London, 22 February 2018
EMA/CHMP/64653/2018
Committee for Medicinal Products for Human Use (CHMP)

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

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/001095/P46/035

Note

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

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1. Introduction

On 5 December 2017, the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study V72_56 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In the study two vaccines were evaluated: GSK Biologicals' MenACWY - CRM197 (Menveo, further referred to as MenACWY in this document) conjugated vaccine, and GSK Biologicals' rMenB vaccine (Bexsero).

The drug product presentation for MenACWY consisted of one vial containing the lyophilized MenA conjugate component and one vial or syringe containing the liquid MenCWY conjugate component. The vaccine ready for IM was obtained by reconstitution of the lyophilized MenA with the liquid MenCWY component to administer the final quantity / dose of 0.5 mL of the reconstituted vaccine, which contained 10 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg Men Y.

rMenB was supplied in a prefilled syringe (0.5 mL volume) administered by intramuscular injection (IM); each dose contained 50 µg of each of the following *N meningitidis* purified antigens (961c, 936-741, 287-953), 25 µg of outer membrane vesicle (OMV) from *N meningitidis* strain NZ98/254, adsorbed in 1.5 mg of aluminium hydroxide.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study V72_56: A Phase 3b, Open-Label, Randomized, Multicenter Study to Assess the Safety and Immunogenicity of Meningococcal group B Vaccine When Administered Concomitantly with MenACWY Conjugate Vaccine to Healthy Infants

2.3.2. Clinical study

V72_56

Description

This was a phase 3 multicentre open label randomised controlled trial aiming to assess the safety and immunogenicity of rMenB+OMV NZ and MenACWY when concomitantly administered compared to

either alone in healthy infants at 3, 5, 7 and 13 months of age. The study was conducted at 7 centres in Mexico (4) and Argentina (3), from June 2017 to October 2016.

Methods

Objectives

Primary objective:

To assess immunological noninferiority of rMenB+OMV NZ and MenACWY when concomitantly administered compared to either alone in healthy infants at 3, 5, 7 and 13 months of age, as measured by the ratio of hSBA geometric mean titers (GMTs) against each of the serogroup B indicator strains (for rMenB+OMV NZ) and serogroups A, C, W-135 and Y (for MenACWY) at one month after the 4th vaccination.

Noninferiority was to be concluded if, at one month following the 4th vaccination, the lower limits of the 2-sided 95% confidence intervals (95% CIs) for the **between-group ratios of GMTs** (rMenB+OMV NZ + MenACWY versus rMenB+OMV NZ, and rMenB+OMV NZ + MenACWY versus MenACWY) were **>0.5** for all serogroup B indicator strains and all serogroups A, C, W-135 and Y.

Secondary Objectives:

To assess the immune response of rMenB+OMV NZ and MenACWY when concomitantly administered compared to either alone in healthy infants at 3, 5, 7 and 13 months of age.

• at 1 month after the 4th vaccination

• at 1 month after the 3rd vaccination

• at 6 months after the 3rd vaccination

Safety Objective:

To assess the safety and tolerability of rMenB+OMV NZ and MenACWY when concomitantly administered, compared to either alone, in infants at 3, 5, 7 and 13 months of age.

Study design

Subjects were to be randomized to one of the three treatment arms in a 1:1:1 ratio to receive at 3, 5, 7 and 13 months of age:

• Vaccine Group rMenB+ACWY: rMenB vaccine given concomitantly with MenACWY (referred to as Group A in protocol),

• Vaccine Group rMenB: rMenB vaccine alone (referred to as Group B in protocol),

• Vaccine Group MenACWY: MenACWY vaccine alone (referred to as Group C in protocol).

Table 1 Overview of study design

Study Groups	Visit 1/ Study Day 1	Visit 2/ Study Day 61	Visit 3/ Study Day 121	Visit 4/ Study Day 151	Visit 7/ Study Day 301	Visit 8/ Study Day 331
rMenB+ACWY	Blood draw; Vaccination: rMenB; MenACWY	Vaccination: rMenB; MenACWY	Vaccination: rMenB; MenACWY	Blood draw	Blood draw; Vaccination: rMenB; MenACWY	Blood draw
rMenB	Blood draw; Vaccination: rMenB	Vaccination: rMenB	Vaccination: rMenB	Blood draw	Blood draw; Vaccination: rMenB	Blood draw
MenACWY	Blood draw; Vaccination: MenACWY	Vaccination: MenACWY	Vaccination: MenACWY	Blood draw	Blood draw; Vaccination: MenACWY	Blood draw

The study ran for approximately 11 months. Enrolled subjects were randomly assigned to study groups according to a randomization list. The randomization was stratified by centre, to ensure balance in the assignment to the 3 vaccine groups within each centre. This trial was designed as an open-label trial.

