London, 31 January 2019
EMA/906862/2019
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/P46/038.1

Note

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

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1. Introduction

On 27 March 2018, the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

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.

In the parent study V102_02 Menveo was used as a comparator vaccine. In study V102_02E2 the antibody persistence at approximately 48 months after vaccination performed in study V102_02 was evaluated.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the phase 2, open-label, controlled, multi-centre extension study to evaluate 4-year antibody persistence and booster response following MenABCWY vaccination in healthy adolescents and young adults who previously participated in studies V102_02 and V102_02E1 (Protocol V102_02E2) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The MenABCWY+OMV investigational vaccine.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final reports for:

- A phase 2, open-label, controlled, multi-centre extension study to evaluate 4-year antibody persistence and booster response following MenABCWY vaccination in healthy adolescents and young adults who previously participated in studies V102_02 and V102_02E1 (Protocol V102_02E2)

2.3.2. Clinical study

V102_02E2

Description

Study V102_02E2 is an extension study of V102_02 aimed at 1) measuring the antibody persistence approximately 4 years after receiving MenABCWY vaccination or MenACWY and 2) evaluating the

response to against *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains 30 days after a single dose of MenABCWY in previously vaccinated subjects, and in vaccine-naïve subjects of similar age.

Methods

Objectives

Primary objectives

1. To assess antibody persistence against *Neisseria meningitidis* serogroups A, C, W, and Y and serogroup B test strains in subjects who previously received MenABCWY+outer membrane vesicle (OMV) or MenACWY approximately 4 years earlier, as measured by the percentage of subjects with serum bactericidal assay (SBA) using human complement (hSBA) titers ≥ lower limit quantitation (LLQ) and other thresholds, hSBA geometric mean titers (GMTs) and geometric mean ratios (GMRs).

2. To evaluate immune response against *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains 30 days after a single dose of MenABCWY+OMV in previously vaccinated subjects, and in vaccine-naïve subjects of similar age, as measured by the percentage of subjects with hSBA titers ≥ LLQ and other thresholds, hSBA GMTs and GMRs.

Secondary objectives

Secondary objectives included the evaluation of safety and reactogenicity of the MenABCWY vaccine given as 1 or 2 doses in subjects previously vaccinated with MenABCWY+OMV or MenACWY, and in vaccine-naïve subjects; the evaluation of the kinetics of the immune response using different immunogenicity endpoints following a dose of MenABCWY, in subjects who previously received 2 doses of MenABCWY or 1 dose of MenACWY, and following 1 and 2 doses of MenABCWY in vaccine-naïve subjects; and the evaluation of the immunogenicity of 2 doses of MenABCWY+OMV in subjects who previously received 1 dose of MenACWY and vaccine-naïve subjects, using different endpoints.

Assessor's comment:

in the present procedure the focus will be on Menveo. Therefore, results for all the objectives described above will not be evaluated in this report, only when it concerns the response to or persistence after receiving Menveo.

Study design

The study is an open label controlled extension study of parent study V102_02 and extension study V102_02E1. Subjects who received 2 doses of MenABCWY+OMV in the V102_02 parent study were scheduled to receive a single booster dose of MenABCWY+OMV on day 1 only. Other subjects were to receive 2 doses of MenABCWY+OMV on days 1 and 31. The duration of this extension study was approximately 1 month for subjects in ABCWY+OMV group, and approximately 2 months for subjects in the ACWY and Naïve groups. An overview of the vaccinations received in relation to the study groups is provided in the table below.

Table 2-1 Overview of V102_02, V102_02E1, and V102_02E2 Study Groups

Group # V102_02	No. of Enrolled Subjects	Study Vaccine Month 0, Month 2	Group # V102_02E1	No. of Enrolled Subjects	Study Vaccine Month 6	Group # V102_02E2	Study Vaccine
I	80	MenABCWY (no OMV)	Ia	25	MenABCWY (no OMV)		
			Ib	49	Tdap		
II	82	MenAB(x2)CWY	IIa	24	MenAB(x2)CWY		
			IIb	49	Tdap		
III	83	MenABCWY+OMV	IIIa	25	MenABCWY+OMV		
			IIIb	48	Tdap	ABCWY+OMV[4]	MenABCWY+OMV*
IV	82	MenABCWY+1/4OMV	IVa	25	MenABCWY+1/4OMV		
			IVb	49	Tdap		
V	85	rMenB	Va	23	rMenB		
			Vb	50	Tdap		
VI	83	MenACWY; placebo	VI	73	Tdap	ACWY***	MenABCWY+OMV**
						Naïve***	MenABCWY+OMV**

Source: Table 1 from protocol version 2.0 dated 18 Nov 14.
Abbreviations: OMV, outer membrane vesicle; Tdap, tetanus diphtheria and pertussis.
*One dose.
**Two doses separated by 1 month.
***ACWY and Naïve groups to be divided into 2 groups each ACWY1, ACWY2, Naïve1, and Naïve2 based on blood draw schedule.
Subjects in ABCWY+OMV group received 2 doses of MenABCWY+OMV previously, and received 1 dose of MenABCWY+OMV in V102_02E2.
Subjects in ACWY group received 1 dose of MenACWY previously, and received 2 doses of MenABCWY+OMV in V102_02E2.
Subjects in the Naïve group had received no meningococcal vaccines previously, and received 2 doses of MenABCWY+OMV in V102_02E2.

