had an unsolicited AEs possibly/probably related to vaccination.

The MAH concludes that the 4-dose vaccination series with MenACWY was able to induce robust immune responses after completion of the schedule, with good persistence of immunogenicity at 1 year. No new clinical concerns were raised with respect to the safety data available in this study.

Due to the absence of an appropriate control in this study, results need to be interpret cautiously and the conclusion of the MAH is therefore not completely supported as no inference should be made concerning the value of the responses seen.

It can be concluded that the study does not give rise to any concern and has no consequences for the licensing of Menveo in Europe, mostly as the vaccine is not licensed for infants in Europe and as little inference can be made based upon the present study.

3. Rapporteur's overall conclusion and recommendation

The submitted study does not influence the benefit-risk balance of Menveo. No further regulatory action is required.

☒ Fulfilled:

No regulatory action required.