Study population /Sample size

Healthy infants aged 3 months (85-119 days, inclusive) were to be enrolled. In and exclusion criteria were in line with common criteria for vaccine trials in infants.

Subjects were to be randomized to one of the 3 vaccine groups in a 1:1:1 ratio with approximately 250 subjects per arm for an overall target enrollment of approximately 750 infants, 3 months of age at the enrollment. Assuming an approximate drop-out or not evaluable sample rate of 20%, a total sample size of 600 evaluable subjects was expected to be included in immunogenicity analyses (200 evaluable subjects per vaccine group). A sample size of 200 evaluable subjects per arm was to provide at least 86.9% overall power to demonstrate noninferiority of rMenB given together with MenACWY versus rMenB given alone and versus MenACWY given alone, at 1 month after the 4th vaccination, as measured by the lower limit of the 2-sided 95% CI of between-group ratio of human serum bactericidal assay (hSBA) GMTs (rMenB+ACWY versus rMenB alone, and rMenB+ACWY versus MenACWY alone) being greater than 0.5 (noninferiority margin) for all serogroups A, C, W-135 and Y, and 4 serogroup B indicator strains, ie, noninferiority must be simultaneously demonstrated for all 8 serogroups/strains.

CHMP comments

Of note, MenACWY is currently not licensed for this age group in Europe.

As non-inferiority had to be demonstrated for all serogroups/strains, multiplicity is no issue.

Treatments

Subjects either received MenACWY, given as four doses at 3, 5, 7 and 13 months of age on day 1, 61, 121 and 301; rMenB, given as four doses on the same days as MenACWY; or MenACWY together with rMenB according to the same schedule (see table 1).

Each dose of rMenB contained 50 µg of each of the following N meningitidis purified antigens (961c, 936-741, 287-953), 25 µg of outer membrane vesicle (OMV) from *N meningitidis* strain NZ98/254, adsorbed in 1.5 mg of aluminum hydroxide.

MenACWY comprised meningococcal serogroups A, C, W-135, and Y oligosaccharides that were each conjugated to the protein carrier CRM197. The vaccine ready for IM was obtained by reconstitution of the lyophilized MenA with the liquid MenCWY component to administer the final dose of 0.5 mL of the reconstituted vaccine, which contained 10 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg Men Y.

Outcomes/endpoints

Primary Immunogenicity Endpoints:

The **hSBA GMTs** against each of the serogroup B indicator strains (for rMenB) and serogroups A, C, W-135 and Y (for MenACWY) at 1 month after the 4th vaccination, and corresponding between-group ratios of GMTs for rMenB+ACWY vs. rMenB (serogroup B indicator strains), and rMenB+ACWY vs. MenACWY (serogroups A, C, W-135 and Y).

Secondary Immunogenicity Endpoints

The immune response to rMenB at day 1, day 51, day 301, and day 331 when administered alone and concomitantly with MenACWY (rMenB+ACWY vs. rMenB) was assessed by:

- **hSBA GMTs** against each of the serogroup B reference strains;
- the **% of subjects** with **hSBA ≥1:5** and subjects with **hSBA ≥1:8** against each of the serogroup B reference strains.

The immune response to MenACWY at day 1, day 51, day 301, and day 331 when administered alone and concomitantly with rMenB (rMenB+ACWY vs. MenACWY) was assessed by:

- **hSBA GMTs** against each of the serogroups A, C, W-135 and Y;
- the **% of subjects** with **hSBA ≥1:4** and subjects with **hSBA ≥1:8** against each of the serogroups A, C, W-135 and Y.

Additionally, the following were also to be assessed for each of the serogroup B strains and each of the serogroups A, C, W and Y:

- within-subject **geometric mean ratios** (GMRs) will be calculated for GMTs at one month after 4th vaccination (day 331) vs. pre 4th vaccination (day 301),

- the % of subjects with **4-fold increases** in hSBA titers at one month after 4th vaccination (day 331) vs. pre 4th vaccination (day 301).

CHMP comments

Considering the relevance of the different endpoints the discussion of secondary endpoints will focus on the response rates expressed as % of subjects with hSBA ≥1:8 (MenACWY) or ≥1:5 (rMenB). Other endpoints will only be reported if there are anomalies, i.e. they are not in line with primary outcomes (GMTs) or response rates. Of note, this AR applies to MenACWY, not rMenB.

