1 April 2016
EMA/215325/2016
Procedure Management and Committees Support 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/P46/033

Note

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

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1. Introduction

On 16 September 2015, 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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A phase 2, Randomized, Controlled, Observer-Blind, Multi-Center study assessing the safety and immunogenicity of one dose of Novartis' Meningococcal ACWY-CRM vaccine and GlaxoSmithKline Biologicals' Meningococcal ACWY-TT vaccine in healthy toddlers V59_67 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

In study V59_67 two vaccines are evaluated, MenACWY-CRM vaccine (Menveo, Novartis Vaccines and Diagnostics) and MenACWY-TT vaccine (Nimenrix, GlaxoSmithKline). The pharmaceutical formulation is powder and solution for solution for injection (powder and solution for injection) and powder and solvent for solution for injection respectively.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study V59_67; A Phase 2, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Safety and Immunogenicity of One Dose of Novartis' Meningococcal ACWY-CRM Vaccine and GlaxoSmithKline Biologicals' Meningococcal ACWY-TT Vaccine in Healthy Toddlers

2.3.2. Clinical study

Clinical study number and title

Study V59_67; A Phase 2, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Safety and Immunogenicity of One Dose of Novartis' Meningococcal ACWY-CRM Vaccine and GlaxoSmithKline Biologicals' Meningococcal ACWY-TT Vaccine in Healthy Toddlers

Description

This was a phase 2, randomized (1:1), controlled, observer-blind, multicenter study in healthy toddlers with 2 study groups. The study was designed to assess the reactogenicity of 2 meningococcal conjugate vaccines, MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics) and MenACWY-TT (Nimenrix, GlaxoSmithKline Biologicals), using a single common list of solicited AEs. The immunogenicity of both vaccines was also evaluated, using Novartis hSBA as a primary measure, and rSBA for additional characterization, in 12-15 month old toddlers.

Methods

Objectives

Primary safety objective:

1. To assess the reactogenicity of MenACWY-cross reactive material (CRM) and MenACWY-tetanus toxoid (TT) vaccines, given to healthy toddlers at 12-15 months of age, as measured by the percentage of subjects with at least 1 severe solicited adverse event (AE) reported between 6 hours and day 7 post vaccination.

Secondary immunogenicity objectives:

1. To assess the immunogenicity of 1 dose of MenACWY-CRM or MenACWY-TT, as measured by the percentage of subjects with serum bactericidal assay (SBA) using human complement (hSBA) titer $\geq$ 8, the percentage of subjects with seroresponse, and hSBA geometric mean titers (GMTs) directed against N meningitidis serogroups A, C, W, and Y on day 29 after vaccination;
2. To assess the immunogenicity of 1 dose of MenACWY-CRM or MenACWY-TT, as measured by the percentage of subjects with SBA using rabbit complement (rSBA) titer $\geq$ 8, the percentage of subjects with rSBA titer $\geq$ 128, 4-fold rise, and rSBA GMTs directed against N meningitidis serogroups A, C, W, and Y on day 29 after vaccination;
3. To assess the persistence of the immune response on day 180 after vaccination with either 1 dose of MenACWY-CRM or MenACWY-TT, as measured by the percentage of subjects with hSBA titer $\geq$ 8, the percentage of subjects with seroresponse, and hSBA GMTs against N meningitidis serogroups A, C, W, and Y;
4. To assess the persistence of the immune response on day 180 after vaccination with either 1 dose of MenACWY-CRM or MenACWY-TT, as measured by the percentage of subjects with rSBA titer $\geq$ 8, the percentage of subjects with rSBA titer $\geq$ 128, 4-fold rise, and rSBA GMTs directed against N meningitidis serogroups A, C, W, and Y.

Secondary safety objective:

To evaluate the reactogenicity and safety of the study vaccines as measured by solicited AEs (between 6 hours and day 7), unsolicited AEs (days 1-29), AEs with medically attended visits, AEs leading to withdrawal from the study and serious AEs (SAEs).

Study design

Phase 2, randomized, observer-blind, controlled, multicentre study

Study population /Sample size

Healthy children aged 12 to 15 months old inclusive who were born with an estimated gestational age $\geq$ 37 weeks were randomised to receive either 1 dose of either MenACWY-CRM (n=100) or MenACWY-TT (n=102).

Inclusion criteria were: Children from 12-15 months of age, generally in good health, and available for all study visits, whose parents/legal guardians had given written informed consent at the time of enrolment.

Exclusion criteria were:

- Serious, acute, or chronic illnesses.
- Previous or suspected disease caused by *N meningitidis.*
- Previous immunization with any meningococcal vaccine.
- Exposure to individuals with clinically proven meningococcal disease or clinical bacterial meningitis without further microbiologic characterization.

Treatments

Children received either a single dose of MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics, final quantity/dose: 10 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg MenY) or of MenACWY-TT (Nimenrix, GlaxoSmithKline Biologicals, final quantity/dose: 5 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg MenY).

Outcomes/endpoints

Primary endpoint:

- Percentage of subjects with at least 1 severe solicited AE* within 7 days after vaccination (6 hours through day 7).

**Solicited AEs included tenderness, erythema, induration, irritability, sleepiness, change in eating habits, vomiting, diarrhoea, and fever.*

Secondary immunogenicity endpoints:

- Percentage of subjects with hSBA titer ≥ 8 against serogroups A, C, W, and Y at day 1, day 29 and day 180 post vaccination.
- Percentage of subjects with hSBA seroresponse against serogroups A, C, W, and Y at day 29 and day 180 post vaccination, defined as:
    - for subjects with pre vaccination hSBA titer < 4, post vaccination hSBA titer ≥ 8;
    - for subjects with pre vaccination hSBA titer ≥ 4, an increase of at least 4 times the pre vaccination hSBA.
- hSBA GMTs for serogroups A, C, W, and Y at day 1, day 29 and day 180 post vaccination.
- Percentage of subjects with rSBA titer ≥ 8 against serogroups A, C, W, and Y at day 1, day 29 and day 180 post vaccination.
- Percentage of subjects with rSBA titer ≥ 128 against serogroups A, C, W, and Y at day 1, day 29 and day 180 post vaccination.
- Percentage of subjects with 4-fold rise in rSBA titers against serogroups A, C, W, and Y at day 29 and day 180 post vaccination.
- rSBA GMT for serogroups A, C, W, and Y at day 1, day 29 and day 180 post vaccination

Secondary safety endpoints:

- Solicited local and systemic AEs reported from day 1 (6 hours) to day 7 after vaccination;
- Other indicators of reactogenicity (eg, use of analgesics/antipyretics, body temperature) during the 7 days after vaccination;

- Unsolicited AEs reported from day 1 to day 29 after vaccination;
- Medically attended AEs reported during the entire study period;
- AEs leading to premature withdrawal during the entire study period;
- SAEs reported during the entire study period.