Study population /Sample size

All subjects who met predefined eligibility criteria (i.e. received either MenABCWY or MenACWY in the parent study and who received no other meningococcal vaccines and gave informed consent) were to be asked to participate in the extension study. Additionally, a proportional number of vaccine-naïve subjects aged 15 through 23 years were to be recruited at each site.

Assessor's comments

Subjects in the Naïve group had received no meningococcal vaccines previously, and received 2 doses of MenABCWY+OMV in V102_02E2.The MAH should confirm that 'vaccine naïve subjects' did indeed not receive any meningococcal vaccines, including monovalent MenC vaccines.

Treatments

Subjects received either a single or two doses of MenABCWY investigational vaccine.

Outcomes/endpoints

Primary immunogenicity endpoints

- hSBA GMTs against *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains.
- Percentages of subjects with hSBA titres ≥ 8 against *N meningitidis* serogroups A, C, W, and Y.
- Percentages of subjects with hSBA titres ≥ 5 against serogroup B test strains.
- Percentages of subjects with hSBA titres ≥ LLQ against *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains.
- Between group GMRs comparing GMTs against *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains.

- Within group GMRs comparing baseline GMTs to GMTs at later time points *against N meningitidis* serogroups A, C, W, and Y and serogroup B test strains.

The high throughput hSBA (HT-hSBA) is an automated version of the SBA, and was to be used in this study to measure immunogenicity to N meningitidis serogroups A, C, W, Y, and serogroup B test strains. All assays were to be performed in GlaxoSmithKline Biologicals, in a blinded manner towards the treatment arm and the visit and subject.

Secondary safety endpoints:

Safety of the study vaccine was to be assessed in all subjects in terms of the frequency and percentage of reported AEs including:

- Any unsolicited and solicited AEs reported within 30 minutes after vaccination;
- Solicited local (ie, pain, erythema and induration) and systemic (ie, chills, loss of appetite, headache, fatigue, myalgia, arthralgia, nausea, fever (body temperature $\geq 38^{\circ}$ C [100.4° F]) AEs reported from day 1 (6 hours) through day 7 after each vaccination;
- All unsolicited AEs reported during the entire study period;
- Medically attended AEs reported during the entire study period;
- AEs leading to premature withdrawal from the study during the entire study period;
- SAEs reported during the entire study period.

Statistical Methods

There were no statistical hypotheses associated with the primary objectives. All analyses were to be run descriptively. The sample size was estimated based on the number of subjects from the parent study V102_02 and the previous extension study V102_02E1 who could be available for this extension study.

For immunogenicity endpoints based on unadjusted GMTs, the estimates were to be provided along with the associated 95% confidence intervals (CIs) obtained by exponentiating (base 10) the unadjusted means and the lower and upper limits of the 95% CIs of the log transformed titers (base 10), for each study group and *N meningitidis* serogroups A, C, W, and Y and serogroup B test strains on days 1, 31, and 61.

The percentages of subjects with hSBA titer $\geq$ LLQ and associated 2-sided 95% CIs were to be computed for each study group and N meningitidis serogroups A, C, W, and Y and serogroup B test strains on days 1, 31, and 61. The analysis was to be repeated for percentages of subjects with hSBA titer ≥ 8 against serogroups A, C, W, and Y and ≥ 5 against serogroup B test strains. No statistical criteria were established to assess adequacy of the antibody persistence.

Analyses related to the secondary objectives were to be descriptive; no statistical tests were to be performed.

Safety analyses were to be performed on the appropriate safety sets.

Results

Recruitment/ Number analysed

In the parent study V120_02, a total of 495 subjects were enrolled, 83 of which were randomized to Group VI (MenACWY/Placebo). In the first extension study, V120_02E1, a total of 440 subjects were enrolled. In Group VI (1 dose of MenACWY), 73 subjects were enrolled and received study vaccination and 72 subjects completed the extension study following the protocol.

A total of 129 subjects were enrolled – 46 in the MenACWY group. All of the enrolled subjects received at least one dose of the study vaccine and completed the study. The first subject was enrolled on 30 June 2015, the last subject completed the study on 10 December 2015.

Centres were located in Colombia, Panama and Chile.

Assessor's comments

There is a decline in the number of subjects with each extension study – from 495 in the parent study to 129 in this second extension study; for the MenACWY group from 83 in V120_02, 73 in V120_02E1 to 46 in this study. *The MAH is requested to demonstrate that there is no inadvertent selection in subjects included in the extension study, i.e. that the response to MenACWY vaccination as measured in the parent study was comparable between the 46 subjects included in V102_02E2 and the 37 subjects NOT included in study V102_02E2 – considering both immunogenicity endpoints as reactogenicity endpoints.*

Baseline data

The mean age of the subjects was 18.4 ± 2.04 years. There were lesser number of males than females in MenABCWY+OMV (33% males vs 67% females) and MenACWY (41% males vs 59% females) groups. All of the subjects, except for one subject in the ABCWY+OMV group, were of the Hispanic or Latino ethnic origin.

Efficacy results

4-year Persistence for Serogroups A, C, W, and Y

At 4 years after the last vaccination in study V102_02 the persistence of immunity in subjects who previously received MenACWY was:

- **hSBA ≥ 8** were 41% against serogroup A, 43% against serogroup C, 78% against serogroup W, and 59% against serogroup Y.
- **hSBA GMTs** were numerically higher than those in the Naïve group against all serogroups: A (6.64 vs 1.20), C (6.62 vs 5.11), W (25 vs 8.37), and Y (12 vs 2).