Safety Endpoints

- The frequencies and percentages of subjects with solicited local and systemic AEs during the 7 days (including the day of vaccination) after day 1, 61, 121, and 301 for all vaccine groups.
- The frequencies and percentages of subjects with any other (unsolicited) AEs, AEs leading to withdrawal and medically attended AEs during the 7 days (including the day of vaccination) at day 1, 61, 121, and 301 for all vaccine groups.
- The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal and medically attended AEs throughout the study period.

Statistical Methods

Analysis populations

The primary immunogenicity analyses were based on the **per-protocol set**, which included all subjects who:

- correctly received the vaccine (ie, received the vaccine to which the subjects were randomized and at the scheduled time points).
- had no reportable Protocol Deviations (PDs) leading to exclusion as defined prior to creation of protected snapshot / analysis.
- were not excluded due to other reasons defined prior to creation of protected snapshot or analysis.

The secondary immunogenicity analyses on the **full analysis set** (FAS) which involved all subjects in the 'All Enrolled Set' (see below) who were randomized, received at least one study vaccination and provided evaluable immunogenicity data at respective vaccination visit.

The safety analyses were based on the **safety set**: All subjects in the 'all enrolled set' who received a study vaccination with solicited AE data for each of the vaccinations and/or with unsolicited AE data.

Summaries of demographic, baseline characteristics and individual subject listing were based on the **All Enrolled analysis set**: All screened subjects who provided informed consent and provided demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the trial, and received a subject identification number (ID).

Statistical analysis

To evaluate the immune response to vaccination with rMenB, the hSBA GMTs at 1 month after the 4th vaccination (day 331) were compared between vaccine groups rMenB+ACWY vs. rMenB. Noninferiority of vaccine group rMenB+ACWY to rMenB was determined if, at 1 month following the 4th vaccination (day 331), the lower limit of the 2-sided 95% CI for the between-group ratios of GMTs (rMenB+ACWY vs. rMenB) was >0.5 (noninferiority margin) for each of the 4 serogroup MenB indicator strains.

Similarly, the immune response to vaccination with MenACWY was evaluated by determining if rMenB+ACWY was noninferior to vaccine group MenACWY if the lower limit of the 2-sided 95% CI for the ratio of GMTs (rMenB+ACWY vs. MenACWY), at 1 month after the 4th vaccination (day 331) was >0.5 for each of the *N meningitidis* serogroups A, C, W-135 and Y.

Noninferiority was only to be concluded if all these 8 inferiority hypotheses were rejected, ie, the 8 hypotheses were co-primary.

Summary tables are provided for adjusted GMTs of each vaccine group and between group ratios of each vaccine group comparison. The 2-sided 95% CIs for each between group ratio of GMTs were constructed using the common estimate of error from an analysis of variance (ANOVA) with vaccine group and centre as factors in the model.

An interim analysis was performed to provide Health Authorities with preliminary information on the safety, tolerability and immune response of rMenB and MenACWY, in order to support the inclusion of these 2 vaccines in the national immunization programs. The interim analysis was applied to the subset of subjects who completed visit 4 (ie, 1 month post 3rd vaccination) at the time of interim data lock point. In this context, early terminated subjects were included in the interim analysis subset if they had the possibility of reaching visit 4 prior to the interim data lock point (ie, enrolled 150 days prior to the interim data lock point). The results are presented in an interim CSR (dated 02 OCT 2015).

The data or the results from this interim analysis were not used to make any decision on the continuation of this open label trial. This analysis was descriptive, with the relevant endpoints, analysis sets and methods aligning with the secondary objectives of this study. Therefore, the MAH concludes that no impact on the conduct or subsequent full data analysis of the trial was expected.

CHMP comments

It is not possible to exclude the possibility that the results of the interim analysis impacted further conduct of this trial. For example, it is not known whether the results of this interim analysis were communicated to investigators or other people involved in the conduct of the trial. Therefore an alpha correction would have been in place. Nonetheless if the results are in line with previous results, an alpha correction is not expected to impact the conclusions of the trial significantly.

Results

CHMP comments

A serious GCP compliance issue occurred during the study that led to exclusion of 1 study center – site 112, from the analysis set. Data collected for the study have not been used for any analysis of study data with the exception of the safety data which has been included in the study report.