Statistical Methods

The analyses of reactogenicity, immunogenicity and safety were descriptive and hence no statistical tests were performed. For the primary endpoint and secondary immunogenicity endpoints, 2-sided 95% confidence intervals (CIs) were calculated. For the primary study endpoint, 2-sided 95% CI for the difference in the percentages of subjects with severe solicited AEs between the 2 vaccine groups (ACWY-CRM and ACWY-TT) were computed.

Table 2-2 shows the precision estimates for anticipated rates of severe solicited AEs.

Table 2-2 Precision Estimates for Anticipated Rates of Severe Solicited Adverse Events Reported Within 7 Days After Vaccination

Observed Rate	Sample Size	95% CI*
2%	100	0.2%, 7.0%
5%	100	1.6%, 11.3%
10%	100	4.9%, 17.6%
15%	100	8.7%, 23.5%
20%	100	12.7%, 29.2%

Source: Table 7.4.2.4-1 of protocol version 2.0 dated 04 FEB 14.
Abbreviation: CI, confidence interval.
*Clopper Pearson CI.

Results

Recruitment/ Number analysed

A total of 202 subjects were enrolled and randomized to either ACWY-CRM group (N = 100) or ACWY-TT group (N = 102). Among 202 subjects enrolled, study vaccine was administered to 99% of subjects in the ACWY-CRM group (n=99) and all subjects in the ACWY-TT group (n=102).

Table 11.1-1 Overview of Study Population as Randomized– All Enrolled Set

	Number (%) of Subjects		
	ACWY-CRM (N = 100)	ACWY-TT (N = 102)	Total (N = 202)
Enrolled	100 (100%)	102 (100%)	202 (100%)
Exposed	99 (99%)	102 (100%)	201 (99.5%)
FAS Day 29	95 (95%)	97 (95.1%)	192 (95%)
FAS Day 180	98 (98%)	97 (95.1%)	195 (96.5%)
PPS Day 29	89 (89%)	91 (89.2%)	180 (89.1%)
PPS Day 180	95 (95%)	90 (88.2%)	185 (91.6%)

Reasons for exclusion from FAS included early termination, blood draw not done and no serological results availabe. Reasons for exclusion from the PPS included administration of concomitant vaccine

(forbidden in protocol), subject did not meet entry criteria, did not comply with blood draw schedule and subjects received antibiotics within 7 days prior to the blood draw.

Baseline data

Demographic and other baseline characteristics were well balanced among the 2 groups. Mean ± SD age of the subjects enrolled in the study was 12.7 ± 0.9 months. Percentage of male subjects in the study was higher compared to percentage of female subjects (53.5% vs 46.5%). Most of the subjects enrolled in the study were Caucasian (95%). Mean weight of the enrolled subjects was 10 ± 1.2 kg.

All subjects in the ACWY-TT group received the study vaccine, whereas 1 subject in ACWY-CRM group did not receive any study vaccination (table 11-1-1).

Efficacy results

Analysis of Immunogenicity and antibody persistence, as measured by hSBA, after vaccination with 1 dose of either MenACWY-CRM or MenACWY-TT

At day 29 (1 month after vaccination), the percentages of subjects with hSBA titers $\geq$ 8 against serogroup A and C were substantial in both ACWY-CRM (90% and 96%, respectively) and ACWY-TT groups (88% and 86%, respectively). Against serogroups W and Y, the percentages of subjects with hSBA titers $\geq$ 8 were lower, although still substantial, for both vaccine groups (ACWY-CRM: 62% and 41%, respectively and ACWY-TT: 72% and 56%, respectively). The percentages of subjects with hSBA seroresponse followed the same trend. Geometric mean titers (GMTs) increased at day 29

In both vaccine groups, to a larger extent against serogroups A (14- to 18-fold increase over baseline) and C (~9- to 12-fold increase over baseline) and to a lesser extent against serogroups W (~4- to ~6-fold increase over baseline) and Y (~3-to ~4-fold increase over baseline) (Figure 2.5.4.2-1; Table 11.4.1-1).

Overall, the immune response at 1 month after vaccination was comparable between subjects administered MenACWY-CRM or MenACWY-TT, with no appreciable differences in the increase in antibody titers against all 4 serogroups.

Table 11.4.1-1 **Number (%) of Subjects with hSBA titers ≥ 8, hSBA Seroresponse, hSBA GMTs, and GMRs against *N meningitidis* Serogroups A, C, W and Y at Baseline and Day 29 Following Vaccination (95% CI) – FAS Day 29**

Serogroups			ACWY-CRM	ACWY-TT
A	hSBA titer ≥ 8	Baseline	2 (2%) (0.27% - 7.9%) (N = 89)	0 (0%) (0% - 3.9%) (N = 92)
		Day 29	82 (90%) (82.1% - 95.4%) (N = 91)	85 (88%) (79.4% - 93.4%) (N = 97)
	hSBA seroresponse	Day 29	78 (88%) (79% - 93.7%) (N = 89)	80 (87%) (78.3% - 93.1%) (N = 92)
	hSBA GMT	Baseline	2.19 (2.02 – 2.38) (N = 89)	2.04 (1.89 – 2.21) (N = 92)
		Day 29	41 (31 – 55) (N = 91)	30 (23 – 40) (N = 97)
	GMR	Day 29/Baseline	18 (13 - 25) (N = 89)	14 (11 - 19) (N = 92)
C	hSBA titer ≥ 8	Baseline	3 (3%) (0.7% - 9.2%) (N = 92)	1 (1%) (0.03% - 5.8%) (N = 93)
		Day 29	90 (96%) (89.5% - 98.8%) (N = 94)	83 (86%) (77% - 91.9%) (N = 97)
	hSBA seroresponse	Day 29	87 (95%) (87.8% - 98.2%) (N = 92)	78 (84%) (74.8% - 90.7%) (N = 93)
	hSBA GMT	Baseline	2.44 (2.16 – 2.76) (N = 92)	2.24 (1.99 – 2.52) (N = 93)
		Day 29	30 (23 – 39) (N = 94)	20 (16 – 26) (N = 97)
	GMR	Day 29/Baseline	12 (9.38 - 16) (N = 92)	8.76 (6.86 - 11) (N = 93)

