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EMA/391588/2015
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/P46/030.1

Note

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

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Administrative information

Invented name of the medicinal product:	Menveo
INN (or common name) of the active substance(s):	Meningococcal group A, C, W135 and Y oligosaccharides all conjugated to Corynebacterium diphtheriae CRM197 protein.
MAH:	Novartis Vaccines and Diagnostics S.r.l.
Currently approved Indication(s)	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.
Pharmaco-therapeutic group (ATC Code):	Meningococcal vaccines, ATC code: J07AH08
Pharmaceutical form(s) and strength(s):	One dose (0.5 ml of the reconstituted vaccine) contains: (Originally contained in the powder) • Meningococcal group A oligosaccharide 10 microgramsConjugated to Corynebacterium diphtheriae CRM197 protein 16.7 to 33.3 micrograms (Originally contained in the solution) • Meningococcal group C oligosaccharide 5 micrograms Conjugated to Corynebacterium diphtheriae CRM197 protein 7.1 to 12.5 micrograms • Meningococcal group W135 oligosaccharide 5 micrograms Conjugated to Corynebacterium diphtheriae CRM197 protein 3.3 to 8.3 micrograms • Meningococcal group Y oligosaccharide 5 micrograms Conjugated to Corynebacterium diphtheriae CRM197 protein 5.6 to 10.0 micrograms
Rapporteur:	Hans Hillege

1. Introduction

On 10 November 2014, 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 study V59_36 *a Phase 3b, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Immunogenicity of 2 or 3 Doses of MenACWY Conjugate Vaccine in Healthy Infants and the Effects of a Booster Dose of MenACWY Administered in the Second Year of Life* is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Not applicable

2.3. Clinical aspects

2.3.1. Introduction

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide and despite early treatment with antibiotics, morbidity and mortality rates are high.

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N meningitidis* have been identified. Serogroups A, B, C, W-135, and Y are being responsible for the large majority of invasive meningococcal infections worldwide.

The MAH has developed a conjugate vaccine Menveo (referred to as MenACWY throughout this document), containing bacterial capsular oligosaccharides for serogroups A, C, W and Y, conjugated to a protein carrier CRM-197 (a non-toxic mutant of diphtheria toxin).

The MenACWY vaccine is licensed in Europe for use in children aged 2 years and above, and approved in more than 63 countries worldwide, and approximately 30,000 subjects have been exposed to MenACWY in completed clinical trials.

2.3.2. Clinical study

Study V59_36 *a Phase 3b, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Immunogenicity of 2 or 3 Doses of MenACWY Conjugate Vaccine in Healthy Infants and the Effects of a Booster Dose of MenACWY Administered in the Second Year of Life.*

Conducted in Canada and VS.

Study period: 11 October 2010 till 10 May 2012

Description

Methods

Objective(s)

Primary objectives

1. To demonstrate a sufficient immune response of four doses of MenACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥ 1:8, directed against*N. meningitidis* serogroups A, C, W and Y.

2. To demonstrate immunological non-inferiority of two MenACWY infant doses and a toddler dose (doses at 2, 4 and 12 months of age) to three infant doses and a toddler dose (doses at 2, 4, 6 and 12 months of age) as measured by percentage of subjects with hSBA ≥ 1:8 against *N. meningitidis* serogroups C, W and Y at 13 months of age.

Secondary objectives included evaluation of the effect of concomitant administration of MenACWY on immune response to PCV-13 antigens after 2 or 3 doses of MenACWY (measured at 7 months of age), and after 3 or 4 doses (measured at 13 months of age), using a noninferiority test.

Secondary objectives also included assessment of the kinetics of immune response following the first, second and third infant doses (measured at 2, 3, 4, 5, 7 and 12 months of age).

Safety Objectives:

1. To assess the percentage of subjects presenting, during days 1-7 after any vaccination, at least one severe systemic reaction after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

2. To assess the safety and tolerability of MenACWY when given concomitantly with routine infant vaccines.

Study design

This was a phase 3b, open-label, randomized, multicenter study. The study assessed the immunogenicity of a 3-dose vaccination schedule of MenACWY vaccine (2 infant doses at 2 and 4 months of age followed by a toddler dose at 12 months of age) compared to a 4-dose vaccination schedule (3 infant doses at 2, 4 and 6 months of age followed by a toddler dose at 12 months of age).

Study population /Sample size

Individuals were healthy 2-month-old infants (≥55 to ≤89 days old). Babies must have been born after a full-term pregnancy with an estimated gestational age ≥37 weeks and a birth weight ≥2.5 kg.

Main exclusion criteria were: prior receiving of any meningococcal vaccine or any vaccine against DTP, IPV or OPV, Hib. Prior doses of BCG vaccine (1 dose) and/or HBV (up to 2) were permitted.

A total of 750 subjects were planned (see treatments for description of the four groups); approximately 125 subjects in group 1(ACWY4a) and in group 2 (ACWY4b), respectively; 250 subjects in group 3 (ACWY3) and 250 subjects in the Routine non-MenACWY group 4 were to be enrolled. Assuming an approximately 10% drop-out rate, each group would have approximately 113, 113, 225, or 225 evaluable subjects, respectively.

Assuming that subjects in this study had similar antibody responses as in the previous study V59P5 in infants receiving three doses .- The responses of this study for C, W and Y were 100% with 95% CI 90/91%,100% see table 9.7.2-1.- And assuming the percentage of subjects with hSBA ≥1:8 was 0%, 2%, or 4% lower in ACWY3 group compared to ACWY4, the power for the noninferiority comparison between ACWY3 and ACWY4 groups with a 2-sided type I error of 5% is shown in Table 9.7.2-2.

Table 9.7.2-1: Percentages of Infants with hSBA Titer ≥8 and Their Confidence Intervals 1 Month after the 12 Month Dose (V59P5 Study, Vaccination at 2, 4 and 12 Months of Age) by Serogroup

Serogroups	N	% hSBA ≥1:8 (95% CIs)
C	40	100% (91%, 100%)
W	35	100% (90%, 100%)
Y	38	100% (91%, 100%)

Table 9.7.2-2: Power Estimation for Primary Objective 2 by Serogroup

Serogroup	% Subjects with hSBA ≥ 1:8		Power for Various Sample Sizes		
	ACWY3	ACWY4	N=90	N=150	N=225
C, W, Y	98%	98%	97%	>99%	>99%
	96%	98%	72%	91%	>99%
	94%	98%	41%	62%	83%

Assessor's comment:

The response to serotype A was not accounted for. The MAH should comment.

Treatments

Subjects were randomized into one of 4 groups at a 1:1:2:2 ratio, stratified by study center.

Groups 1 (ACWY4a) and 2 (ACWY4b) were to receive 3 infant doses at 2, 4 and 6 months of age and a toddler dose at 12 months of age; however, they were to have different schedules for the first blood draw (at 3 and 4 months, respectively).