Table 11.4.1-1a Number (%) of Subjects With hSBA ≥ 8 Against Serogroups A, C, W, and Y and Vaccine Group Differences at Day 1 – FAS Persistence

Serogroup	Number (%) of Subjects (95% CI)			Vaccine Group Differences (95% CI)		
	ABCWY+OMV	ACWY	Naïve	ABCWY+OMV minus Naïve	ABCWY+OMV minus ACWY	ACWY minus Naïve
	N = 33	N = 46	N = 50			
A	9 (27%) (13.3%-45.5%)	19 (41%) (27%-56.8%)	1 (2%) (0.05%-10.6%)	25% (11.5%-42.6%)	-14% (-33.7%-7.6%)	39% (25%-54.1%)
C	22 (69%) (50%-83.9%) n = 32	20 (43%) (28.9%-58.9%)	22 (45%) (30.7%-59.8%) n = 49	24% (1.5%-43.4%)	25% (2.7%-45.1%)	-1% (-21%-18.4%)
W	24 (75%) (56.6%-88.5%) n = 32	36 (78%) (63.6%-89.1%)	25 (53%) (38.1%-67.9%) n = 47	22% (-0.14%-41%)	-3% (-23.4%-15.4%)	25% (5.8%-42.7%)
Y	12 (38%) (21.1%-56.3%) n = 32	26 (59%) (43.2%-73.7%) n = 44	9 (19%) (9.1%-33.3%) n = 47	18% (-1.6%-38.4%)	-22% (-42.2%-1.3%)	40% (20.3%-56.7%)

Source: Table 14.2.1.1.12.

Abbreviations: CI, confidence interval; FAS, full analysis set; hSBA, human serum bactericidal assay.

Subjects in ABCWY+OMV group received 2 doses of MenABCWY+OMV previously, and received 1 dose of ABCWY+OMV in V102_02E2.

Subjects in ACWY group received 1 dose of MenACWY previously, and received 2 doses of MenABCWY+OMV in V102_02E2.

Subjects in the Naïve group had received no meningococcal vaccines previously, and received 2 doses of MenABCWY+OMV in V102_02E2.

Table 11.4.1-1b Geometric Mean hSBA Titers (95% CI) and Vaccine Group Ratios by Serogroups A, C, W, and Y at Day 1 - FAS Persistence

Serogroup	GMTs (95% CI)			Vaccine Group Ratios (95% CI)		
	ABCWY+OMV	ACWY	Naïve	ABCWY+ OMV vs Naïve	ABCWY+ OMV vs ACWY	ACWY vs Naïve
	N = 33	N = 46	N = 50			
A	4.06 (2.22-7.44)	6.64 (3.56-12)	1.20 (1.05-1.37)	3.38 (1.70-6.73)	0.61 (0.30-1.23)	5.53 (2.96-10)
C	17 (7.80-37) n = 32	6.62 (4.10-11)	5.11 (3.49-7.48) n = 49	3.34 (1.57-7.11)	2.58 (1.20-5.54)	1.30 (0.66-2.56)
W	28 (15-53) n = 32	25 (15-40)	8.37 (4.78-15) n = 47	3.35 (1.49-7.57)	1.14 (0.51-2.59)	2.93 (1.40-6.12)
Y	6.17 (3-13) n = 32	12 (6.29-22) n = 44	2 (1.40-2.85) n = 47	3.09 (1.38-6.92)	0.52 (0.23-1.18)	5.94 (2.84-12)

Assessor's comments

The table below is taken from appendix 16.1.9.5.6 of the final study report of V102_02E1, showing the % subjects with hSBA>1:8 at 0,1,3,6,7 and 12 months after vaccination in the 1ACWY arm.

	Serogroup			
Month	MenA	MenC	MenW	MenY
0	4%	31%	67%	38%
	1%-12%	20%-43%	55%-78%	27%-50%
1	87%	82%	97%	100%
	77%-94%	71%-90%	90%-100%	95%-100%
3	71%	85%	97%	100%
	59%-81%	74%-92%	90%-100%	95%-100%
6	55%	76%	97%	85%
	43%-67%	64%-85%	90%-100%	74%-92%
7	58%	68%	96%	85%
	45%-69%	56%-79%	88%-99%	74%-92%
12	55%	60%	90%	80%
	43%-67%	47%-71%	80%-96%	69%-89%

Four years after vaccination, 41%, 43%, 78% and 59% respectively had hSBA >1:8 against Men A,C,W and Y – the decline in % subjects with hSBA>1:8 continued between M12 and M48.

In comparison with vaccine naïve subjects, it can be concluded that there is persistence of vaccine induced immunity against MenA, W and Y, as rates with hSBA>1:8 and GMTs are significantly higher compared to the vaccine naïve group. Whilst 43% of subjects still had hSBA >1:8 against MenC 4 years after vaccination, the rate is similar as for those subjects who were not vaccinated. Also subjects who received MenACWY in the parent study V120_02 appear to have similar GMTs for MenC as compared to those who are vaccine naïve. Of course this could be a result of natural circulation of MenC however this would indicate that the persistence of vaccine induced immunity following Menveo for MenC is minimal to non-existent after 4 years, which is not in line with the information currently included in the SmPC. The MAH is requested to comment.

Safety results

There are no new safety results for Menveo, as Menveo was not given in this study.

2.3.3. Discussion on clinical aspects

This report contains the clinical study report of V102_02E2. This study was conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitides* serogroups (A, B, C, W and Y). Menveo was only given as a comparator vaccine in one control arm in the parent study V102_02.