Serogroups			ACWY-CRM	ACWY-TT
W	hSBA titer ≥ 8	Baseline	5 (6%) (2% - 13.8%) (N = 81)	3 (4%) (0.8% - 10.8%) (N = 78)
		Day 29	52 (62%) (50.7% - 72.3%) (N = 84)	63 (72%) (61.8% - 81.5%) (N = 87)
	hSBA seroresponse	Day 29	44 (54%) (42.9% - 65.4%) (N = 81)	57 (73%) (61.8% - 82.5%) (N = 78)
	hSBA GMT	Baseline	2.58 (2.12 – 3.15) (N = 81)	2.40 (1.96 – 2.95) (N = 78)
		Day 29	9.34 (6.72 – 13) (N = 84)	14 (9.91 – 19) (N = 87)
	GMR	Day 29/Baseline	3.55 (2.47 - 5.12) (N = 81)	6.13 (4.21 - 8.93) (N = 78)
Y	hSBA titer ≥ 8	Baseline	3 (4%) (0.7% - 10.1%) (N = 84)	2 (2%) (0.29% - 8.3%) (N = 84)
		Day 29	36 (41%) (30.9% – 52.4%) (N = 87)	51 (56%) (45.2% - 66.4%) (N = 91)
	hSBA seroresponse	Day 29	33 (39%) (28.8% - 50.5%) (N = 84)	45 (54%) (42.4% - 64.5%) (N = 84)
	hSBA GMT	Baseline	2.23 (2.02 – 2.48) (N = 84)	2.16 (1.94 – 2.40) (N = 84)
		Day 29	5.89 (4.27 – 8.13) (N = 87)	8.20 (5.96 – 11) (N = 91)
	GMR	Day 29/Baseline	2.73 (1.95 - 3.83) (N = 84)	3.76 (2.66 - 5.32) (N = 84)

At day 180, against serogroup A the percentage of subjects with hSBA titers ≥ 8 had declined from day 29 in both vaccine groups: from 90% to 65% in the ACWY-CRM group, and from 87% to 30% in the ACWY-TT group; however, residual antibody titers were substantial. hSBA GMT titers had also declined by day 180 but were still higher than baseline: 5.91-fold over baseline in the ACWY-CRM group and 2.25-fold over baseline in the ACWY-TT group (Figure 2.5.4.2-1; Figure 2.5.4.2-2).

Against serogroup C, there was a minor decrease in the percentage of subjects with hSBA titers ≥ 8 at day 180 in the MenACWY-CRM group (from 96% at day 29 to 88% at day 180); in the MenACWY-TT vaccine group there was an increase (from 87% at day 29 to 95% at day 180). hSBA GMTs at day 180

against serogroup C showed a similar trend: a minor decrease in ACWY-CRM group (from 12- to ~10-fold over baseline) and an increase in the ACWY-TT group (~9-fold to 18-fold over baseline) (Figure 2.5.4.2-1; Figure 2.5.4.2-2).

Figure 2.5.4.2-1 **Percentage of Subjects (95% CI) with hSBA Titers ≥ 8, Against Serogroups A, C, W, and Y at Baseline, Day 29, and Day 180 Following Vaccination – FAS Day 180**

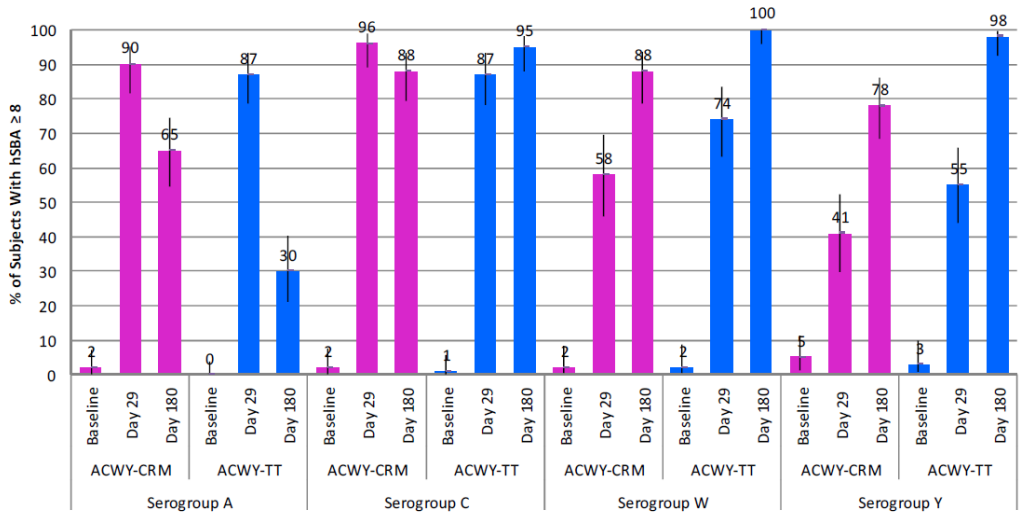
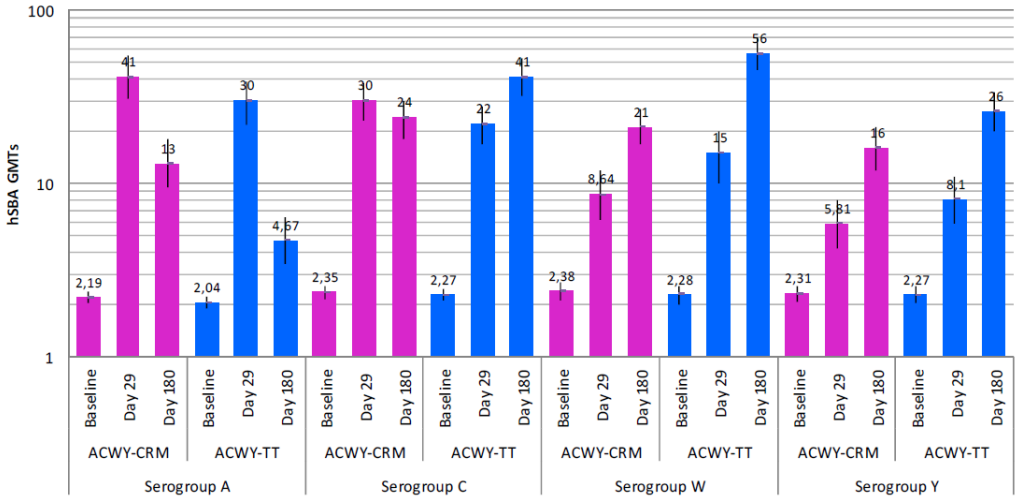


Figure 2.5.4.2-2 **hSBA GMTs Against Serogroups A, C, W, and Y at Baseline, Day 29, and Day 180 Following Vaccination – FAS Day 180**



Against serogroup W, hSBA GMTs and the percentages of subjects with hSBA titers ≥ 8 increased from day 29 to day 180 in both vaccine groups. In the ACWY-CRM group, hSBA GMTs against serogroup W was 8.61-fold over baseline at day 180; in the ACWY-TT group, hSBA GMTs was 24-fold over baseline at day 180 (Figure 2.5.4.2-1; Figure 2.5.4.2-2).