The responsible Principal Investigator of site 112 failed to conduct the study according to ICH GCP including the provision of resources throughout the duration of the study and direct oversight of the study conduct, ie,:

- Randomization of subject without being eligible,

- Failure to provide adequate resources for the duration of the study (lack of meeting payment obligations to site staff),

- Failure to maintain access to the subject randomization and electronic data capture systems,

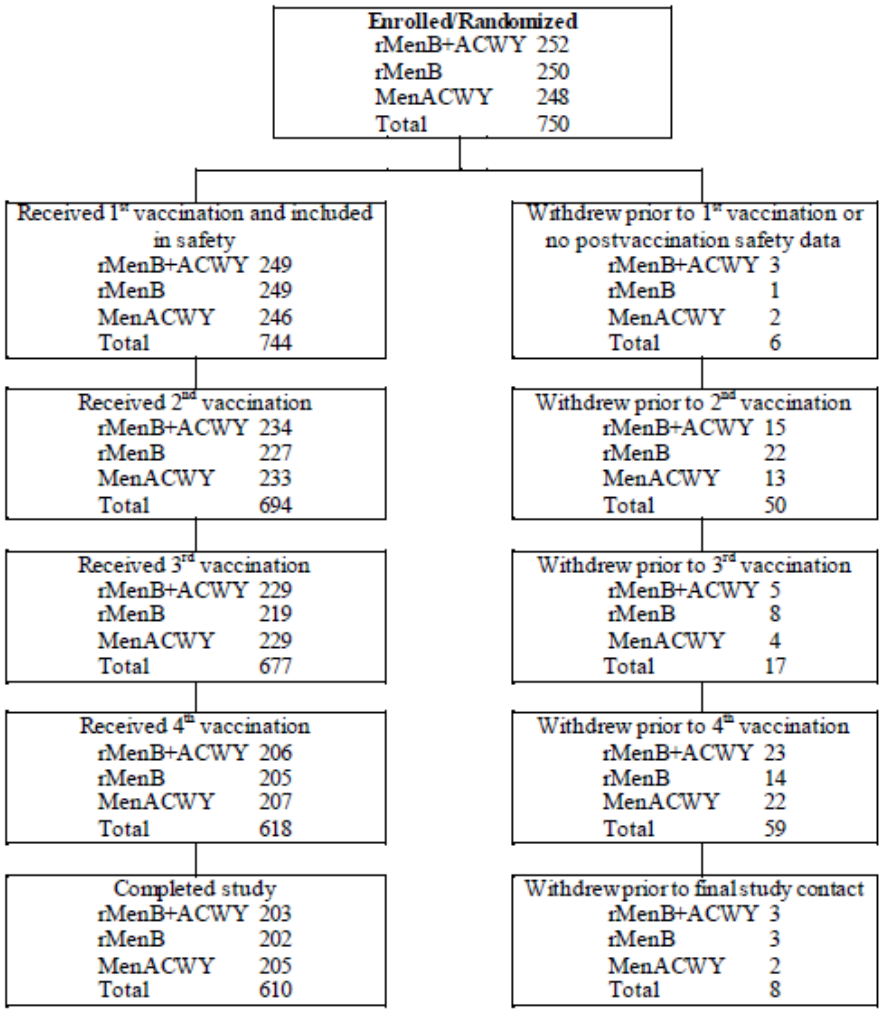
- General lack of understanding of GCP principles.

This serious GCP compliance issue resulted in the decision to terminate the participation of the investigator in this study. A total of 38 subjects were enrolled and affected.

Enrolled subjects completed the trial in order to complete the vaccination schedule. Intensified monitoring was implemented to ensure proper completion and documentation of study for already enrolled subjects. All 38 subjects enrolled were followed up for safety for solicited and non-solicited AEs for the duration as defined in the protocol.

Recruitment/ Number analysed

A total of 750 subjects were enrolled: 252 subjects in rMenB+ACWY group, 250 in rMenB group, and 248 in MenACWY group out of which 249 (99%) in rMenB+ACWY group, 249 (>99%) in rMenB group, and 246 (99%) in MenACWY group received the study vaccination.



Source: Table 14.1.1.1, Table 14.1.1.1.1, Table 14.1.1.2.

Figure 1 Subject Disposition Flow Chart

The numbers of premature withdrawals were balanced across the vaccine groups (17%-19%). The main reason for premature withdrawal was 'lost to follow up' with 25 (10%) in rMenB+ACWY group, 20 (8%) in rMenB group, and 13 (5%) in MenACWY group. Two (1%) subjects in rMenB group (due to pyrexia and anaemia, respectively) and 1 (<1%) subject in MenACWY group (due to atopic dermatitis) were withdrawn due to an AE. One subject in rMenB group was withdrawn from the study due to PD.