Group 3 (ACWY3) were to have 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.

Group 4 (Routine) was to receive routine vaccines and not receive MenACWY vaccination.

Outcomes/endpoints

The primary measures of immunogenicity were the percentage of subject with hSBA ≥1:8 for meningococcal serogroups A, C, W and Y.

The main secondary endpoint was percentage of subjects with IgG antibody concentration ≥0.35 µg/mL and ≥1.0µg/mL against pneumococcal capsular polysaccharides for each PCV-13 serotype.

Statistical Methods

Primary Immunogenicity Objectives

The **first primary immunogenicity** objective was to demonstrate a sufficient immune response of 4 doses of MenACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8, directed against *N meningitidis* serogroups A, C, W and Y.

H_0: PACWY4 (A) ≤ 80% or PACWY4 (C) ≤ 85% or PACWY4 (W) ≤ 85% or PACWY4 (Y) ≤ 85%

H_a: PACWY4 (A) > 80% and PACWY4 (C) > 85% and PACWY4 (W) > 85% and PACWY4 (Y) > 85% where PACWY4 (A), PACWY4 (C), PACWY4 (W) and PACWY4 (Y) are the true percentages of subjects with hSBA ≥1:8 in serogroups A, C, W, and Y in the ACWY4 group, respectively.

The **second primary immunogenicity** objective was to demonstrate noninferiority of the immune response after 2 infant doses and a toddler dose of MenACWY at 2, 4, and 12 months of age (ACWY3 group) as compared to 3 infant doses and a toddler dose of MenACWY at 2, 4, 6 and 12 months of age (ACWY4a and ACWY4b groups combined) as measured by the percentage of subjects with hSBA ≥1:8 against *N meningitides* serogroups C, W and Y at 1 month after the toddler dose.

H0: PACWY3 – PACWY4 ≤-10%

H1: PACWY3 – PACWY4 >-10%

ACWY3 group was noninferior to ACWY4 (ie, ACWY4a+ACWY4b), if the lower limit of the 2-sided 95% confidence interval around the difference between the groups (PACWY3 minus PACWY4) in the percent of subjects with hSBA ≥1:8 was greater than -10%.

The **secondary immunogenicity objectives** of evaluating the immune response to PCV-13 antigens as affected by the concomitant administration of 2 or 3 doses of MenACWY in the first year of life (measured at 7 months of age), and of a 3 or 4-dose series ending in a toddler dose at 12 months (measured at 13 months of age), were performed using a noninferiority tests.

At 7 months of age, noninferiority was as measured by the percentage of subjects with IgG antibody concentration ≥0.35 µg/mL against pneumococcal capsular polysaccharides for each serotype. ACWY4 or ACWY3 group would be noninferior to the Routine group if the lower limit of the 2-sided 95% confidence interval around the group difference in percentage of subjects with IgG ≥0.35 µg/mL against each PCV-13 serotype (ACWY4 minus Routine or ACWY3 minus Routine) was greater than -10%. A tiered approach was applied, utilizing a hierarchical sequential testing procedure that grouped the serotypes into 2 families (Family 1 serotypes included 1, 4, 6A, 7F, 14, 18C, 19A, 19F; and Family 2 serotypes included 9V, 23F, 5, 6B and 3).

At 13 months of age (ie, post-toddler dose), noninferiority was as measured by the GMCs for each PCV-13 serotype. The ACWY4 or ACWY3 group would be noninferior to the Routine group if the lower limit of the 2-sided 95% confidence interval around the ratio of GMCs between the groups was greater than 0.5. No hierarchical testing procedure was used.

Results

Recruitment / Number analysed

A total of 751 subjects were enrolled of which 571 (76%) subjects completed the study. The most common reason for premature withdrawal was due to withdrawal of consent (12%), followed by subjects being lost to follow-up (7%). Similar patterns were observed in the individual study groups.

Overall 733 subjects (98%) received the study vaccination and were included in the exposed set.

For the analyses of immune responses at 7 months of age following the infant vaccinations, 595 subjects (79%) were included in the Infant ACWY FAS and 553 subjects (74%) in the corresponding PPS. For the analyses of immune responses at 13 months of age 545 subjects (73%) were included in the Toddler ACWY FAS and 472 subjects (63%) in the PPS.

For the analyses of immune responses to PCV-13 antigens at 7 months of age (infant PCV), the FAS and PPS included 70% and 61% of subjects respectively, and at the 13-month time point (Toddler PCV) 66% and 52%, respectively.

Baseline data

The mean age of subjects at enrolment was 66.6 days, with subjects having a mean weight of 5.39 kg and height of 58.342 cm. The most common race was Caucasian (58%), followed by Hispanic (18%). Overall, a slightly higher percentage of male subjects were enrolled compared with females (53% vs 47).

Table 11.2-1: Demographic and Other Baseline Characteristics - Enrolled Set

	ACWY3	ACWY4a	ACWY4b	Routine	Total
	N=249	N=127	N=129	N=246	N=751
Age (days)	66.4±7.1	67.2±7.8	66.2±7.0	66.7±7.0	66.6±7.2
Sex:					
Male	123 (49%)	67 (53%)	66 (51%)	140 (57%)	396 (53%)
Female	126 (51%)	60 (47%)	63 (49%)	106 (43%)	355 (47%)
Race:					
Asian	1 (<1%)	2 (2%)	2 (2%)	3 (1%)	8 (1%)
Black	31 (12%)	12 (9%)	12 (9%)	32 (13%)	87 (12%)
Caucasian	144 (58%)	75 (59%)	81 (63%)	138 (56%)	438 (58%)
Hispanic	50 (20%)	25 (20%)	21 (16%)	42 (17%)	138 (18%)
Other	23 (9%)	13 (10%)	13 (10%)	31 (13%)	80 (11%)
Weight (kg)	5.396±0.691	5.422±0.607	5.405±0.694 N=128	5.360±0.746 N=245	5.390±0.696 N=749
Height (cm)	58.368±2.936 N=248	58.654±2.741	57.884±2.973 N=127	58.391±2.684 N=243	58.342±2.833 N=745

Assessor's comment:
Overall the baseline characteristics of the three MenACWY groups were similar. The routine control group had a slightly different gender distribution; as the patients were randomized this is likely to be a coincidence.

Efficacy results

The **primary objective** of demonstrating a sufficient immune response would be met if, at 13 months of age, the lower limit of the 2-sided 95% CI for the percentage of subjects with hSBA ≥1:8 was greater than 80% for serogroup A and greater than 85% for serogroups C, W and Y.

One month after completion of a 4-dose series of MenACWY at 13 months of age, 96% of subjects had hSBA ≥1:8 against serogroup A, and 99% of subjects had hSBA ≥1:8 against serogroups C, W and Y

The lower limit of the 95% CI was greater than 80% for serogroup A and greater than 85% for the other 3 serogroups, meeting the prespecified sufficiency criteria for immune response following administration of a 4-dose vaccination series (Table 11.4.1-1).