Against serogroup Y, hSBA GMTs and the percentages of subjects with hSBA titers ≥ 8 were also higher at day 180 compared with day 29 in both vaccine groups. In the ACWY-CRM group, hSBA GMTs against serogroup Y were 6.79-fold over baseline at day 180; in the ACWY-TT group, hSBA GMTs against serogroup Y were 11-fold over baseline at day 180 (Figure 2.5.4.2-1; Figure 2.5.4.2-2).

At day 180, the percentages of subjects with seroresponse against serogroup A declined in both MenACWY-CRM and MenACWY-TT vaccine groups. Against serogroup C, there were no consistent

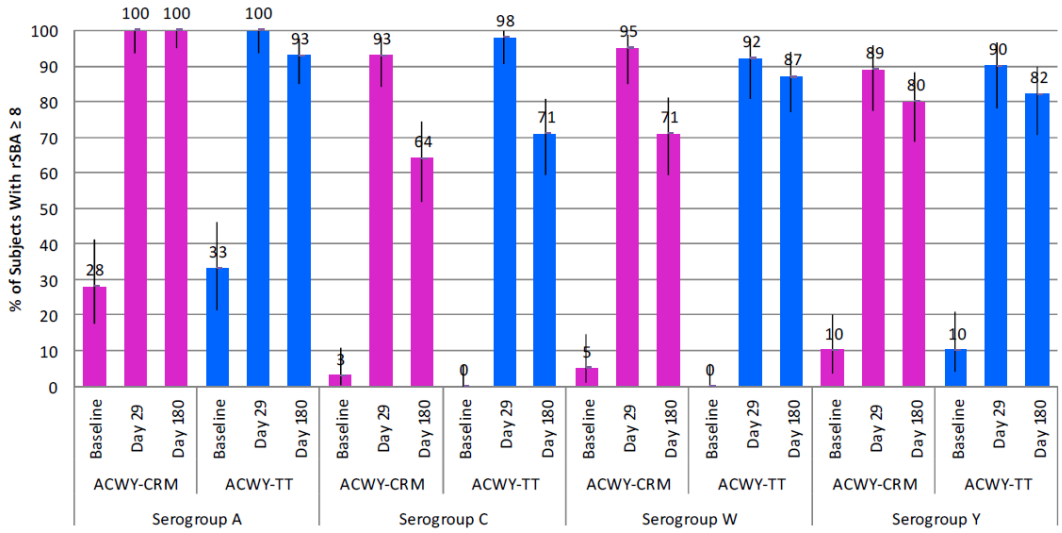
trends observed in either ACWY-CRM or ACWY-TT group. Against serogroups W and Y, the percentages of subjects with seroresponse were higher at day 180 than at day 29 in both vaccine groups.

Immunogenicity and antibody persistence, as measured by rSBA after vaccination with 1 dose of either MenACWY-CRM or MenACWY-TT

At day 29, 100% of subjects in both ACWY-CRM and ACWY-TT groups had rSBA titers ≥ 8 and ≥ 128 against serogroup A. Against serogroups C, W and Y, the percentage of subjects with rSBA titer ≥ 8 and ≥ 128 was also substantial in both ACWY-CRM (78%-92%) and ACWY-TT groups (65%-97%) on day 29.

At day 29, rSBA GMTs increased exponentially against serogroup A in the ACWY-CRM group (816-fold increase over baseline); in the ACWY-TT group the rSBA GMTs was 239-fold over baseline. Against serogroup C, the increase was more modest (63-fold over baseline in ACWY-CRM group and 64-fold over baseline in ACWY-TT group). Against serogroups W and Y, in ACWY-CRM group, there was a 228- to 303-fold increase in rSBA GMTs over baseline, and in the ACWY-TT group there was a 206- to 297-fold increase rSBA GMTs over baseline.

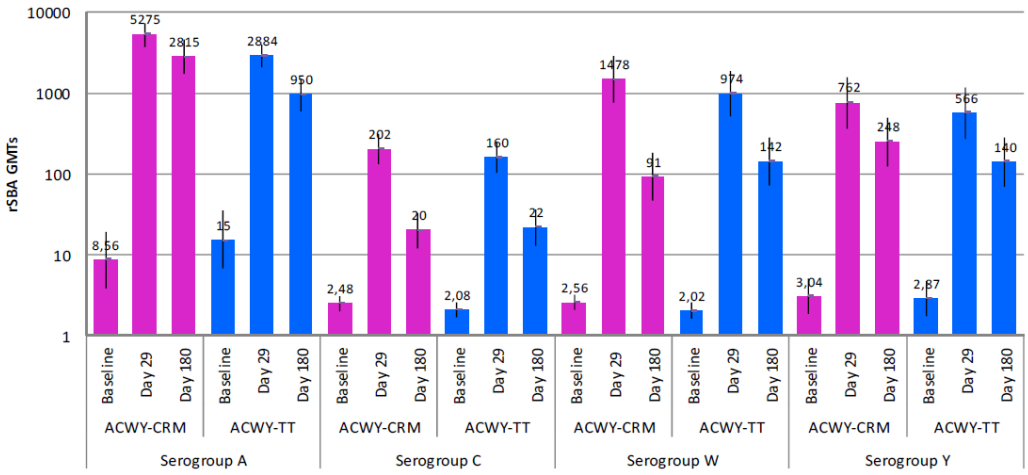
Figure 2.5.4.3-1 **Percentage of Subjects (95% CI) with rSBA Titers ≥ 8, Against Serogroups A, C, W, and Y at Baseline, Day 29, and Day 180 Following Vaccination – FAS Day 180**



At day 180, rSBA titers remained high against serogroup A in terms of percentage of subjects with rSBA titer ≥ 8, rSBA titer ≥ 128 in both vaccine groups (in the ACWY-CRM group 100% of subjects each had rSBA titer ≥ 8 and rSBA titer ≥ 128, in the ACWY-TT group 93% of subjects had rSBA titer ≥ 8, while 91% had rSBA titer ≥ 128) (Figure 2.5.4.3-1). Against serogroup C, residual antibody titers at day 180 declined sharply from day 29 in both study groups - the percentage of subjects with rSBA titer ≥ 8 and rSBA titer ≥ 128 in the ACWY-CRM group at day 180 was 64% and 25%, and in the ACWY-TT group at day 180 was 71% and 33% (Figure 2.5.4.3-1). Against serogroups W and Y, there was a steady decline in the percentage of subjects with rSBA titer ≥ 8 and rSBA titer ≥ 128 from day 29 to day 180 although the percentages of subjects were still substantial: 62%-80% in the ACWY-CRM group and 62%-87% in the ACWY-TT group at day 180 (Figure 2.5.4.3-1).