Table 2 Overview of datasets analysed for immunogenicity, as randomised, all enrolled set

	Number (%) of Subjects		
Group	rMenB+ACWY	rMenB	MenACWY
Enrolled set	252 (100%)	250 (100%)	248 (100%)
Exposed set	249 (99%)	249 (>99%)	246 (99%)
FAS secondary objective - 1 month post 3rd vaccination	215 (85%)	209 (84%)	214 (86%)
FAS secondary objective - pre 4th vaccination[a]	205 (81%)	204 (82%)	204 (82%)
FAS secondary objective - 1 month post 4th vaccination	199 (79%)	201 (80%)	204 (82%)
PPS primary and secondary objectives - 1 month post 4th vaccination	161 (64%)	163 (65%)	156 (63%)

Source: Table 14.1.1.1, Table 14.1.1.1.1.

Baseline data

The mean age of the subjects enrolled into the study was 104±10.72 days in rMenB+ACWY group, 101.4±10.57 days in rMenB group, and 102.7±10.9 days in MenACWY group.

Table 3 Demography and other baseline characteristics - all enrolled set

Vaccine Group	rMenB+ACWY	rMenB	MenACWY	Total
	N = 252	N = 250	N = 248	N = 750
Age (days)	104 ± 10.72	101.4 ± 10.57	102.7 ± 10.9	102.7 ± 10.77
Weight (kg)	6 ± 0.89	6 ± 0.83 N = 248	6 ± 0.8	6 ± 0.85 N = 748
Height (cm)	60.3 ± 3.65	60.2 ± 3.76 N = 248	60.3 ± 3.6 N = 247	60.2 ± 3.66 N = 747
Sex				
Male	132 (52%)	132 (53%)	109 (44%)	373 (50%)
Female	120 (48%)	118 (47%)	139 (56%)	377 (50%)
Race				
White	17 (7%)	20 (8%)	17 (7%)	54 (7%)
Other	235 (93%)	230 (92%)	231 (93%)	696 (93%)
Met entry criteria	252 (100%)	249 (>99%)	247 (>99%)	748 (>99%)

Source: Table 14.1.1.3.
Note: Categorical parameters: N (%); non-categorical parameter: mean ± standard deviation.

All demographic and baseline characteristics were balanced across the vaccine groups.

Efficacy results

Primary objective:

At one month after the 4th vaccination (day 331), the lower limits of the 2-sided 95% CIs for the between-group ratios of GMTs (rMenB+ACWY vs. rMenB, and rMenB+ACWY vs. MenACWY) were >0.5 for all serogroup B indicator strains and all serogroups A, C, W-135 and Y. Thus, rMenB and MenACWY when concomitantly administered (rMenB+ACWY), were noninferior to rMenB or MenACWY administered alone according to the predefined criteria.

Table 4 Geometric Mean hSBA Titres and Vaccine Group Ratios against N meningitidis serogroup B strains (for rMenB) and serogroups A,C,W,Y (for MenACWY) at 1 month post 4th vaccination – per protocol set month post 4th vaccination.

		Vaccine Group Ratios (95% CI)	
rMenB Strains	**rMenB+ACWY**	**rMenB**	**rMenB+ACWY:rMenB**
H44/76 (fHbp)	**N = 115**	**N = 153**	
1 month post 4th vaccination	92 (67-128)	104 (77-141)	0.89 (0.71-1.10)
5/99 (NadA)	**N = 113**	**N = 148**	
1 month post 4th vaccination	1850 (1122-3050)	1790 (1128-2842)	1.03 (0.74-1.45)
NZ98/254 (PorA P1.4)	**N = 148**	**N = 158**	
1 month post 4th vaccination	39 (29-53)	38 (28-52)	1.01 (0.82-1.25)
M10713 (NHBA)	**N = 131**	**N = 157**	
1 month post 4th vaccination	13 (7.82-21)	12 (7.72-20)	1.03 (0.77-1.40)
MenACWY Serogroups	**rMenB+ACWY**	**MenACWY**	**rMenB+ACWY:MenACWY**
Serogroup A	**N = 159**	**N = 156**	
1 month post 4th vaccination	409 (300-556)	165 (122-224)	2.48 (1.97-3.11)
Serogroup C	**N = 157**	**N = 149**	
1 month post 4th vaccination	452 (312-655)	421 (294-602)	1.07 (0.83-1.38)
Serogroup W	**N = 144**	**N = 143**	
1 month post 4th vaccination	721 (493-1053)	536 (370-776)	1.34 (1.04-1.74)
Serogroup Y	**N = 161**	**N = 156**	
1 month post 4th vaccination	410 (293-575)	391 (280-546)	1.05 (0.82-1.35)

Source: Table 14.2.1.5; Table 14.2.1.5.1.