Table 11.4.1-1: Number (%) of Subjects With hSBA ≥1:8 (95%CI) Against *N meningitidis* Serogroups A, C, W, and Y at 13 Months of Age Following a 4-Dose Vaccination Schedule – Toddler ACWY PPS

Serogroup	Number (%) of Subjects	Criterion for sufficient immune response met
	ACWY4	
A	N=141	Yes
	135 (96%) (91%-98%)	
C	N=152	Yes
	150 (99%) (95%-100%)	
W	N=138	Yes
	137 (99%) (96%-100%)	
Y	N=146	Yes
	145 (99%) (96%-100%)	

Assessor's comment:

This primary endpoint was met. As mentioned above a lower limit of 90% would have been supported by the data of the previous study. However, the results of the current study are also within a more stringent range, i.e. the lower 95% CIs are all above 90%.

The **second primary objective** was to demonstrate immunological non-inferiority of the 3-dose MenACWY series to the 4-dose series, as measured by percentage of subjects with hSBA ≥ 1:8 against N meningitidis serogroups C, W and Y at 13 months of age.

Noninferiority would be established if the lower limit of the 2-sided 95% CI for the difference in percentage of subjects with hSBA ≥ 1:8 against N meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, was greater than -10%. Immune responses to serogroup A were not included in the noninferiority assessment.

One month after the 3- or 4-dose vaccination series (ie, at 13 months of age), the percentages of subjects with hSBA ≥ 1:8 against serogroups C, W, and Y were similar for the ACWY4 and ACWY3 groups (C: 99% vs 95%, respectively, W: 99% each, Y: 99% vs 100%). The lower limits of the 2-sided 95% CI for the difference in percentages were -8%, -3% and -2% for serogroups C, W and Y, respectively, greater than -10% for all 3 serogroups, meeting the prespecified criteria.

Table 11.4.1-2: Noninferiority of a 3-Dose Vaccination Schedule to a 4-Dose Vaccination Schedule of MenACWY as Measured by Number (%) of Subjects with hSBA ≥1:8 (95%CI) Against *N meningitidis* Serogroups C, W, and Y at 13 Months of Age – Toddler ACWY PPS

Serogroup	Number (%) of Subjects with hSBA ≥1:8		Vaccine Group Difference	Noninferiority criterion met
	ACWY3	ACWY4	ACWY3 – ACWY4	
A	N=146 129 (88%) (82%-93%)	N=141 135 (96%) (91%-98%)	-7% (-14%,-1%)	NA[a]
C	N=160 152 (95%) (90%-98%)	N=152 150 (99%) (95%-100%)	-4% (-8%,0%)	Yes
W	N=153 152 (99%) (96%-100%)	N=138 137 (99%) (96%-100%)	0% (-3%,3%)	Yes
Y	N=154 154 (100%) (98%-100%)	N=146 145 (99%) (96%-100%)	1% (-2%,4%)	Yes

Assessor's comment:

This primary endpoint was met: based upon the current chosen non-inferiority margin of -10% the three serogroups C, W and Y were non-inferior in the 3 dose group compared to the 4 dose group. No criterion was set for serotype A. However the criterion set for C, W and Y i.e. -10% was not met by serotype A.

Although the drop out rate was much higher than anticipated the primary endpoints of the study were met.

Effect of concomitant administration of 2 or 3 infant doses of MenACWY on immune responses to PCV-13 antigens

At 7 months of age, 93.7% to 100% of subjects in ACWY3, 92.6% to 100% in ACWY4 and 94.2% to 100% in Routine group had IgG concentrations ≥0.35 µg/mL for all 8 Family 1 serotypes ((1, 4, 6A, 7F, 14, 18C, 19A, 19F). For Family 2 (9V, 23F, 5, 6B and 3), 79.3% to 93% of subjects in ACWY3, 87.6% to 96.3% in ACWY4 group and 82.3% to 92.4% in the Routine group had IgG concentrations ≥ 0.35 µg/mL

The lower limit of the 2-sided 95% CIs around the vaccine group differences, for the ACWY3 group versus the Routine group, was greater than -10% for all serotypes. The prespecified noninferiority criterion was hence met for the ACWY3 group for all 8 serotypes in Family 1. Noninferiority was demonstrated for 2 serotypes of family 2 (9V and 23F). The lower limit of the 2-sided 95% CI for the group difference for serotype 5 was lower than -10%, resulting in sequential noninferiority testing not being done for other serotypes (6B and 3).

Noninferiority was demonstrated in the ACWY4 group for 7 out of 8 Family 1 serotypes, as the lower limit of the 2-sided 95% CI for the group difference for serotype 19A was lower than -10%. Testing was stopped in Family 2 as noninferiority was not demonstrated for all Family 1 serotypes.

Overall, after the infant vaccination series, the lower limit of the 2-sided 95% CI for the group difference of percentage of subjects with anti-pneumococcal antibodies ≥ 0.35 µg/mL was greater than the prespecified margin of -10% for 11 of 13 serotypes in ACWY3 group (except serotypes 3 and 5) and for 12 of 13 serotypes in group ACWY4 (except serotype 19A).

Table 2.5.4.4-2 Number (%) of Subjects with IgG Antibody Concentration ≥ 0.35 µg/mL Against PCV-13 (Family 1) at 7 Months of Age Following Concomitant Administration of 2 or 3 Doses of MenACWY with PCV-13 – Infant PCV PPS

Serotypes	Number (%) of Subjects (95% CI)			Vaccine Group Difference			
	ACWY3	ACWY4	Routine	ACWY3 – Routine	NI criterion met	ACWY4 – Routine	NI criterion met
1	N=159 149 (93.7%) (88.7%-96.9%)	N=136 136 (100%) (97.3%-100%)	N=156 147 (94.2%) (89.3%-97.3%)	-0.5% (-6.1%,5%)	Yes	5.8% (3%,10.5%)	Yes
4	N=160 151 (94.4%) (89.6%-97.4%)	N=137 133 (97.1%) (92.7%-99.2%)	N=157 152 (96.8%) (92.7%-99%)	-2.4% (-7.5%,2.3%)	Yes	0.3% (-4.4%,4.7%)	Yes
6A	N=159 156 (98.1%) (94.6%-99.6%)	N=136 135 (99.3%) (96%-100%)	N=156 153 (98.1%) (94.5%-99.6%)	0.04% (-3.7%,3.8%)	Yes	1.2% (-2.2%,4.8%)	Yes
7F	N=158 158 (100%) (97.7%-100%)	N=136 136 (100%) (97.3%-100%)	N=156 155 (99.4%) (96.5%-100%)	0.6% (-1.7%,3.5%)	Yes	0.6% (-2.1%,3.5%)	Yes
14	N=158 157 (99.4%) (96.5%-100%)	N=136 136 (100%) (97.3%-100%)	N=158 154 (97.5%) (93.6%-99.3%)	1.9% (-1.2%,5.7%)	Yes	2.5% (-0.2%,6.3%)	Yes
18C	N=158 154 (97.5%) (93.6%-99.3%)	N=136 133 (97.8%) (93.7%-99.5%)	N=157 157 (100%) (97.7%-100%)	-2.5% (-6.3%,0.2%)	Yes	-2.2% (-6.2%,0.2%)	Yes
19A	N=158 151 (95.6%) (91.1%-98.2%)	N=135 125 (92.6%) (86.8%-96.4%)	N=156 153 (98.1%) (94.5%-99.6%)	-2.5% (-7.1%,1.6%)	Yes	-5.5% (-11.3%,-0.9%)	No
19F	N=159 159 (100%) (97.7%-100%)	N=136 136 (100%) (97.3%-100%)	N=158 157 (99.4%) (96.5%-100%)	0.6% (-1.7%,3.4%)	Yes	0.6% (-2.1%,3.4%)	Yes