At day 180, rSBA GMTs titers against serogroup A were lower than at day 29 but substantially higher than at baseline (296-fold higher than baseline in ACWY-CRM group and 59-fold higher than baseline in ACWY-TT group) (Figure 2.5.4.3-2).

Figure 2.5.4.3-2 rSBA GMTs Against Serogroups A, C, W, and Y at Baseline, Day 29, and Day 180 Following Vaccination – FAS Day 180



Against serogroup C, rSBA GMTs also declined to a similar extent in both groups (~7- to ~9-fold higher than baseline in the ACWY-CRM and ACWY-TT groups, respectively). Against serogroup W, rSBA GMTs also declined by day 180 to 91 in the ACWY-CRM group (24-fold higher than baseline) and 142 in the ACWY-TT group (54-fold higher than baseline). Against serogroup Y, rSBA GMTs did decline in both groups by day 180 compared to day 29 (88-fold higher than baseline in ACWY-CRM group and 55-fold higher than baseline in ACWY-TT group).

Safety results

Safety population

Of 201 exposed subjects, 200 subjects (99 in ACWY-CRM and 101 in ACWY-TT) were included in the safety analyses. One subject did not provide any post vaccination safety data and was excluded from analysis. All the subjects (N = 200) in the overall safety set were included in both the solicited and the unsolicited AEs safety sets.

Solicited AEs

The primary objective of this study was to assess the percentage of subjects with at least 1 severe solicited AE, as reported between 6 hours and day 7 post vaccination. Severe solicited AEs were reported by 4 subjects (4%) in the ACWY-CRM group and 2 subjects (2%) in the ACWY-TT group. There was no appreciable difference in the incidence of severe solicited AEs between the 2 groups – the 95% CI of the vaccine group difference included 0 (95% CI: −3.4% - 8.2%).

Local solicited AEs

Tenderness was the most commonly reported local solicited AE in both ACWY-CRM (29.9%) and ACWY-TT vaccine groups (26%). The only incidence of severe local solicited AE was 1 report of induration in the ACWY-CRM group.

Table 2.5.5.2-2 Number (%) of Subjects with Any and Severe Solicited Local Adverse Events Reported From 6 Hours Through Day 7 Following Vaccination – Solicited Safety Set

		Number (%) of Subjects with Solicited Local AEs	
		ACWY-CRM (N = 97)	ACWY-TT (N = 101)
Tenderness	Any	29 (29.9%)	26 (26%) (n = 100)
	Severe	0	0
Erythema (mm)	Any	4 (4.1%)	2 (2%) (n = 100)
	> 50 mm	0	0
Induration (mm)	Any	6 (6.2%)	4 (4%)
	> 50 mm	1 (1%)	0

Source: CSR V59_67, Table 12.2.3-1.

Systemic solicited AEs

The majority of the solicited systemic AEs reported in this study were mild to moderate. Irritability, sleepiness and change in eating habits were the most common solicited systemic AEs in both groups, reported by 31.3%, 24% and 22.9% of subjects, respectively in the ACWY-CRM group and 39.4%, 26.5%, and 26% of subjects, respectively in the ACWY-TT group (Table 2.5.5.2-3).

Percentages of subjects using analgesics/antipyretics as a prophylactic were 1% and 4% in ACWY-CRM and ACWY-TT groups, respectively while therapeutic use of analgesics/antipyretics was seen in a similar number of subjects (13.3% of subjects in ACWY-CRM group and 13% of subjects in ACWY-TT group) (Table 2.5.5.2-3). Very few subjects reported severe systemic AEs. In the ACWY-CRM group, 3 subjects (3.1%) each reported severe irritability and severe change in eating habits and 2 subjects (2.1%) reported severe sleepiness. In the ACWY-TT group, severe irritability, severe change in eating habits, severe diarrhea and severe vomiting were reported by 1 subject each (1%). There were no instances of severe fever (temperature $\geq 40.0^{\circ}$ C) (Table 2.5.5.2-3).

Table 2.5.5.2-3 Number (%) of Subjects with Any and Severe Solicited Systemic AEs Reported From 6 Hours Through Day 7 Following Vaccination – Solicited Safety Set

Systemic AEs		Number (%) of Subjects with Solicited Systemic AEs	
		ACWY-CRM (N = 99)	ACWY-TT (N = 101)
Change in eating habits	Any	22 (22.9%) (n = 96)	26 (26%) (n = 100)
	Severe	3 (3.1%)	1 (1%)
Sleepiness	Any	23 (24%) (n = 96)	26 (26.5%) (n = 98)
	Severe	2 (2.1%)	0
Irritability	Any	30 (31.3%) (n = 96)	39 (39.4%) (n = 99)
	Severe	3 (3.1%)	1 (1%)
Vomiting	Any	6 (6.3%) (n = 96)	9 (9.1%) (n = 99)
	Severe	0	1 (1%)
Diarrhea	Any	17 (17.7%) (n = 96)	18 (18.2%) (n = 99)
	Severe	0	1 (1%)
Fever	≥ 38°C	14 (14.1%)	13 (13%) (n = 100)
	≥ 40.0°C	0	0
Prophylactic use of analgesics/antipyretics	Yes	1 (1%) (n = 97)	4 (4%) (n = 100)
Therapeutic use of analgesics/antipyretics	Yes	13 (13.3%) (n = 98)	13 (13%) (n = 100)

Unsolicited AEs

Unsolicited AEs reported throughout the study (until study termination at day 180) were 73.7% in the ACWY-CRM group and 70.3% in the ACWY-TT group. Frequencies of possibly or probably related unsolicited AEs were similar in both vaccine groups (12.1% in ACWY-CRM and 13.9% in ACWY-TT) (Table 2.5.5.3-1). There were 8.1% of subjects in the ACWY-CRM and 3% in ACWY-TT groups who reported SAEs; none of the reported SAEs were considered possibly or probably related to study

vaccination. There were no AEs leading to premature withdrawal and no deaths that occurred during the study.