V102_02E2 was an open-label, extension study conducted to evaluate 4-year antibody persistence and booster response following MenABCWY vaccination in healthy adolescents and young adults who previously participated in studies V102_02 and V102_02E1 and had received either 2 doses of MenABCWY+OMV vaccine or 1 dose of ACWY Vaccine. The study also enrolled vaccine naïve subjects who had not previously received any meningococcal vaccine. In response to RSI, the MAH clarified that these vaccine naïve subjects did indeed not receive any meningococcal vaccines including monovalent MenC vaccine.

For the present P46 AR, only the measurement of persistence of antibodies 4 years after vaccination is directly relevant to Menveo. Menveo was not administered in the extension study.

A total of 129 subjects were enrolled – 46 in the MenACWY group; in the parent study V120_02 83 subjects were included in the MenACWY group, in V120_02E1, 73 subjects were enrolled in the MenACWY group. This is a marked decline; the MAH was requested to demonstrate that there is no inadvertent selection in subjects included in the extension study, i.e. that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2 – considering both immunogenicity endpoints as reactogenicity endpoints in V120_02. The MAH in their response provided evidence to suggest that the response as measured in the parent studies in those subjects included in V102_02E2 is similar to the response of ALL subjects included in the parent study considering the immunogenicity. In a further post-hoc analysis, the MAH showed that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 was similar to the response in those NOT included in study V102_02E2 considering both immunogenicity endpoints as reactogenicity endpoints**.**

Four years after vaccination, 41%, 43%, 78% and 59% of subjects who received Menveo in the parent study V120_02 had hSBA >1:8 against Men A,C,W and Y respectively. When compared to the vaccine naïve group, which included age matched subjects who had received no meningococcal vaccines previously – 'vaccine naïve subjects', the rates of subjects with hSBA>1:8 and GMTs are significantly higher in those who received Menveo in V120_02 for Men A, W and Y suggesting persistence of vaccine-induced immunity.

For MenC however, the rates of subjects with hSBA>1:8 are similar compared to the vaccine naïve group. Whilst 43% of subjects still had hSBA >1:8 against MenC 4 years after vaccination, the rate is similar as for those subjects who were not vaccinated; GMTs are also similar. This could be a result of natural circulation of MenC however this would indicate that the persistence of immunity following Menveo for MenC is minimal after 4 years, which is not in line with the information currently included in the SmPC. As results are based on small numbers and the study was not designed nor powered to detect differences between Menveo-primed and vaccine naïve individuals it is possible that differences result from chance therefore no update to the SmPC is needed.

3. Rapporteur's overall conclusion and recommendation

As study V120_02E2 focused on the evaluation of an experimental MenABCWY vaccine, and subjects only received Menveo in a control group in parent study V120_02, there is only few new data for Menveo contained in this study.

An update of the SmPC is not considered necessary.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is requested to demonstrate that there is no inadvertent selection in subjects included in the extension study, i.e. that the response to vaccination as measured in the parent

study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2 – considering both immunogenicity endpoints as reactogenicity endpoints in V120_02.

2. The MAH should confirm that 'vaccine naïve subjects' enrolled in study V102_02E2 did indeed not receive any meningococcal vaccines, including monovalent MenC vaccines.

3. Whilst 43% of subjects still had hSBA >1:8 against MenC 4 years after vaccination in study V102_02E2, the rate is similar as for those subjects who were not vaccinated ('vaccine naïve subjects'); GMTs are also similar. This could be a result of natural circulation of MenC however this would indicate that the persistence of immunity following Menveo for MenC is minimal after 4 years, which is not in line with the information currently included in the SmPC. This should be adequately discussed by the MAH.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

1. The MAH is requested to demonstrate that there is no inadvertent selection in subjects included in the extension study, i.e. that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2 – considering both immunogenicity endpoints as reactogenicity endpoints in V120_01.

Response MAH

The Company acknowledges the Rapporteur request and would like to clarify the following:

V102_02E2 study was a phase 2, open-label, controlled, multi-center extension study to evaluate approximately 4-year antibody persistence of 2 MenABCWY+OMV doses or one Menveo dose and MenABCWY+OMV boostability in healthy adolescents and young adults who previously participated in studies V102_02 and V102_02E1.

Participation to V102_02E2 study for follow-on subjects was solely based on fulfilment of all inclusion criteria and no exclusion criteria and subjects' willingness and consent to participate to this second extension study. Participation to V102_02E2 study was not based on immune responses or reactogenicity/safety outcomes observed in the parent study or in its extension 1.

This is generally accepted as an appropriate method to avoid selection bias and it was deemed accurate to enable that the subset of subjects included in study V102_02E2 was representative of the whole sample.

The available data that helps descriptively comparing V102_02 and its extension 2 populations enrolled in the Menveo arm is provided in the table below. Table 1 in fact shows V102_02 immune responses after a single dose of Menveo in two populations:

- all subjects enrolled in the V102_02 Menveo arm (Group A);
- the subset of subjects enrolled in the V102_02 Menveo arm that also subsequently participated to V102_02E2 study (Group B).

Immune responses one month after one Menveo dose are similar in the overall group of subjects enrolled in the parent study (Group A) and in those subsequently enrolled in the extension study (Group B), with 95% CIs overlapping for any of the *Neisseria meningitidis* serogroups, indicating that

the subset of subjects enrolled in V102_02E2 are representative of the overall enrolled subjects in the parent study.