Table 2.5.4.4-3 Number (%) of Subjects with IgG Antibody Concentration ≥ 0.35 µg/mL Against PCV-13 (Family 2) at 7 Months of Age Following Concomitant Administration of 2 or 3 Doses of MenACWY with PCV-13 – Infa PCV PPS

Serotypes	Number (%) of Subjects (95% CI)			Vaccine Group Difference			
	ACWY3	ACWY4	Routine	ACWY3 - Routine	NI criterion met	ACWY4 - Routine	NI criterion met
9V	N=159 142 (89.3%) (83.4%-93.6%)	N=136 131 (96.3%) (91.6%-98.8%)	N=157 145 (92.4%) (87%-96%)	-3.1% (-9.7%,3.4%)	Yes	4% (-1.5%,9.7%)	-[b]
23F	N=158 147 (93%) (87.9%-96.5%)	N=136 130 (95.6%) (90.6%-98.4%)	N=158 144 (91.1%) (85.6%-95.1%)	1.9% (-4.2%,8.2%)	Yes	4.5% (-1.4%,10.5%)	-[b]
5	N=156 131 (84%) (77.3%-89.4%)	N=133 124 (93.2%) (87.5%-96.9%)	N=154 136 (88.3%) (82.2%-92.9%)	-4.3% (-12.1%,3.4%)	No	4.9% (-1.9%,11.8%)	-[b]
6B	N=160 135 (84.4%) (77.8%-89.6%)	N=137 130 (94.9%) (89.8%-97.9%)	N=157 133 (84.7%) (78.1%-90%)	-0.3% (-8.4%,7.7%)	-[a]	10.2% (3.4%,17.2%)	-[b]
3	N=150 119 (79.3%) (72%-85.5%)	N=129 113 (87.6%) (80.6%-92.7%)	N=147 121 (82.3%) (75.2%-88.1%)	-3% (-11.9%,6%)	-[a]	5.3% (-3.3%,13.7%)	-[b]

Abbreviations: CI, confidence interval; NI, noninferiority; PPS, per protocol set.
[a] Testing was not performed due to previous serotype not having met the noninferiority criterion.
[b] Testing was not performed as noninferiority criterion was not met for all Family 1 serotypes.

At 13 months of age, the ACWY4 or ACWY3 group would be noninferior to the Routine group if the lower limit of the 2-sided 95% CI around the ratio of GMCs between the groups was greater than 0.5.

Noninferiority was demonstrated for all PCV-13 antigens in both ACWY4 and ACWY3 groups compared to the Routine group in terms of GMC ratio at month 13, 1 month after the toddler vaccination see table

Table 2-8: Noninferiority of Immune Response as Measured by Geometric Mean Concentrations (GMC) of Antibodies Against Pneumococcal Capsular Polysaccharides at 13 Months of Age Following Concomitant Administration of 3 or 4 Doses of MenACWY with PCV-13 – Toddler PCV PPS

Serotypes	Geometric Mean Concentration (95% CI)			Ratio of GMCs			
	ACWY3	ACWY4	Routine	ACWY3 : Routine	NI criterion met	ACWY4 : Routine	NI criterion met
1	N=145 2 (1.7-2.36)	N=116 2.16 (1.83-2.56)	N=123 2.14 (1.8-2.54)	0.94 (0.77-1.13)	Yes	1.02 (0.83-1.25)	Yes
4	N=146 1.19 (0.99-1.42)	N=117 1.45 (1.21-1.75)	N=123 1.53 (1.27-1.86)	0.77 (0.62-0.96)	Yes	0.94 (0.75-1.18)	Yes
6A	N=146 6.89 (5.78-8.21)	N=117 9.01 (7.52-11)	N=124 8.16 (6.77-9.82)	0.85 (0.69-1.04)	Yes	1.1 (0.88-1.37)	Yes
7F	N=147 3.96 (3.42-4.58)	N=116 5.14 (4.41-5.98)	N=123 4.95 (4.23-5.78)	0.8 (0.67-0.95)	Yes	1.04 (0.87-1.25)	Yes
14	N=147 7.76 (6.51-9.26)	N=117 7.86 (6.55-9.43)	N=124 7.54 (6.25-9.09)	1.03 (0.84-1.27)	Yes	1.04 (0.83-1.3)	Yes
18C	N=146 1.52 (1.28-1.8)	N=116 2.34 (1.96-2.79)	N=123 2.13 (1.78-2.55)	0.72 (0.59-0.87)	Yes	1.1 (0.89-1.36)	Yes
19A	N=144 5.51 (4.61-6.6)	N=114 5.23 (4.34-6.3)	N=124 5.39 (4.45-6.51)	1.02 (0.83-1.27)	Yes	0.97 (0.77-1.21)	Yes
19F	N=147 5.79 (4.9-6.85)	N=117 6.19 (5.21-7.35)	N=124 5.8 (4.86-6.92)	1 (0.82-1.22)	Yes	1.07 (0.86-1.32)	Yes
9V	N=146 1.37 (1.17-1.61)	N=117 1.85 (1.56-2.18)	N=123 1.73 (1.46-2.05)	0.79 (0.66-0.96)	Yes	1.07 (0.87-1.31)	Yes
23F	N=147 4.21 (3.49-5.09)	N=117 4.84 (3.98-5.89)	N=124 5.44 (4.45-6.65)	0.77 (0.62-0.97)	Yes	0.89 (0.7-1.13)	Yes
5	N=140 1.29 (1.11-1.49)	N=114 1.35 (1.16-1.57)	N=117 1.26 (1.08-1.48)	1.02 (0.86-1.21)	Yes	1.07 (0.89-1.29)	Yes
6B	N=147 4.29 (3.6-5.11)	N=117 5.23 (4.36-6.27)	N=124 5.04 (4.18-6.08)	0.85 (0.69-1.05)	Yes	1.04 (0.83-1.3)	Yes
3	N=139 0.88 (0.74-1.05)	N=113 0.97 (0.81-1.15)	N=118 0.77 (0.64-0.93)	1.14 (0.93-1.4)	Yes	1.25 (1.01-1.55)	Yes

Assessor's comment:

It should be noted that the study was not sufficiently powered to evaluate possible interaction at 13 months. Therefore no firm conclusion can be drawn.