Table 2.5.5.3-1 Overview of Subjects with Unsolicited Adverse Events After Any Vaccination – Unsolicited Safety Set

	Numbers (%) of Subjects with Unsolicited AEs	
	ACWY-CRM (N = 99)	ACWY-TT (N = 101)
Any unsolicited AEs	73 (73.7%)	71 (70.3%)
Possibly or probably related unsolicited AEs	12 (12.1%)	14 (13.9%)
AEs leading to premature withdrawal	0	0
SAEs	8 (8.1%)	3 (3%)
Possibly or probably related SAEs	0	0
Medically attended AEs	73 (73.7%)	68 (67.3%)
Death	0	0

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

Unsolicited AEs occurring within 29 days after vaccination were reported by similar numbers of subjects in both the ACWY-CRM (45.5%) and ACWY-TT (40.6%) vaccine groups, of which 12.1% and 12.9%, respectively were considered possibly or probably related to study vaccination. The most commonly reported unsolicited AE belonged to the "infections and infestations" (23.2% in ACWY-CRM group and 17.8% in ACWY-TT group) system organ class (SOC) as coded by the Medical Dictionary for Regulatory Activities (MedDRA). Among these, 4% of subjects reported at least 1 possibly related AE in each group (Table 2.5.5.3-2).

Table 2.5.5.3-2 Number (%) of Subjects with Any and Possibly or Probably Related Unsolicited Adverse Events Reported Within 29 Days After Vaccination, By System Organ Class – Unsolicited Safety Set

System Organ Class	Number (%) of Subjects With Unsolicited AEs			
	Any		Possibly or Probably Related AEs	
	ACWY-CRM (N = 99)	ACWY-TT (N = 101)	ACWY-CRM (N = 99)	ACWY-TT (N = 101)
Any AE	45 (45.5%)	41 (40.6%)	12 (12.1%)	13 (12.9%)
Blood and lymphatic system disorders	0	1 (1%)	-	-
Gastrointestinal disorders	12 (12.1%)	7 (6.9%)	5 (5.1%)	2 (2%)
General disorders and administration site conditions	13 (13.1%)	14 (13.9%)	6 (6.1%)	5 (5%)
Infections and infestations	23 (23.2%)	18 (17.8%)	4 (4%)	4 (4%)
Injury, poisoning and procedural complications	2 (2%)	0	-	-
Nervous system disorders	2 (2%)	4 (4%)	2 (2%)	2 (2%)
Psychiatric disorders	4 (4%)	3 (3%)	2 (2%)	2 (2%)
Respiratory, thoracic and mediastinal disorders	9 (9.1%)	12 (11.9%)	1 (1%)	1 (1%)
Skin and subcutaneous tissue disorders	1 (1%)	2 (2%)	1 (1%)	1 (1%)
Vascular disorders	1 (1%)	0	1 (1%)	0

Assessor's comments:

A discrepancy in possibly or probably related AEs reported for the MenACWY-TT group is noted between table 2.5.5.3-2 and table 2.5.5.3-1 in the clinical overview. The difference between the two tables is the timeframe of reporting, table 2.5.5.3-2 concerns all AEs reported within 29 days whilst for table 2.5.5.3-1 there is no time limit defined. It is the assumption that the one additional AE reported for this group in table 2.5.5.3-1 was reported outside the first 29 days. Considering this has no bearing on the overall conclusions of the study it is not pursued.

2.3.3. Discussion on clinical aspects

Study V59_67 was designed to compare the reactogenicity of two conjugated quadrivalent meningococcal ACWY vaccines, MenACWY-CRM and MenACWY-TT. The primary outcome of interest was the percentage of subjects with at least 1 severe solicited AE, these were reported by 4 subjects (4%) in the ACWY-CRM group and 2 subjects (2%) in the ACWY-TT group. The difference between the vaccine groups was 2% (95% CI: −3.4% - 8.2%). In conclusion, as the 95% CI of the vaccine group difference included 0 there was no evidence of a difference between the two vaccine groups. It could be questioned whether this is the most appropriate endpoint and method to compare the reactogenicity profile of two vaccines, as no official non-inferiority comparison was made and the primary outcome as defined is probably not the most sensitive to detect differences between vaccine groups. Nonetheless, it is agreed with the MAH that overall there is no evidence for a clinically relevant difference in the reactogenicity and safety profile of MenACWY-CRM and MenACWY-TT.

The immunogenicity 29 days (1 month) after vaccination and 6 months after vaccination was determined with the hSBA and rSBA.

The immune response at 1 month after vaccination was comparable between subjects administered MenACWY-CRM or MenACWY-TT, with no significant difference in the increase in antibody titers against all 4 serogroups. There is a tendency for a higher response against MenC in the MenACWY-CRM group (~10% difference), and a tendency for a higher response against MenW (~10% difference), and MenY (~15% difference) in the MenACWY-TT group as well as a larger increase in GMTs and larger % with hSBA$\geq$8. However, confidence intervals are wide and overlap. The rSBA analyses at day 29 were higher than the hSBA analyses for all serogroups except serogroup C, which had a slightly lower response for the MenACWY-CRM group when measured with the rSBA compared to the hSBA. rSBA GMTs showed an exponential increase in both ACWY-CRM and ACWY-TT groups at day 29 for serogroups A, W and Y and a more modest increase against serogroup C.

Persistence was measured at 6 months. A sharp decline was seen in the hSBA response for MenA which is already described in the SmPC. Persistence of MenA over 180 days seems better in subjects vaccinated with MenACWY-CRM (25% drop in % hSBA$\geq$8 compared to a 57% in the MenACWY-TT group, CI's at D180 do not overlap). A similar decline was not seen using the rSBA assay, with all subjects in the ACWY-CRM group and > 90% in the ACWY-TT group retaining antibody titers $\geq$ 8 and $\geq$ 128 against serogroup A.

The immune response was both assessed by rSBA and hSBA. Both a rSBA titre of $\geqslant$8 as an hSBA titre $\geqslant$4 are established correlates for protection for serogroup C (Andrews et al, Clin. Diagn. Lab. Immunol., 10 (2003), pp. 780–786; Borrow et al. Vaccine, 23 (2005), pp. 2222–2227) and are commonly applied for the other serogroups as well. It has been found however that the two assays do not correlate well for serogroups A, W-135 and Y (Gill et al Vaccine 30 (2011) 29– 34). The present study shows several differences in the response when measured by rSBA or hSBA for all serogroups:

- The decline in MenA between D29 and D180 is more clearly with the hSBA compared to the rSBA.
- When measured with the hSBA there is an increase in response to MenY and MenW between D29 and D180.

The MAH mentions that this trend was previously observed by Vesikari et al. 2012 for serogroups W and Y between 1 and 12 months after a single dose of MenACWY-TT in toddlers and suggests that this may indicate that the kinetics of hSBA response following a 1-dose vaccination with conjugate meningococcal vaccines in this age group is serogroup-specific. This increase was not seen with the rSBA; here a small decline was seen.

- Finally, there is an increase in hSBA response to MenC in the MenACWY-TT group between D29 and D180, but not in the MenACWY-CRM group. When measured with the rSBA there is a substantial decline in the response to both vaccines between D29 and D180.