Table 1: V102_02 immunogenicity results: Percentages of subjects with hSBA titers ≥8 and hSBA GMTs, by group

Serogroup	Time Point	% subjects with titers ≥8		hSBA GMTs	
		Group A All subjects enrolled in the Menveo arm	Group B Subset of subjects enrolled also in V102_02E2	Group A All subjects enrolled in the Menveo arm	Group B Subset of subjects enrolled also in V102_02E2
A	Baseline	5% (1%-12%) N=82	7% (1.4%-17.9%) N=46	1.4 (1.18-1.67) N=82	1.47 (1.11-1.94) N=46
	1 month after 1 dose	88% (79% -95%) N=78	91% (78.8% -97.5%) N=45	105 (68-160) N=78	128 (68-240) N=45
C	Baseline	32% (22%-43%) N=81	28% (16%-43.5%) N=46	4.04 (3.05-5.35) N=81	3.30 (2.32-4.69) N=46
	1 month after 1 dose	84% (74%-91%) N=79	80% (65.4%-90.4%) N=45	59 (42-84) N=79	45 (23-85) N=45
W	Baseline	68% (57%-78%) N=82	63% (47.5%-76.8%) N=46	19 (13-29) N=82	14 (7.79-25) N=46
	1 month after 1 dose	98% (91%-100%) N=80	100% (92.1%-100%) N=45	188 (142-248) N=80	244 (174-342) N=45
Y	Baseline	40% (30%-52%) N=82	32% (18.6%-47.6%) N=44	5.76 (4.54-7.31) N=82	4.29 (3.03-6.09) N=44
	1 month after 1 dose	100% (96%-100%) N=81	100% (92%-100%) N=44	77 (57-104) N=81	89 (62-128) N=44

Assessment Response

The MAH was requested to demonstrate that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2.

Rather the MAH provided evidence that the response of subjects included in V102_02E2 is not significantly different to the response of all subjects in the V102_02 Menveo arm. This provides some reassurance however is not what was asked for. As the issue as to why the observations regarding the (pattern of) persistence of antibodies against the MenC component in this study is not in line with earlier observations has not been clarified (see also Q2) the MAH is requested to provide the requested data. The question remains open.

Conclusion

Issue not solved.

2. The rates of subjects who received MenACWY in parent study V120_02 with hSBA>1:8 against MenC approximately four years after vaccination are similar compared to the vaccine naïve group; 43% (95%CI: 28.9%-58.9%) compared to 45% (95% CI: 30.7%-59.8%). GMTs are also similar. This would indicate that the persistence of vaccine induced immunity following Menveo for MenC is minimal after 4 years, which is not in line with the information currently included in the SmPC. The MAH is requested to comment and discuss whether the information in the SmPC should be updated, in particular the warning in section 4.4 regarding the persistence for MenA.

Response MAH

The Company acknowledges the Rapporteur's request and would like to clarify that evidence coming from V102_02E2 study is not proposed to modify current Menveo SmPC considering the following factors:

- V102_02E2 study was a purely descriptive phase 2 study, with a small sample size, aimed to assess persistence and boostability of the MenABCWY+OMV investigational vaccine. The number of subjects enrolled in the Menveo group is low (N=46), and as such, any results should be interpreted with caution. Indeed, the Menveo group was only intended to serve as a control for descriptive comparisons of persistence and boostability with the MenABCWY+OMV vaccine;
- The assay used for antibody titer estimation in the V102 studies is a highthroughput hSBA (HT-hSBA). This assay is different than the one used for studies in the Menveo clinical development (manual hSBA), and from which the Menveo SmpC is based. The HT-hSBA is only used for phase 2 assessments for the investigational MenABCWY+OMV vaccine;
- In the Updated Assessment Report dated 23 Feb 2017 for study V102_03E1 (EMEA/H/C/001095/P46/034), for trends of apparent lower antibody persistence for serogroups W and Y in the Menveo group compared with previously generated persistence data for Menveo, the Authority concurred that results obtained using different assays, which have different sensitivity aspects, cannot be directly compared;
- Furthermore, in a study recently conducted in the US (V59_77, 2016-2017) assessing persistence of bactericidal antibody titers 4-6 years after administration of either Menveo or Menactra and response to a booster dose of Menveo, the manual hSBA was used for titer estimation. Seroprotection rates against MenC was 61.82% (95% CI: 56.02%-67.38%) among subjects primed with Menveo 4-6 years previously, compared with 35.42% (95% CI: 25.92%-45.84%) in vaccinenaïve control subjects. These data are in line with previously generated persistence data

after Menveo priming (reference is made to the Art.46 clinical expert statement for V59_77 submitted to EMA on August 11, 2018.

- Based on all the above mentioned considerations, the Company does not foresee an update of current Menveo SmPC.

Assessment Response

In their response the MAH points to 1) the limited size of the study therefore limited power and ability to make any inferences; 2) the difference in assay preventing direct comparisons with other studies – a point which has earlier been accepted by CHMP and 3) that the observations are not in line with other studies, specifically referring to study V59_77.

It is not agreed with the company that because of these reasons the observation that the persistence in the MenC arm is similar as compared to the age matched, vaccine-naïve enrolled control subjects, can be disregarded. Whilst the small numbers in this study, all persistence data in the SmPC is based upon small numbers.

Nonetheless, this is always kept in mind during assessments – e.g. the observation can be due to chance and is in fact not a (lack of) effect of the vaccine. First however other causes have to be dismissed. Subject selection and use of other MenC vaccines are two that have been provided by the assessor- there may be others the MAH can think of.