Kinetics of immune response

Secondary objectives aimed to evaluate the kinetics of immune response to 2 or 3 doses of MenACWY given during the first 6 months of life. Immune responses against the 4 MenACWY serogroups, as measured by the percentages of subjects with hSBA ≥1:8 and hSBA GMTs was assessed at the following time points in the different groups:

- At baseline (2 months of age, the Routine group);
- 1 Month after 1st dose (3 months of age, ACWY4a group);
- 2 Months after 1st dose (4 months of age, ACWY4b group);
- 1 Month after 2nd dose (5 months of age, ACWY3 group);
- 3 Months after 2nd dose (7 months of age, ACWY3 group)
- 1 Month after 3rd dose (7 months of age, ACWY4 group).

At baseline (2 months of age), the percentages of subjects with hSBA ≥1:8 against serogroups A, C, W and Y were 4%, 9%, 20% and 7%, respectively.

At 1 month following the first vaccination (3 months of age), values for A, C, W and Y serogroups were 9%, 28%, 15% and 8%, respectively. At 2 months after the first vaccination (4 months of age), values against serogroups A, C, W and Y were 4%, 41%, 35% and 7%, respectively.

At 1 month following the second vaccination (5 months of age), percentages of subjects with hSBA ≥ 1:8 had increased against all 4 serogroups (A: 43%, C: 86%, W: 86%, Y: 67%).

At 1 month following the third infant vaccination (7 months of age, ACWY4 group), majority of subjects had hSBA ≥1:8 against the 4 serogroups (A: 84%, C: 95%, W: 99%, Y: 94%).

At 3 months following the second of 2 infant vaccinations (7 months of age, ACWY3 group), percentages had decreased compared to values at 1 month following the second vaccination ie, at 5 months of age (A: 23%, C: 71%, W: 74%, Y: 48%). Percentages were well above those in the Routine group at 7 months of age (≤1% for all serogroups).

Table 2.5.4.5-1 **Number (%) of Subjects With hSBA ≥ 1:8 (95% CI) Against *N meningitidis* Serogroups A, C, W, and Y at Baseline and 1 Month After the First, Second and Third Infant Dose of MenACWY – Infant ACWY PPS**

		Number (%) of Subjects with hSBA ≥ 1:8		
		ACWY3	ACWY4	Routine
A		N=169	N=157	N=171
	Baseline (2 months of age)	NA	NA	6 (4%) (1%-8%) N=166
	1 Month after 1st dose[a] (3 months of age)	NA	7 (9%) (4%-17%) N=82	NA
	1 Month after 2nd dose (5 months of age)	67 (43%) (35%-51%) N=157	NA	NA
	1 Month after 3rd dose (7 months of age)		132 (84%) (77%-89%)	1 (1%) (0.015%-3%)
C		N=185	N=176	N=187
	Baseline (2 months of age)	NA	NA	15 (9%) (5%-14%) N=167
	1 Month after 1st dose[a] (3 months of age)	NA	24 (28%) (19%-39%) N=85	NA
	1 Month after 2nd dose (5 months of age)	146 (86%) (80%-91%) N=170	NA	NA
	1 Month after 3rd dose (7 months of age)		167 (95%) (91%-98%)	1 (1%) (0.014%-3%)
W		N=179	N=162	N=181
	Baseline (2 months of age)	NA	NA	32 (20%) (14%-28%) N=157
	1 Month after 1st dose[a] (3 months of age)	NA	13 (15%) (9%-25%) N=84	NA
	1 Month after 2nd dose (5 months of age)	140 (86%) (80%-91%) N=162	NA	NA
	1 Month after 3rd dose (7 months of age)		160 (99%) (96%-100%)	1 (1%) (0.014%-3%)
Y		N=170	N=163	N=173
	Baseline (2 months of age)	NA	NA	11 (7%) (4%-13%) N=150
	1 Month after 1st dose[a] (3 months of age)	NA	6 (8%) (3%-16%) N=80	NA
	1 Month after 2nd dose (5 months of age)	102 (67%) (59%-75%) N=152	NA	NA
	1 Month after 3rd dose (7 months of age)		154 (94%) (90%-97%)	0 (0%) (0%-2%)

Assessor's comment:

There is a clear increase of response after every dose for serotype A and also for serotype Y, for serotype C and W the increase after the second dose is less pronounced. A small percentage of infants in the routine group appeared to have antibodies. This is unlikely to be due to vaccination as vaccination with a meningococcal vaccine was an exclusion criterion.

The percentages of subjects with hSBA ≥1:8 at 12 months of age following administration of either 2 (ACWY3) or 3 vaccinations (ACWY4) in the first year of life are given in Table 11.4.1-5.

Table 11.4.1-5: Number (%) of Subjects With hSBA ≥1:8 (95%CI) Against *N meningitidis* Serogroups A, C, W, and Y at 12 Months of Age Following 2 and 3 Infant Doses of MenACWY – Toddler ACWY PPS

	Number (%) of Subjects with hSBA ≥1:8			Vaccine group difference
	ACWY3	ACWY4	Routine	ACWY3 – ACWY4
	N=141	N=138	N=138	
A	8 (6%) (2%-11%)	30 (22%) (15%-30%)	1 (1%) (0.018%-4%)	-16% (-24%, -8%)
	N=149	N=147	N=151	
C	29 (19%) (13%-27%)	70 (48%) (39%-56%)	2 (1%) (0%-5%)	-28% (-38%, -18%)
	N=149	N=142	N=148	
W	49 (33%) (25%-41%)	94 (66%) (58%-74%)	4 (3%) (1%-7%)	-33% (-44%, -22%)
	N=145	N=139	N=144	
Y	36 (25%) (18%-33%)	77 (55%) (47%-64%)	2 (1%) (0%-5%)	-31% (-41%, -20%)

Assessor's comment:

At 12 months, before the booster dose, the percentages in the ACWY4 group are significantly higher compared to the ACWY3 group. A substantial proportion of subjects in both the ACWY3 and ACWY4 groups had no protective levels of bactericidal antibodies at that time. After the booster vaccination the proportion of subjects with protective levels of bactericidal antibodies increased in both groups significantly. To what extend the 2 and 3 dose primarily schedule has an impact on disease burden in the first year of life or persistence of vaccine efficacy after the first booster-dose needs to be established if a 2 or 3 dose primary schedule for infants from the age of 2 months would be proposed.