The discrepancies between the assays and vaccine groups could be explained by different kinetics of antibody responses in the studied age-groups, natural boosting or alternatively, a response to subcapsular antigens that cross react with the indicator strain in the assay could explain some of the variability. These explanations, however, would not provide an answer for the differences between the two vaccine groups - unless the two vaccines have a different impact on carriage. Moreover, intrinsic variability in the assays could also play a role. The interpretation of results remains challenging and it remains unclear if the true reflection of loss of VE might be due to waning antibodies, or an increase in VE due to natural boosting.

The sharp decline as measured by hSBA compared to rSBA for MenA has indeed been observed earlier, and is described in the SmPC of conjugated tetravalent MenACWY vaccines including Menveo. The explanation provided by the MAH would seem to suggest that the rSBA overestimates the response compared to the hSBA, as human factor H would be a key factor in explaining the lack of correlation between the rSBA and hSBA. The discrepant results for the other serogroups, however, do not point to any real concern regarding VE for Menveo at this time and no further action is needed.

Based on the results from this study, the MAH concludes that there is no change to the benefit-risk profile for the MenACWY-CRM vaccine and no update of summary of product characteristics (SmPC) is required as Menveo is not licensed in Europe in children below 2 years of age. This is agreed.

3. Rapporteur's overall conclusion and recommendation

Rapporteur's overall conclusion and recommendation

Overall, study V59_67 found no apparent difference in the reactogenicity profile of the MenACWY-CRM vaccine and the MenACWY-TT vaccine. Regarding the immunogenicity several discrepancies are noted in the response as measured by rSBA or hSBA.

Whilst the hSBA and rSBA have been correlated to clinical effectiveness and natural immunity for MenC this correlation has not absolutely been established for the other serogroups and for pragmatic reasons the correlation between the functional assays and protection against Men A, W and Y is assumed to be similar as has been established for MenC - due to the low incidence of invasive meningococcal disease would be impossible to establish. Although both assays are accepted for demonstrating vaccine benefit, the results of study V59_67 underline that caution is needed in the interpretation of the assays and the need to follow-up vaccine failures in the field after vaccines are licensed. No further regulatory action is required.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

Based on the data submitted, the MAH should provide further clarifications regarding the discrepancies between the response measured by rSBA vs hSBA as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested

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

There are several pertinent differences noted in the response when measured by rSBA or hSBA:

- A sharp decline in the response for MenA is seen when measured with hSBA yet not with the rSBA
- When measured with the hSBA there is an increase in response to MenY and MenW between D29 and D180. This increase was not seen with the rSBA; here a small decline was seen.
- There is an increase in response to MenC in the MenACWY-TT group between D29 and D180, but not in the MenACWY-CRM group. When measured with the rSBA there is a substantial decline in the response to both vaccines between D29 and D180 for MenC.

These discrepancies in responses between the rSBA and hSBA should be discussed including current up to date understanding of the different assays. The MAH should elaborate what could possibly explain the differences in immunogenicity increases and decreases between D29 and D180 for the different serogroups and vaccine groups. It is at present not clear which assay provides the most reliable insight in the persistence of protection provided by vaccination.

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

MAH responses to Request for supplementary information

The company acknowledges that while a decline was observed in the response for serogroup A when measured with assay using human complement (hSBA), the same was not the case when measured with rabbit complement (rSBA). We postulate that the antibody response to serogroup A may be assay-specific.

The rapid decline in hSBA response for serogroup A is a trend that is well documented. Baxter et al. reported that hSBA titers against serogroup A at 1 year post single dose of MenACWY-TT (Nimenrix®) in adolescents were markedly lower than against serogroups C, W and Y (Baxter et al. 2015). In other studies, hSBA antibodies against serogroup A declined to a similar degree over a 5-year period, both in subjects given MenACWY-CRM and in those given the meningococcal ACWY-D conjugate vaccine (Menactra®) (Gill et al. 2010, Baxter et al. 2014a, Baxter et al. 2014b).

The hSBA assay, the serologic marker of protection for meningococcal vaccines, is difficult to standardize across laboratories (even if the same standard operating procedure is followed), primarily due to the biological nature of the reagents used and a lack of a reference standard (Borrow et al. 2005, Maslanka et al. 1997, Balmer et al. 2007). The key variable components are the source of the human complement, the meningococcal strain chosen for the assay, the method by which the bacteria are cultivated to prepare for the assay, and the growth conditions during the assay.

One of the most critical components of the assay, human complement, is the most variable and difficult to acquire due to the complex biological nature of the complement proteins. To obtain the human complement, either serum from vaccinated individuals is processed to preserve the complement and the SBA is performed using intrinsic, or endogenous complement, or an external source of complement is used. If an external source of complement is to be used, it must be obtained from healthy individuals whose serum lacks bactericidal activity against the strain to be tested. To obtain complement void of naturally acquired antibodies, it is necessary to screen sera from a number of individuals in order to identify those who lack bactericidal activity against the strain to be tested.

As a result of the difficulty in sourcing human complement, the rSBA assay, which uses baby rabbit complement, is a widely accepted alternative to the hSBA and many meningococcal vaccines in use today were licensed based on a modified rSBA assay. The rSBA assay was used in the UK immunization program during an epidemic as part of the licensure for 2 of the 3 meningococcal serogroup C conjugate vaccines used in the epidemic. After the national immunization campaign, the number of cases of serogroup C invasive meningococcal infection fell rapidly in the target age groups (Campbell et al. 2010) and subsequent analysis of serum in immunized subjects showed a correlation between rSBA titers and effectiveness of the vaccines. A critical difference between rabbit and human complement is the complement protein, factor H (fH), a down-regulator of the alternative pathway. All meningococci harbour the species-specific surface protein, factor H-binding protein (fHbp). This protein selectively binds human factor H, therefore when human complement is used in the SBA, the fH present binds the bacteria which then is more resistant to killing. Rabbit fH does not bind to the meningococcal fHbp, consequently when rabbit complement is used in the SBA, no human fH is bound to the bacteria, the alternative pathway is no longer in check, and complement-mediated bacterial killing is not inhibited, leading to higher titers because less antibody is needed to kill the more susceptible bacteria (Gill et al. 2011, Granoff et al. 2009). Depending on the amount of fHbp on the strain tested, the titers may be more or less elevated in the rSBA because the bacteria are more or less susceptible. In general, rSBA titers tend to be higher than hSBA titers in the same individual when the sera is tested in the 2 assays against the same strain, and also decline at a lower rate (McIntosh et al. 2015, Gill et al. 2011). At 21 months (Gill et al. 2010) and 3 years (Baxter et al. 2014a) after a single vaccination in adolescents, there were sustained high percentages of subjects (96–99%) with rSBA titers $\geq$ 8 against serogroup A, compared with low percentages of subjects with hSBA titers $\geq$ 8 (40% at 21 months and 37% at 3 years). This difference in antibody persistence between the hSBA and rSBA assays for serogroup A was not observed for the other serogroups at any time point after vaccination.