Regarding the difference in assays, it is acknowledged that a direct comparison between titres generated in one study to titres generated in a different study should be avoided in particular if the assays were different. However the issue here is different – it is the observations that after 4 years titres were comparable to those in a age matched vaccine-naïve group that is of concern. This has not been seen in other studies for the MenC component, as correctly pointed out by the MAH, nor is this risk included in the labelling.

The latter – inclusion in the labelling - will only be done if it is considered that the risk is vaccine related, and this remains unclear. This should be adequately discussed by the MAH.

Conclusion

Issue not solved. Whether or not inclusion in the labelling is deemed necessary will depend on whether the risk is vaccine related which depends on the answers to the two remaining questions.

3. In addition, the MAH should confirm that 'vaccine naïve subjects' did indeed not receive any meningococcal vaccines, including monovalent MenC vaccines.

Response MAH

For study V102_02E2, subjects eligible to be enrolled in the Menveo arm were those who received MenACWY vaccine in the parent study V102_02 and received no subsequent meningococcal vaccines. Indeed, history of any meningococcal vaccine administration other than vaccination given in the parent V102_02 study was an exclusion criterion.

Furthermore, all 46 subjects enrolled in the Menveo arm in the study met the predefined eligibility criteria (Table 14.1.1.3.1 of V102_02E2 CSR).

Assessment Response

The MAH did not clarify whether the enrolled, age-matched, vaccine naïve subjects received a Meningococcal C vaccine or an other meningococcal vaccine – which might explain the similar levels of hSBA compared to subjects who received Menveo 4 years previous. The MAH is requested to confirm that 'vaccine naïve subjects' did indeed not receive any meningococcal vaccines, including monovalent MenC vaccines.

Conclusion

Issue not solved.

5. Additional clarification requested

1. The MAH is requested to demonstrate that there is no inadvertent selection in subjects included in the extension study, i.e. that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2 – considering both immunogenicity endpoints as reactogenicity endpoints in V120_02.

Response MAH

GSK would like to underline that study V102_02E2 was a purely descriptive study not powered nor designed to formally assess any group difference. GSK provided the investigators of study V102_02E2 with a complete list of all subjects who completed the previous studies (parent study V102_02 and its first extension study V102_02E1) and who were eligible for screening. Subjects were eligible to be enrolled into the Menveo group in the V102_02E2 extension trial if they:

- received a single dose of Menveo followed by a dose of placebo in parent study V102_02, with the last study vaccine (placebo) in parent study V102_02 given approximately 48 to 56 months before study V102_02E2
- received Tdap vaccine only in study V102_02E1 (the first extension to study V102_02)
- received no other meningococcal vaccines prior to enrolment in study V102_02E2.

There were no other criteria (eg, immunogenicity and/or safety results in previous trials) employed to select participants in this trial. This is generally accepted as an appropriate method to avoid selection bias in vaccine clinical trials and it was deemed sufficient to ensure that the subset of subjects included in study V102_02E2 was representative of the whole sample.

Post-hoc analysis

To further explore whether subjects who participated in study V102_02 and were enrolled in study V102_02E2 differed in terms of vaccine responses from those who enrolled in the parent trial but not in the second extension study, GSK analysed immunogenicity and safety endpoints in both groups of subjects, as requested by the Agency. The results of these post-hoc analyses are provided with the submission and a summary of the results is presented below.

Immunogenicity

Human serum bactericidal assay (hSBA) geometric mean titers (GMTs) and percentages of subjects with hSBA titers ≥ 8 against Neisseria meningitidis serogroups A, C, W, and Y at baseline and at 1

month after vaccination in study V102_02, both for subjects who subsequently participated in study V102_02E2 and for those who did not, are presented in Table 1.

Point estimates for GMTs and the percentages of subjects with hSBA titers ≥ 8 at 1 month after vaccination in study V102_02 were lower for serogroup C in the group that enrolled in study V102_02E2, whereas for serogroups A, W, and Y they were generally higher in the group that enrolled in study V102_02E2. In all cases, however, confidence intervals (CIs) were wide and largely overlapping.

Table 1 V102_02 immunogenicity results: Percentages of subjects (95% CI) with hSBA titers ≥ 8 and hSBA GMTs (95% CI), by group (enrolled/not enrolled in study V102_02E2)

		GMT (95% CI)		Percentage of subjects (95% CI) with hSBA titers ≥ 8	
Serogroup	**Time Point**	**Subjects enrolled in V102_02E2**	**Subjects not enrolled in V102_02E2**	**Subjects enrolled in V102_02E2**	**Subjects not enrolled in V102_02E2**
A	Baseline	1.49 (1.09-2.05) N=46	1.28 (0.90-1.82) N=37	7% (1%-18%) N=46	3% (0%-14%) N=37
	1 month after 1 dose	137 (68-276) N=45	66 (30-147) N=35	91% (79%-98%) N=45	83% (66%-93%) N=35
C	Baseline	3.73 (2.52-5.52) N=46	4.73 (3.06-7.33) N=36	28% (16%-43%) N=46	39% (23%-57%) N=36
	1 month after 1 dose	55 (31-96) N=45	75 (39-142) N=36	80% (65%-90%) N=45	89% (74%-97%) N=36
W	Baseline	15 (8.19-28) N=46	25 (13-48) N=37	63% (48%-77%) N=46	76% (59%-88%) N=37
	1 month after 1 dose	261 (171-400) N=45	154 (96-246) N=37	100% (92%-100%) N=45	95% (82%-99%) N=37
Y	Baseline	5.13 (3.55-7.40) N=46	7.48 (4.98-11) N=37	33% (20%-48%) N=46	51% (34%-68%) N=37
	1 month after 1 dose	95 (65-139) N=46	85 (55-129) N=37	100% (92%-100%) N=46	100% (91%-100%) N=37