Study V59_36 showed that Menveo administered to infants concomitant with routine vaccines (DTaP-IPV-HiB and PCV13) at a 2+1 or 3+1 schedule (at 2, 4 and 12 or 2, 4, 6 and 12 MoA, respectively) induces a sufficient immune protection (hSBA > 1:8), with no interference with immune responses to PCV13 serotypes. This is considered important information to be included in the SmPC

The MAH is asked to submit a type II variation with respective changes to the SmPC section 4.2 and section 5.1. The SmPC should also include information on waning antibody levels between primary and booster doses at that age, particularly after a 2-dose primary series.

Safety results

Out of a total of 751 subjects enrolled in the study, 733 (98%) subjects were exposed to at least 1 study vaccination, and hence included in the exposed set. Postvaccination solicited data were provided by a total of 708 subjects (94%) comprising the solicited safety set.

Assessor's comment:

The percentage of subjects who dropped out per group and the reasons for dropping out were similar in the different groups. Percentage of subject dropping out due to an adverse event were overall <1% and in the different groups as follows; ACWY3 <1%, ACWY4a 0%, ACWY4b 2%, ACWY4 <1% routine <1%.

Solicited adverse events

The majority of subjects reported at least 1 solicited AE after the first vaccination (80% to 86%), with frequencies decreasing following the second and third infant vaccinations (70% to 79% and 66% to 70%). No reduction in rates was reported following the fourth (ie toddler) vaccination.

Local solicited adverse events

The most commonly occurring local AE across groups within a 7 day period following all 4 vaccinations was tenderness: 30% to 36% after first vaccination, 25% to 28% after second, 19% to 24% after third and 24% to 31% after the fourth vaccination.

Most of the local AEs were mild or moderate in nature. Severe tenderness was reported in a maximum of 6% of subjects following any vaccination, but did not continue beyond day 3 for most subjects.

Table 2.5.5.2-1 Percentage of Subjects With The Most Commonly Reported Any and Severe Solicited Local AEs Reported Between 6 Hours and Day 7 Following Each Vaccination – Solicited Safety Set

AEs	Number of Vaccination	Percentage of Most Commonly Reported Solicited Local AEs		
		ACWY3	ACWY4	Routine
Tenderness Any % (Severe %)[a]	1st	N=235 30% (3%)	N=239 36% (3%)	N=224 33% (3%)
	2nd	N=224 25% (1%)	N=218 25% (1%)	N=213 (28%) (<1%)
	3rd	N=201 24% (2%)	N=198 19% (0%)	N=192 22% (2%)
	4th	N=179 29% (1%)	N=180 24% (1%)	N=167 31% (1%)
Erythema Any % (Severe %)[b]	1st	N=234 9% (0%)	N=238 13% (0%)	N=224 16% (0%)
	2nd	N=224 11% (0%)	N=218 11% (0%)	N=213 20% (0%)
	3rd	N=201 17% (0%)	N=197 15% (0%)	N=192 18% (0%)
	4th	N=179 14% (0%)	N=180 15% (0%)	N=164 15% (0%)
Induration Any % (Severe %)[b]	1st	N=234 6% (<1%)	N=238 6% (0%)	N=224 14% (0%)
	2nd	N=224 8% (0%)	N=218 8% (0%)	N=211 20% (0%)
	3rd	N=201 17% (0%)	N=198 8% (0%)	N=192 15% (0%)
	4th	N=179 8% (0%)	N=180 6% (0%)	N=165 11% (0%)

Assessor's comment:

There was a tendency of decreasing frequency of tenderness after the second and third vaccination in all three groups. Overall the frequencies of the other solicited local adverse events remained roughly similar after the first, second, third and fourth vaccination.

Systemic solicited adverse events

The most commonly reported systemic AE following each vaccination was irritability (first vaccination: 46% to 54%, second vaccination: 41% to 47%, third vaccination: 36% to 39%, fourth vaccination: 36% to 43%). The second most commonly reported systemic AE was sleepiness (first vaccination: 47% to 49%, second vaccination: 34% to 42%, third vaccination: 30% to 33%, fourth vaccination: 27% to 35%). Similar to local AEs, a sequential decrease in percentages of subjects with systemic AEs was seen following each of the first 3 vaccinations.

Fever, defined as body temperature ≥38.0 ºC, was reported in 4% to 5% of subjects following the first vaccination, 7% to 9% following the second, 6% to 10% following the third, and 8% to 11% following the fourth vaccination. Body temperatures ≥40 ºC were reported by 2 subjects in the ACWY4 group

following the third and fourth vaccination, and 1 subject in the ACWY3 group after the fourth vaccination.

At least one severe solicited was reported by 18% in ACWY3 group, 21% in the ACWY4 group and18% in the routine group. As the occurrences of severe systemic AEs were similar across groups, no additional testing or inter-group comparisons were performed.

Assessor's comment:

Out of 751 enrolled subjects, 733 (98%) were exposed to at least 1 study vaccination and provided postvaccination unsolicited safety data.

In accordance with the specified safety objectives of Study V59_36 the MAH is requested to provide **the percentage of subjects presenting, during days 1-7 after any vaccination, at least one severe systemic reaction, after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone** and comment on differences observed (if applicable).

Table 2.5.5.2-2 Percentage of Subjects With The Most Commonly Reported Any and Severe Solicited Systemic AEs Reported Between 6 Hours and Day 7 Following the First Through to Fourth Vaccination – Solicited Safety Set

		Percentage of Most Commonly Reported Solicited Systemic AEs		
AEs	Number of vaccination	ACWY 3	ACWY 4	Routine
Irritability Any % (Severe %)	1st	N=235 52% (3%)	N=238 54% (5%)	N=224 46 (2%)
	2nd	N=224 47% (3%)	N=218 42% (4%)	N=213 41% (3%)
	3rd	N=202 39% (3%)	N=198 36% (3%)	N=191 38% (3%)
	4th	N=179 43% (2%)	N=180 36% (2%)	N=167 36% (2%)
Sleepiness Any % (Severe %)	1st	N=234 47% (3%)	N=238 48% (3%)	N=224 49% (4%)
	2nd	N=224 42% (3%)	N=218 34% (3%)	N=213 38% (3%)
	3rd	N=202 33% (2%)	N=198 30% (1%)	N=192 32% (2%)
	4th	N=179 35% (2%)	N=180 27% (0%)	N=166 31% (1%)

Assessor's comment:

There was a tendency of decreasing frequencies of systemic solicited adverse events with the second, third and fourth vaccination in all three groups.

Analgesic and/or antipyretic medication was administered to 67% to 72% of subjects after any vaccination.

Unsolicited adverse events

Unsolicited AEs after any vaccination were reported by the majority of subjects (87% to 90%) across groups, with 4% to 13% considered possibly related to study vaccines.

Unsolicited AEs with onset within 28 days after any study vaccination were reported by 70% to 75% of subjects across groups. Unsolicited AEs with onset within 28 days after any study vaccination that were considered possibly or probably related to the administered study vaccinations were reported in 3% to 13% of subjects across groups. The most commonly reported possibly related unsolicited AEs belonged to the SOC 'general disorders and administration site conditions' (3% to 10%).