The results in the FAS population were similar.

CHMP comments

It is noted that all 8 hypotheses were rejected and thus non-inferiority has been demonstrated. The response to combined administration of rMenB+MenACWY is higher for serogroup A (409 vs 165) and slightly better for serogroup W (721 vs 536). This has no impact on the use of the vaccine as such, as it would favour concomitant administration.

Secondary Objectives:

Percentages of subjects with hSBA ≥1:5 following administration of rMenB vaccine

Number (%) of Subjects With hSBA ≥1:5 and Vaccine Group Differences (rMenB+ACWY vs. rMenB Alone) Against Serogroup B Strains at Baseline, 1 Month Post 3rd, Pre 4th and 1 Month Post 4th Vaccination - Full Analysis Set

Strains	Number (%) of Subjects (95% CI)		Vaccine Group Differences (95% CI)
	rMenB+ACWY	rMenB	rMenB+ACWY - rMenB
H44/76 (fHbp)			
Baseline	0 (0)% (0%-2.3%) N=162	1 (1%) (0.01%-2.8%) N = 198	-1% (-2.8%-1.8%)
1 month post 3rd vaccination	149 (100%) (97.6%-100%) N = 149	199 (100%) (98.2%-100.0%) N=199	0% (-2.5%-1.9%)
Pre 4th vaccination[a]	96 (74%) (65.4%-81.2%) N = 130	142 (75%) (67.9%-80.7%) N = 190	-1% (-10.9%-8.7%)
1 month post 4th vaccination	141 (100%) (97.4%-100%) N = 141	187 (99%) (97.1%-99.99%) N = 188	1% (-2.1%-3%)
5/99 (NadA)			
Baseline	2 (1%) (0.15%-4.5%) N = 157	2 (1%) (0.13%-3.7%) N = 192	0% (-2.6%-3.6%)
1 month post 3rd vaccination	137 (100%) (97.3%-100%) N = 137	188 (100%) (98.1%-100.0%) N = 188	0% (-2.7%-2%)
Pre 4th vaccination[a]	139 (100%) (97.4%-100%) N = 139	184 (97%) (93.9%-99.1%) N = 189	3% (-0.08%-6%)
1 month post 4th vaccination	141 (99%) (95%-99.83%) N = 143	177 (97%) (93%-98.8%) N = 183	2% (-2.0%-5.8%)
NZ98/254 (PorA P1.4)			
Baseline	1 (1%) (0.01%-2.9%) N = 191	1 (0%) (0.01%-2.7%) N = 206	0% (-2.2%-2.5%)
1 month post 3rd vaccination	174 (96%) (92.2%-98.4%) N = 181	199 (97%) (93.7%-98.9%) N = 205	-1% (-5.2%-2.9%)
Pre 4th vaccination[a]	72 (42%) (34.2%-49.3%)	74 (36%) (29.7%-43.3%)	5% (-4.5%-15.2%)

	N = 173	N = 204	
1 month post 4th vaccination	181 (100%) (98.0%-100%) N = 181	192 (98%) (94.9%-99.4%) N = 196	2% (-0.06%-5.1%)
MI0713 (NHBA)			
Baseline	30 (16%) (11.4%-22.7%) N = 182	22 (11%) (6.9%-15.9%) N = 203	6% (-1.2%-12.8%)
1 month post 3rd vaccination	118 (70%) (62.7%-77%) N = 168	140 (68%) (61.1%-74.3%) N = 206	2% (-7.2%-11.6%)
Pre 4th vaccination[a]	50 (33%) (25.7%-41.2%) N = 151	61 (31%) (24.5%-37.7%) N = 198	2% (-7.5%-12.3%)
1 month post 4th vaccination	140 (87%) (80.8%-91.7%) N = 161	169 (87%) (81.6%-91.5%) N = 194	0% (-7.5%-6.9%)

Source: Table 14.2.1.2.2 (for baseline and 1 month post 3rd vaccination); Table 14.2.1.2.3 (for pre 4th vaccination); Table 14.2.1.2 (for 1 month post 4th vaccination).

The percentages of subjects with hSBA ≥1:5 at each of the timepoints were similar between the rMenB+ACWY and rMenB groups against each of the serogroup B strains as the 95% CI of the vaccine group differences included 0.

The responses following administration of rMenB vaccine considering the other secondary endpoints were in line with this. The hSBA GMTs at each of the timepoints were similar between the rMenB+ACWY and rMenB groups against each of the serogroup B strains as the 95% CI of the vaccine group ratios included 1. The vaccine group differences indicated similar percentages of subjects with at least 4-fold increase in titers at 1 month after the 4th vaccination (day 331) over pre 4th vaccination (day 301)in both vaccine groups at 1 month after the 4th vaccination.