The trend of poor correlation between hSBA and rSBA with conjugated MenACWY vaccine (either 1 or 2 doses) is one that is well documented (Gill et al. 2011, Klein et al. 2013, Vesikari et al. 2012). Gill et al. analyzed the strength of correlation between the 2 assays, they found that the correlations between hSBA and rSBA was strongest for serogroup C ranging from 0.46 to 0.78, and was weak for serogroups A, W and Y (range −0.15 to 0.57) (Gill et al. 2011).

In conclusion, the results of the V59_67 study reflect these prior observations, showing a sharper decline in hSBA titers than in rSBA titers against serogroup A.

MenW and MenY – hSBA increase from D29 and D180 in assay

The company also acknowledges that results from this study show an increase in hSBA titers against serogroups W and Y from day 29 to day 180 while rSBA titers decreased in this same time period. Vesikari et al. 2012 reported a similar declining trend in rSBA titers against serogroups W and Y between 1 and 12 months after a single dose of MenACWY-TT in toddlers, while hSBA titers against serogroup W and Y increased slightly over the same time period. Of note, this trend has not been observed in other age groups for either MenACWY-CRM or MenACWY-TT. We postulate that the increase in hSBA titers against serogroups W and Y may be caused by differing kinetics of antibody responses against the different serogroups in this age group or natural boosting. Furthermore, the differences in the hSBA and rSBA responses may be caused by intrinsic differences in the assay methodologies, as detailed earlier.

MenC response in MenACWY-TT vs MenACWY-CRM group

Finally, the company acknowledges that there was an increase in antibody titers against serogroup C in the MenACWY-TT group between day 29 and day 180, but not in the MenACWY-CRM group, while rSBA titers declined substantially between day 29 and day 180 in both groups. The waning of the

immunoresponse against serogroup C from day 29 to day 180 is expected for the MenACWY-CRM group for both hSBA and rSBA, and has been shown in several other studies. Indeed, waning of antibody responses against serogroup C is a well-known phenomenon for all meningococcal vaccines and across age groups (De Wals et al. 2006; Borrow et al. 2013). For MenACWY-TT, however, data from other studies are not consistent with the results of study V59_67, as other studies have reported waning then followed by an increase in titers. For example, in a study by Vesikari et al. 2012, rSBA and hSBA titers for serogroup C after a single dose of MenACWY-TT in toddlers showed a decline from month 1 (day 29) to year 1, and a further decline from year 1 to year 2, followed by an increase from year 2 to year 3. This increase from year 2 to 3 was not a frequent observation in other studies, and was hypothesized to be due to natural boosting (Vesikari et al. 2012).

Although study V59_67 showed an increase in antibody titers in the MenACWY-TT group against serogroup C between day 29 and day 180 and the Vesikari et al. study showed waning, it is important to note SBAs are prone to interlaboratory differences due to the biological nature of the assay; therefore, SBA results should really only be directly compared if the serum is tested in the same laboratory at the same time using the same complement source and the same indicator strains.

With regards to which assay provides the most reliable insight into the persistence of protection provided by vaccination, it is important to note that both rSBA and hSBA assays are considered by EMA health authority and hSBA by the FDA, and prior to the licensure of serogroup C conjugate meningococcal vaccines in the UK, results using the rSBA assay provided the basis for EMA licensure for many studies (Campbell et al. 2010, Andrews et al. 2003).

Assessor's comments

With their response the MAH has discussed the methodological limitations of the hSBA and rSBA assays, and acknowledge the difficulties in interpretation as a result of these limitations, or variabilities.

The main point made by the MAH is the difficulty in standardization due to the biological nature of the assay - key variable components named by the MAH are the source of the complement, the assay strain, cultivation method and growth conditions during the assay. Inter-laboratory differences can be expected due to these factors however when performing a single study it is assumed that these conditions are standardized and that the assays are used in a single laboratory. According to the documentation provided by the MAH, hSBA assays were run by Clinical Laboratory Sciences (CLS), Novartis Vaccines and Diagnostics, Marburg. The rSBA test was performed in an external lab (PHA, England). These factors (source of the complement, the assay strain, cultivation method and growth conditions during the assay) ought to be standardized for all measurement points for which results were compared between vaccine groups. It is acknowledged however that aside from these factors other variables can still introduce variability in the assay and could explain the observed discrepancies.

Although the MAH touches on other potential reasons for the observed difference, they do not go into detail to explain these (differing kinetics of antibody responses, natural boosting). Alternatively, a response to subcapsular antigens that cross react with the indicator strain in the assay could explain some of the variability. These explanations however would not provide an answer for the differences between the two vaccine groups - unless the two vaccines have a different impact on carriage. Whilst variability in the assay might explain some of the observations, the interpretation of results remains challenging and it remains unclear what is a true reflection of loss of VE due to waning antibodies, or increase in VE due to natural boosting.

The sharp decline as measured by hSBA compared to rSBA for MenA has indeed been observed earlier, and is described in the SmPC of conjugated tetravalent MenACWY vaccines including Menveo. The explanation provided by the MAH would seem to suggest that the rSBA overestimates the response

compared to the hSBA, as human factor H would be a key factor in explaining the lack of correlation between the rSBA and hSBA. The discrepant results for the other serogroups do not point to any real concern regarding VE for Menveo at this time and no further action is needed.

Whilst the hSBA and rSBA have been correlated to clinical effectiveness and natural immunity for MenC this correlation has not absolutely been established for the other serogroups and for pragmatic reasons the correlation between the functional assays and protection against Men A, W and Y is assumed to be similar as has been established for MenC. This has however not been established, and due to the low incidence of invasive meningococcal disease would be impossible to establish. Although both assays are accepted for demonstrating vaccine benefit, the results of study V59_67 underline that caution is needed in the interpretation of the assays and the need to follow-up vaccine failures in the field after vaccines are licensed.

Based on the results from this study, the MAH concludes that there is no change to the benefit-risk profile for the MenACWY-CRM vaccine and no update of summary of product characteristics (SmPC). Although both assays are accepted for demonstrating vaccine benefit, the results of study V59_67 underline that caution is needed in the interpretation of the assays and the need to follow-up vaccine failures in the field after vaccines are licensed. No further regulatory action is required.

Issue resolved.