Source: V102_02 *Post-hoc* analysis Table 1 and Table 2.
hSBA = human Serum Bactericidal Assay
CI = confidence interval

Safety

Solicited adverse events

In study V102_02, solicited adverse events (AEs) were reported by 72% of subjects who enrolled in extension study V102_02E2 and by 64% of subjects who did not enrol in the extension study (Table 2). Overall in V102_02 study, 67% and 59% of subjects subsequently enrolled in the second extension study reported local and systemic solicited AEs, respectively. For subjects not enrolled in V102_02E2, local and systemic solicited AEs were both reported by 50% of subjects.

The most frequently reported local solicited AEs were pain (59%) and induration (30%) in subjects enrolled in study V102_02E2, and pain (39%) and erythema (25%) in subject not enrolled in study V102_02E2 (V102_02 Post-hoc analysis Table 5).

The most frequently reported solicited systemic AEs were headache and myalgia in both groups of subjects (41% and 42% of subjects enrolled in V102_02E2; 42% and 33% of subject not enrolled in V102_02E2).

Results for all solicited local and systemic AEs by event are provided in V102_02 Post-hoc analysis Table 5 and Table 6, respectively.

Table 2 Number (%) of subjects with at least one solicited adverse event reported between day 1 and day 7 after vaccination in study V102_02, by group (enrolled/not enrolled in study V102_02E2)

	Number (%) of subjects	
	Subjects enrolled in V102_02E2	**Subjects not enrolled in V102_02E2**
Adverse event	**N=46**	**N=36**
Any	33 (72%)	23 (64%)
Local	31 (67%)	18 (50%)
Systemic	27 (59%)	18 (50%)
Other[a]	7 (15%)	3 (8%)

Source: V102_02 *Post-hoc* analysis Table 4.

[a] Other = medication to prevent fever, medication to treat fever, medically attended fever, body temperature, stayed home due to reactions. Please note that medication to treat fever and medically attended fever are not reported in V102_02 *Post-hoc* analysis Table 6, since no subjects in the MenACWY group of parent study V102_02 reported these events within 7 days from MenACWY vaccination.

Unsolicited adverse events

The results of the post-hoc analysis of V102_02 data show that 35% of subjects who enrolled in extension study V102_02E2 and 39% of subjects not enrolled in study V102_02E2 reported any unsolicited AE (Table 3). At least possibly related unsolicited AEs were reported by 11% of subjects who enrolled in V102_02E2 and by 19% of subjects not enrolled in V102_02E2.

The most frequently reported at least possibly related unsolicited AEs were induration (9%) and myalgia (4%) in subject enrolled in V102_02E2, and headache (6%) in subjects not enrolled in V102_02E2 (V102_02 Post-hoc analysis Table 8). Results for all unsolicited AEs by event are provided in V102_02 Post-hoc analysis Table 7 (all AEs) and Table 8 (possibly or probably related AEs). No serious adverse events were reported by any subject in the Menveo group of the parent study V102_02.

Table 3 **Number (%) of subjects with at least one unsolicited adverse event after vaccination in study V102_02, by group (enrolled/not enrolled in study V102_02E2)**

	Number (%) of subjects	
	Subjects enrolled in V102_02E2	**Subjects not enrolled in V102_02E2**
Adverse event	**N=46**	**N=36**
Any AE	16 (35%)	14 (39%)
Possibly or probably related AE	5 (11%)	7 (19%)

Source: V102_02 *Post-hoc* analysis Table 7 and Table 8.
AE=adverse event

Conclusions from the post-hoc analysis

When looking at the point estimates, the results of the post-hoc analysis show small differences in the immune response and reactogenicity between subjects who enrolled and those who did not enrol into study V102_02E2. These results of the post-hoc analysis, however, should be interpreted with caution considering that:

- for GMTs and percentages of subjects with hSBA titers ≥ 8 at 1 month after vaccination in study V102_02 the CIs were wide and largely overlapping between the 2 groups of subjects;
- the numbers of subjects included in both groups were relatively low;
- there were no statistical criteria for formal comparison between the 2 groups of subjects.

Any potential difference in terms of immune response or reactogenicity between subjects enrolled in the extension study and subjects not enrolled in the extension study is therefore likely to be due to chance.

Assessment Response

The MAH was requested to demonstrate that the response to vaccination as measured in the parent study in those subjects included in V102_02E2 is similar to the response in those NOT included in study V102_02E2. With their post hoc analysis the MAH has done so.

Whilst there is some variation in vaccine response (immunogenicity) between those who did and did not continue in study V102_02E2, these differences do not all point in the same direction for the different serotypes. And indeed as the MAH states, numbers are small and CIs are wide. Therefore it is likely that these differences are due to chance. Further, the safety in the two groups (subjects included in V102_02E2 vs subjects *not* included in V102_02E2) is similar.

So it is agreed with the MAH that inadvertent selection of subjects has not taken place.

Conclusion

Issue solved.

2. The MAH should confirm that 'vaccine naïve subjects' enrolled in study V102_02E2 did indeed not receive any meningococcal vaccines, including monovalent MenC vaccines.

GSK confirms that vaccine-naïve subjects enrolled in study V102_02E2 did not receive any meningococcal vaccines, including monovalent MenC vaccines, prior to or during study V102_02E2 (except for study vaccine).