Table 5 Number (%) of Subjects With hSBA ≥1:8 and Vaccine Group Differences (rMenB+ACWY vs. MenACWY Alone) Against ACWY Serogroups at Baseline, 1 Month Post 3rd, Pre 4th and 1 Month Post 4th Vaccination - Full Analysis Set

Serogroups	Number (%) of Subjects (95% CI)		Vaccine Group Differences (95% CI)
	rMenB+ACWY	MenACWY	rMenB+ACWY:MenACWY
Serogroup A			
Baseline	1 (0%) (0.01%-2.6%) N = 211	1 (0%) (0.01%-2.7%) N = 206	0% (-2.3%-2.2%)
1 month post 3rd vaccination	213 (100%) (97.4%-99.99%) N = 214	201 (96%) (92%-98%) N = 210	4% (1.2%-7.5%)
Pre 4th vaccination[a]	130 (65%) (58.0%-71.6%) N = 200	116 (58%) (50.8%-64.9%) N = 200	7% (-2.5%-16.4%)
1 month post 4th vaccination	197 (100%) (98.1%-100%) N = 197	195 (96%) (92.4%-98.3%) N = 203	4% (2%-7.6%)
Serogroup C			
Baseline	5 (2%) (0.8%-5.6%) N = 206	4 (2%) (0.5%-4.9%)	0% (-2.8%-3.8%)
1 month post 3rd vaccination	208 (100%) (98.2%-100%) N = 208	204 (100%) (98.2%-100%) N = 204	0% (-1.8%-1.9%)
Pre 4th vaccination[a]	151 (77%) (70.5%-82.7%) N = 196	161 (85%) (79.3%-89.9%) N = 189	-8% (-16.0%--0.31%)
1 month post 4th vaccination	192 (99%) (97.1%-99.99%) N = 193	194 (100%) (98.1%-100%) N = 194	-1% (-2.9%-1.4%)
Serogroup W			
Baseline	7 (4%) (1.5%-7.3%) N = 194	5 (3%) (0.8%-5.9%) N = 196	1% (-2.7%-5%)
1 month post 3rd vaccination	178 (100%) (97.9%-100%) N = 178	187 (99%) (97.1%-99.99%) N = 188	1% (-1.6%-3%)
Pre 4th vaccination[a]	155 (92%) (86.5%-95.4%) N = 169	162 (91%) (85.8%-94.8%) N = 178	1% (-5.5%-6.8%)
1 month post 4th vaccination	179 (100%) (98%-100%) N = 179	184 (100%) (98%-100%) N = 184	0% (-2.1%-2%)
Serogroup Y			
Baseline	0 (0)% (0%-1.7%) N = 213	4 (2%) (0.5%-4.8%) N = 210	-2% (-4.8%--0.11%)
1 month post 3rd vaccination	211 (98%) (95.3%-99.5%) N = 215	213 (100%) (97.4%-99.99%) N = 214	-1% (-4.3%-0.9%)
Pre 4th vaccination[a]	174 (86%) (80.1%-90.2%) N = 203	185 (91%) (85.8%-94.3%) N = 204	-5% (-11.4%-1.3%)
1 month post 4th vaccination	196 (98%) (95.7%-99.69%) N = 199	203 (100%) (97.3%-99.99%) N = 204	-1% (-3.9%-1.4%)

Source: Table 14.2.1.3.4 (for baseline and 1 month post 3rd vaccination); Table 14.2.1.3.6 (for pre 4th vaccination); Table 14.2.1.3 (for 1 month post 4th vaccination);

The percentages of subjects with hSBA ≥1:8 at each of the timepoints as well as trends of change in percentages, were similar in the rMenB+ACWY and MenACWY groups against each of the serogroups

except for the serogroup A in which the percentages were higher in the rMenB+ACWY group than those in the MenACWY group at 1 month post 3rd and 4th vaccinations.

CHMP comments

The response for serogroup A rMenB+ACWY is higher than to MenACWY alone one month after the 3rd and one month after the 4th dose. The response in the concomitant administration group is 100% vs 96% in the MenACWY group. This was also observed for the primary objective, and further confirmed by other secondary outcomes (i.e. fourfold outcome, GMRs).

Safety results

The presentation of safety results will be limited to those subjects who received MenACWY.