See table below:

Table 12.2.3-4: Number (%) of Subjects With Any and at Least Possibly Related Unsolicited Adverse Events Reported Within 28 Days After Any Vaccination, by System Organ Class – Unsolicited Safety Set

System Organ Class	Number (%) of Subjects					
	All			At Least Possibly Related		
	ACWY3 N=242	ACWY4 N=252	Routine N=239	ACWY3 N=242	ACWY4 N=252	Routine N=239
Any adverse event	182 (75%)	179 (71%)	168 (70%)	24 (10%)	32 (13%)	8 (3%)
Blood and lymphatic system disorder	1 (<1%)	6 (2%)	4 (2%)	0	0	0
Congenital and family/genetic disorder	2 (1%)	6 (2%)	5 (2%)	0	0	0
Ear and labyrinth disorders	3 (1%)	4 (2%)	4 (2%)	0	0	0
Eye disorders	22 (9%)	14 (6%)	16 (7%)	0	0	0
Gastrointestinal disorders	40 (17%)	48 (19%)	52 (22%)	2 (1%)	1 (<1%)	2 (1%)
General disorders and administration site conditions	47 (19%)	51 (20%)	39 (16%)	19 (8%)	24 (10%)	6 (3%)
Immune system disorders	2 (1%)	3 (1%)	1 (<1%)	0	0	0
Infections and infestations	118 (49%)	123 (49%)	124 (52%)	3 (1%)	1 (<1%)	0
Injury and poisoning	4 (2%)	8 (3%)	5 (2%)	0	1 (<1%)	0
Investigations	3 (1%)	0	3 (1%)	0	0	0
Metabolism and nutrition disorders	4 (2%)	10 (4%)	5 (2%)	0	0	0
Musculoskeletal, connnective tissue and bone disorder	4 (2%)	3 (1%)	3 (1%)	0	0	0
Neoplasms benign/ malignant (including cysts/polyps)	1 (<1%)	1 (<1%)	2 (1%)	0	0	0
Nervous system disorders	8 (3%)	8 (3%)	5 (2%)	3 (1%)	2 (1%)	0
Pregnancy, puerperium & prenatal condition	1 (<1%)	0	0	0	0	0
Psychiatric disorders	6 (2%)	7 (3%)	4 (2%)	3 (1%)	4 (2%)	0
Renal and urinary disorders	0	1 (<1%)	0	0	0	0
Reproductive system and breast disorders	6 (2%)	4 (2%)	6 (3%)	0	0	0
Respiratory, thoracic and mediastinal disorders	38 (16%)	43 (17%)	38 (16%)	0	4 (2%)	1 (<1%)
Skin and subcutaneous tissue disorders	36 (15%)	40 (16%)	52 (22%)	0	1 (<1%)	1 (<1%)
Surgical and medical procedures	1 (<1%)	1 (<1%)	0	0	0	0

Assessor's comment:

The percentage of subjects with a possibly or probably related unsolicited adverse event was numerically lower in the routine group: i.e. overall 4% versus 10% and 13% in the ACWY3 and ACWY4 group respectively. For onset within 28 days these percentages were respectively: 3%, 10% and 13%. This seems to be driven by general disorders and administration site conditions.

The assessor is of the opinion that the observed higher percentage of possibly or probably related unsolicited adverse events in the ACWY groups does not have clinical significant relevance. The number of antigens in the AWCY groups is higher than in the routine group. For the ACWY4 group, each "vaccination" included MenACWY and concomitant routine vaccines including PCV-13. For the ACWY3 group, the first, second and fourth "vaccination" included MenACWY and routine vaccines while the third "vaccination" included routine vaccines only. For the Routine group, each "vaccination" included routine vaccines only.

Table 2-12: Overview of Subjects With Unsolicited Adverse Events After Any Vaccination – Unsolicited Safety Set

	Number (%) of Subjects		
	ACWY3 N=242	ACWY4 N=252	Routine N=239
Any unsolicited AEs	219 (90%)	220 (87%)	209 (87%)
Possibly or probably related AEs	24 (10%)	32 (13%)	10 (4%)
AE leading to withdrawal	1 (<1%)	2 (1%)	2 (1%)[a]
Medically attended AEs	210 (87%)	211 (84%)	198 (83%)
SAEs	11 (5%)	19 (8%)	11 (5%)
Possibly or probably related SAEs	0	0	0
Death	0	0	1 (<1%)

The most commonly reported SOC of AEs across groups was 'infections and infestations', reported by 49% to 52% of subjects. This was followed by 'gastrointestinal disorders' (17% to 22%), 'skin and subcutaneous tissue disorders' (15% to 22%) and 'respiratory, thoracic and mediastinal disorders' (16% to 17%).

The most commonly reported possibly related unsolicited AEs by preferred term were pyrexia (2% of subjects in ACWY3, 3% in ACWY4) and injection site induration (2% in each group).

A total of 5 subjects had AEs that led to withdrawal from the study: Krabbe's disease (1 subject in ACWY3 group), convulsion (2 subjects in the ACWY4 group), and in the Routine group 1 subject had bronchiolitis, and another had cardiopulmonary arrest and hypoxic-ischemic encephalopathy.

During the course of the study, 41 subjects experienced a total of 53 SAEs: The rates of SAEs across the groups were: 19 subjects in ACWY4, 11 subjects in ACWY3 and 11 subjects in the Routine group. None of the reported SAEs was considered to be possibly or probably related to the study vaccinations. All except 6 subjects had recovered at study termination. One subject in the Routine group died during the study period, due to an SAE of anoxic encephalopathy (hypoxic-ischemic encephalopathy) 48 days after the first vaccination visit and an SAE of cardiopulmonary arrest. Neither of these SAEs was considered related to the administered study vaccination.

Assessor's comment:

It is agreed that the SAEs were considered not possibly or probably related to vaccination.

The reactogenicity profiles for local and systemic adverse events were similar between the three groups.

There were no clinically meaningful differences in unsolicited adverse events between the three groups.

The number of systemic severe reactions during 1-7 days is presented for the solicited systemic adverse reactions, while in the first safety objective all systemic severe reactions are mentioned. The MAH should provide these data.

The safety results are in line with the currently known safety profile and no new safety signals were identified.

2.3.3. Discussion on clinical aspects

The 2 primary objectives of this study were achieved. There was a sufficient immune response following four doses of Men ACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥ 1:8. And noninferiority of two MenACWY primary infant doses followed by a toddler boosterdose (doses at 2, 4 and 12 months of age) to three primary infant doses followed by a toddler dose (doses at 2, 4, 6 and 12 months of age) was demonstrated for serotypes C, W and Y.

Within the design of the study there was not accounted for serotype A. The MAH should comment why this was not done.