Assessment Response

The MAH provided the requested clarification.

Conclusion

Issue solved.

3. Whilst 43% of subjects still had hSBA >1:8 against MenC 4 years after vaccination in study V102_02E2, the rate is similar as for those subjects who were not vaccinated ('vaccine naïve subjects'); GMTs are also similar. This could be a result of natural circulation of MenC however this would indicate that the persistence of immunity following Menveo for MenC is minimal after 4 years, which is not in line with the information currently included in the SmPC. This should be adequately discussed by the MAH.

Response MAH:

Phase 2 study V102_02E2 was designed to evaluate responses to the investigational pentavalent MenABCWY+OMV vaccine. Subjects in the Menveo arm in V102_02E2 study served as a control for descriptive purposes. The study was not designed, nor powered, to determine any statistical or clinical differences between Menveo-primed and vaccine-naïve subjects, and results from study V102_02E2 can't be extrapolated to a wider population.

Enrolment of subjects in the Naïve group in study V102_02E2 with higher baseline hSBA titers due to natural circulation of serogroup C might have occurred, and could potentially account for the relatively small differences between primed and vaccine-naïve subjects seen in this study. These potential differences, however, are most likely due to chance.

As part of the Menveo clinical development plan, GSK recently conducted a study in the United States (study V59_77) to assess the immunogenicity and safety of one dose of Menveo administered to subjects primed with either Menveo or Menactra (Sanofi Pasteur's quadrivalent meningococcal serogroups A, C, W, and Y vaccine) and to vaccinenaïve subjects. Antibody titers against serogroups A, C, W, and Y at 4-6 years after primary vaccination with either Menveo or Menactra was assessed at day 1 (prevaccination) of this study in a much larger group of subjects (N=296), compared to study V102_02E2. The hSBA GMTs and percentages of subjects with hSBA titers ≥ 8 in both study groups at day 1 (pre-vaccination) in study V59_77 are presented in xxx

The results from V59_77 show higher hSBA GMTs and percentages of subjects with hSBA ≥ 8 in the MenACWY-primed groups, irrespective of the quadrivalent vaccine received 4 to 6 years before, compared to the vaccine-naïve subjects. Percentages of subjects with hSBA titers ≥ 8 were higher for Menveo-primed subjects (61.82%) than in vaccine-naïve subjects (35.42%), with non-overlapping CIs. The same was observed for hSBA GMTs (15.99 and 5.24 in Menveo-primed and vaccine-naïve subjects, respectively). The results from study V59_77 are in line with the persistence data already reported in the Menveo SmPC.

Table 4 V59_77 immunogenicity results: hSBA GMTs (95% CI) and percentages of subjects (95% CI) with hSBA titers ≥ 8 at day 1 (pre-vaccination)[a]

		Menveo-primed subjects	Menactra-primed subjects	Vaccine-naïve subjects
Serogroup	Variable	N=296	N=289	N=96
C	GMT (95%CI)	15.99 (13.23-19.31)	10.63 (8.78-12.87)	5.24 (3.76 7.30)
	Percentage of subjects (95% CI) with hSBA titer ≥ 8	61.82% (56.02%-67.38%)	53.63% (47.70%-59.49%)	35.42% (25.92%- 45.84%)

[a] Pre-vaccination = before vaccination in study V59_77, 4-6 years after prior MenACWY vaccination according to field practice.

Given (1) the limitations of the results from study V102_02E2 described above, (2) the very low number of subjects in study V102_02E2, and (3) the fact that the data in the SmPC, as well as in study V59_77, were generated using a different assay (manual hSBA) compared to study V102_02E2 (HT-hSBA), GSK does not foresee an update of the SmPC with the data coming from the phase 2 MenABCWY+OMV study V102_02E2.

Assessment Response

Even though the study was not designed to evaluate differences to determine any statistical or clinical differences between Menveo-primed and vaccine-naïve subjects, the differences observed were striking and form a potential signal that needs to be carefully scrutinized. In their initial analysis the MAH failed to adequately discuss all potential explanations for the observed differences.

Two potential reasons which had not been adequately dismissed were: receipt of prior monovalent MenC vaccine in the 'vaccine naïve group' and inadvertent selection of subjects into the extension cohort. The MAH now confirmed that indeed the vaccine naïve group had not received monovalent MenC vaccine prior to enrolment. Further, their post hoc analysis shows that albeit there is some variation in vaccine response between those who did and did not continue in study V102_02E2, these differences do not all point in the same direction for the different serotypes and therefore it is likely that these are due to chance. So it is agreed with the MAH that selection of subjects will unlikely have resulted in differences observed between Menveo-primed and vaccine-naïve subjects.

The MAH suggests that enrolment of subjects in the naïve group in study V102_02E2 with higher baseline hSBA titers due to natural circulation of serogroup C might have occurred, and could potentially account for differences between primed and vaccine-naïve subjects seen in this study. Additionally the MAH considers the differences small and considers that these would be due to chance.

After determining that the observed difference between the Menveo-primed and vaccine-naïve subjects can not be a result of subject selection into study V102_02E2 nor can it be explained by priming of vaccine naïve individuals with MenC vaccine it is agreed with the applicant that it is likely the differences are indeed due to chance.

Conclusion

Issue solved. As results are based on small numbers and the study was not designed nor powered to detect differences between Menveo-primed and vaccine naïve individuals it is possible that differences result from chance therefore no update to the SmPC is needed.