Exposure

A total of 744 (99%) subjects out of 750 enrolled subjects were exposed to the study vaccine and were included in the overall safety set, solicited safety set (6 hours-day 7) and unsolicited safety set. A total of 704 (94%) subjects after the 1st vaccination, 678 (90%) after the 2nd vaccination, 656 (87%) after the 3rd vaccination, and 607 (81%) after the 4th vaccination was included in the solicited safety set.

Adverse Events

Solicited AEs

After vaccination with MenACWY, the most common solicited local AE was tenderness. After vaccination with MenACWY, severe tenderness was reported in 1%-7% subjects after the 1st vaccination, <1%-4% subjects after the 2nd vaccination, 1%-3% subjects after the 3rd vaccination, and 1%-2% subjects after the 4th vaccination.

Most of the reported local solicited local AEs after each dose of vaccine were mild to moderate in intensity with onset from 6 hours to day 3 after vaccination.

Persistent crying and irritability were the most common solicited systemic AEs reported after each vaccination across the vaccine groups, reported by 36% and 37% of MenACWY recipients after the 1st dose, 29% and 31% after the second dose, 27% and 28% after the 3rd dose and after the 4th dose. In those who received rMenB+ACWY this was 52% and 47% after the 1st dose, 46% and 44% after the 2nd and 41% and 38% after the 3rd dose respectively.

Fever (body temperature measured by axillary route ≥38° C) was reported in 21% (rMenB+ACWY group), and 4% (MenACWY group) subjects after the 1st vaccination, 21% and 7% subjects after the 2nd vaccination, 17%, and 11% subjects after the 3rd vaccination, and 26% and 9% subjects after the 4th vaccination.

Unsolicited AEs:

By system organ class

The most commonly reported unsolicited AEs were classified under the MedDRA SOC of 'infections and infestations' reported in 160 (64%) rMenB+ACWY subjects and 173 (70%) MenACWY subjects. The SOC of 'general disorders and administration site conditions', was reported in 95 (38%) rMenB+ACWY subjects and 19 (8%) MenACWY subjects.

At least possibly related AEs reported throughout the study were most commonly reported under the SOC of 'general disorders and administration site conditions', in 90 (36%) rMenB+ACWY subjects and 14 (6%) MenACWY subjects.

By preferred term

Across vaccine groups, after any vaccination, the most commonly reported unsolicited AEs, by PT, were: nasopharyngitis (32%-35%, across vaccine groups) and viral upper respiratory tract infection (29%-35%).

The most common *at least possibly related AE* reported throughout the study, by PT, was injection site induration that continued beyond day 8 after each vaccination, reported in 35% subjects receiving rMenB vaccine, either alone or in combination with MenACWY; it was reported in only 1% subjects receiving MenACWY alone.

Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Deaths and Serious Adverse events

There were no deaths and none of the Serious Adverse events were considered related to MenACWY. There was one case of anaemia considered potentially related to rMenB vaccination, which will not be discussed here as the subject did not receive MenACWY.

There was one case of Kawasaki's disease in a subject who was vaccinated with rMenB and MenACWY. The subject developed fever 117 days after the 3rd study vaccination and was diagnosed with Kawasaki's disease 4 days later. In the opinion of the investigator, the event Kawasaki's disease was considered serious due to hospitalization and was not related to study vaccine. The SAE was considered resolved, with outcome of complete recovery.

CHMP comments

Considering the time between last vaccination and the occurrence of Kawasaki's disease the assessment of it being unrelated to vaccination is endorsed.

2.3.3. Discussion on clinical aspects

This phase III open label randomised trial assessed the impact of concomitant administration of MenACWY with rMenB vs the administration of both vaccines alone, in healthy infants.

Although questions could be raised surrounding an interim analysis, for which very little detail has been given, it is not expected to impact the conclusions of the trial significantly therefore no questions are raised.

The data showed that the immune response following administration of MenACWY vaccine was higher or similar in the rMenB+ACWY group compared with that in the MenACWY group.

The available safety data do not give rise to any concerns.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted a trial evaluating the safety and immunogenicity of concomitant administration of Menveo with a recombinant MenB vaccine in healthy infants. Non-inferiority of the combined vaccine rMenB+ACWY against the isolated vaccines rMenB or MenACWY was demonstrated. The study demonstrates an acceptable and comparable safety profile when the vaccines are given concomitantly.

The MAH proposes no changes.

MS1 proposed that the MAH submits a type II variation to include MenB vaccine under 4.5, which was supported by MS2. The Rapporteur agrees.

It is agreed that the B/R balance for Menveo remains unchanged.

☒ Fulfilled:

The MAH should submit a type II variation to include concomitant administration with MenB in section 4.5