With regard to the secondary objectives, concomitant administration of MenACWY vaccine to routine vaccines demonstrated noninferiority of the immune response to all 13 PCV antigens at 13 months of age. However, it should be noted that the study was not sufficiently powered for this. Therefore no firm conclusion with regard to this can be drawn.

In addition the kinetics of the immune response up to 12 months are described. At 12 months, before the boosterdose a substantial proportion of subjects in both groups (ACWY3 and ACWY4) had no protective levels of bactericidal antibodies. The response percentages in the ACWY3 group were significantly lower compared to the ACWY4 group. The possible impact of this finding for disease burden during the first year of life and the persistence of vaccine efficacy following a single boosterdose should be clarified before vaccine use in this age category is considered.

There were no clinically meaningful differences in unsolicited adverse events between the three groups.

The number of systemic severe reactions during 1-7 days is presented for the solicited systemic adverse reactions, while in the first safety objective all systemic severe reactions are mentioned. The MAH should provide these data.

The safety results are in line with the currently known safety profile and no new safety signals were identified.

In conclusion study V59_36 showed that Menveo administered to infants concomitant with routine vaccines (DTaP-IPV-HiB and PCV13) at a 2+1 or 3+1 schedule (at 2, 4 and 12 or 2, 4, 6 and 12 MoA,

respectively) induces a sufficient immune protection (hSBA > 1:8), with no interference with immune responses to PCV13 serotypes. This is considered important information to be included in the SmPC.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Study V59_36 showed that Menveo administered to infants concomitant with routine vaccines (DTaP-IPV-HiB and PCV13) at a 2+1 or 3+1 schedule (at 2, 4 and 12 or 2, 4, 6 and 12 MoA, respectively) induces a sufficient immune protection (hSBA > 1:8), with no interference with immune responses to PCV13 serotypes. The immunogenicity and safety results are in line with what is described in the SmPC, therefore there is no need to update the SmPC based upon this study.

The benefit-risk balance of Menveo remains positive.

Recommendation

☒ **Fulfilled**

☐ **Not fulfilled**

4. Additional clarifications requested

1. The second primary objective accounted for serotypes C, W and Y, within the design of the study there was not accounted for serotype A. The MAH should comment why this was not done.
2. In accordance with the specified safety objectives of Study V59_36 the MAH is requested to provide the percentage of subjects presenting, during days 1-7 after any vaccination, at least one severe systemic reaction, after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone and comment on differences observed (if applicable).

5. Assessment of the responses to the request for clarification

Question 1

The second primary objective accounted for serotypes C, W and Y, within the design of the study there was not accounted for serotype A. The MAH should comment why this was not done.

MAH Response

The second primary objective of study V59_36 evaluated non-inferiority of the immune response to serogroups C, W and Y only. As this study was not initially powered for demonstration of non-inferiority, sample size was not sufficient for non-inferiority testing against serogroup A. Furthermore, serogroup A meningococcal disease is rare in Europe and the Americas (Cohn et al, Jafri et al); these analyses are of limited clinical and public health relevance in these regions. Nevertheless, we did

observe that 88% of participants achieved hSBA titers ≥8 against serogroup A one month following completion of a 3- dose MenACWY-CRM vaccination series, exceeding the 85% sufficiency criterion specified in the first primary study objective.

Cohn AC, MacNeil JR, Harrison LH, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. Clin Infect Dis. 2010;50:184-191. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr. 2013;11:17.

Rapporteurs comment:

Serotype A is rare in Europe and Americas, however it is endemic in Africa. For subjects travelling to Africa it could have been relevant information. It is agreed that with the 3-dose the primary endpoint criterion was met for serotype A i.e. the lower limit of the 95% CI was greater than 80% (it was 82%). The study was not powered for serotype A for the second primary objective; this objective was not met for serotype A. i.e the chosen non-inferiority margin of -10% was not met (it was -14% for serotype A). Although the vision of the MAH is not completely agreed the MAH sufficiently commented why the study was not powered for serotype A.

Point resolved.

Question 2

In accordance with the specified safety objectives of Study V59_36 the MAH is requested to provide the percentage of subjects presenting, during days 1-7 after any vaccination, at least one severe systemic reaction, after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone and comment on differences observed (if applicable).

MAH Response

At least 1 severe solicited systemic AE following any vaccination was reported by a similar percentage of subjects who were administered MenACWY with concomitant vaccines (18% in ACWY3 and 21% in ACWY4 groups) compared with subjects who received routine concomitant vaccinations alone (18% in Routine group) (Table 1). As the occurrences of severe systemic AEs were similar across groups, no additional testing or inter-group comparisons were performed.

Table 1: Overview of Subjects With at Least 1 Severe Solicited Systemic Adverse Event Reported From 6 Hours Through Day 7 After Any Vaccination – Solicited Safety Set

	Number (%) of Subjects		
	ACWY3	ACWY4	Routine
	N=238	N=240	N=230
Severe systemic AE	44 (18%)	50 (21%)	42 (18%)

Source: V59_36 CSR Table 14.3.1.1.1.1.1. Abbreviation: AE, adverse event.
Note: The most severe AE across all vaccinations is reported here. Severe systemic AEs include change in eating habits, diarrhea, irritability, persistent crying, sleepiness, vomiting, and rash with severe grading, and fever ≥40°C.

Rapporteurs comment:

The requested information is provided. It is agreed with the MAH that the occurrence of severe systemic AEs can be considered similar.

Point resolved.

Question 3

Study V59_36 showed that Menveo administered to infants concomitant with routine vaccines (DTaP-IPV-HiB and PCV13) at a 2+1 or 3+1 schedule (at 2, 4 and 12 or 2, 4, 6 and 12 MoA, respectively) induces a sufficient immune protection (hSBA > 1:8), with no interference with immune responses to PCV13 serotypes. This is considered important information to be included in the SmPC The MAH is asked to submit a type II variation with respective changes to the SmPC section 4.2 and section 5.1. The SmPC should also include information on waning antibody levels between primary and booster doses at that age, particularly after a 2-dose primary series.

MAH Response

Menveo is currently licensed for active immunisation of children (from 2 years of age), adolescents and adults and the current SmPC, in section 5.1, already includes information relative to the use in children 2 to 23 months of age. All that considered, the Company believes that adding more information on the use in children 2 to 23 months of age - for a product where the use in this age group is not approved - does not provide further value but rather might increase the risk of off-label use.

Rapporteurs comment:

In the recent type II variation number 18(April 2013) was evaluated whether the immunogenicity and safety of Menveo in infants 2 -23 months was considered sufficient to extend the indication and recommend a posology in this age group. In this variation several phase II and three phase three studies were submitted. Also co-administration with pneumococcal vaccines was evaluated *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-Variation/human/001095/WC500144651.pdf*.As the results of study V59_36 are in line with the results found in the studies submitted in the type II variation 18 (April 2013), it is agreed with the MAH that the current information in the SmPC is considered sufficient.

Point resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance