London, 26 April 2018
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Human Medicines Development and Evaluation

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

BEXSERO

Common name: meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no.: EMA/H/C/2333 P46 027

Marketing authorisation holder (MAH): GSK Vaccines S.r.l

Note

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

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1. Introduction

On 7 December 2017, the MAH submitted a completed paediatric study for Bexsero, 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 the study "A Phase 3b, Open-Label, Randomized, Multicenter Study to Assess the Safety and Immunogenicity of Novartis[1] Meningococcal group B Vaccine When Administered Concomitantly with Novartis[1] MenACWY Conjugate Vaccine to Healthy Infants" (protocol number V72_56) is a stand-alone study.

[1] Now GSK Biologicals

2.2. Information on the pharmaceutical formulation used in the study

GSK Biologicals' rMenB, liquid formulation, 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 aluminum hydroxide; needed no reconstitution. The lot numbers were IA 151301, IC 113001A, ID 139201.

GSK Biologicals' MenACWY comprised meningococcal serogroups A, C, W-135, and Y oligosaccharides that were each conjugated to the protein carrier CRM197, a nontoxic mutant of diphtheria toxin. The drug product presentation consisted of one vial containing the lyophilized MenA conjugate component and one vial of 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. The lot numbers were: M13020, M13070, M15038.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- "A Phase 3b, Open-Label, Randomized, Multicenter Study to Assess the Safety and Immunogenicity of Novartis1 Meningococcal group B Vaccine When Administered Concomitantly with Novartis MenACWY Conjugate Vaccine to Healthy Infants" (protocol number V72_56)

2.3.2. Clinical study

A Phase 3b, Open-Label, Randomized, Multicenter Study to Assess the Safety and Immunogenicity of Novartis Meningococcal group B Vaccine When Administered Concomitantly with Novartis1 MenACWY Conjugate Vaccine to Healthy Infants

Description

Methods

Objective(s)

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

· at 1 month after the 4th vaccination

· at 1 month after the 3rd vaccination

· at 6 months after the 3rd vaccination

when concomitantly administered compared to either alone in healthy infants at 3, 5, 7 and 13 months of age.

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.

Exploratory Objective

The exploratory objective was to explore the immune response of the study vaccinations administered in healthy infants at 3, 5, 7 and 13 months of age against *Neisseria Spp*., of interest, at one month after the 3rd and 4th vaccinations; however, the exploratory objective was not assessed in this study.

Study design

This was a phase 3b, multicenter, open label, randomized trial that aimed to enroll approximately 750 healthy infants, aged 3 months at enrollment.

Study population /Sample size

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.

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.

The number of subjects planned and actually enrolled are shown in Table 2-2.

Table 2-2 Number of Subjects Planned and Analyzed

Group	Planned	Analyzed							
		Enrolled	Immunogenicity				Exposed	Safety	
			FAS post 3rd vacc.	FAS pre 4th vacc.	FAS post 4th vacc.	PPS post 4th vacc.		Solicited	Unsolicited
rMenB+ ACWY	250	252	215 (85%)	205 (81%)	199 (79%)	161 (64%)	249 (99%)	240 (95%)	249 (99%)
rMenB	250	250	209 (84%)	204 (82%)	201 (80%)	163 (65%)	249 (>99%)	232 (93%)	249 (>99%)
MenACWY	250	248	214 (86%)	204 (82%)	204 (82%)	156 (63%)	246 (99%)	237 (96%)	246 (99%)

Source: Table 14.1.1.1.
Abbreviations: FAS, full analysis set; PPS, per protocol set; vacc, vaccination.

Treatments

Subjects were to be randomized to one of the three treatment arms in a 1:1:1 ratio to receive:

- Vaccine Group rMenB+ACWY: rMenB3+OMV NZ 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).

at 3, 5, 7 and 13 months of age.

The study comprised 6 clinical visits (performed at study day 1, 61, 121, 151, 301, and 331), 8 reminder calls (performed 2 and 4 days after each vaccination visit) and 2 safety calls (performed at day 201 and at day 251).

Subjects were to be observed for at least 30 minutes after each vaccination for any immediate reactions. Blood (approximately 5 mL) were to be drawn from all subjects before 1st vaccination (day

1), one month after the 3rd vaccination (day 151), before the 4th vaccination (day 301) and 1 month after (day 331) the 4th vaccination for immunogenicity evaluation.

Table 2-1 Overview of the 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

Source: Table 3.1-1 of the protocol (30 JUL 2014).

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 indicator strains;
- the percentage of subjects with hSBA ≥5 and subjects with hSBA ≥8 against each of the serogroup B indicator 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 percentage of subjects with hSBA ≥4 and subjects with hSBA ≥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 percentage of subjects with 4-fold increases in hSBA titers at one month after 4th vaccination (day 331) vs. pre 4th vaccination (day 301).

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.

Exploratory Endpoints:

No exploratory endpoints were assessed in this study.

Statistical Methods

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 meningitides* 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 center as factors in the model.

The primary immunogenicity analyses were based on the per-protocol set; the secondary immunogenicity analyses on the full analysis set (FAS) and the safety analyses on the safety set.

Results

Recruitment / Number analysed

Among 750 enrolled subjects in the study, 744 subjects received a study vaccination. Across vaccine groups, 63%-65% of enrolled subjects were included in the PPS dataset for primary and secondary objectives analysis. Overall, 79%-86% of enrolled subjects were included in the different FAS datasets, which were defined based on the different study visits (Table 11.1-1).

Table 11.1-1 Overview of Datasets Analyzed for Immunogenicity, As Randomized – 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*	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.
Abbreviations: FAS, full analysis set; PPS, per protocol set.
Note: The primary objective was analyzed based on the PPS.
* 6 months after 3rd vaccination is referred as pre 4th vaccination.

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 (Table 12.1-1). 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 were included in the solicited safety set (Table 12.1-1).

Table 12.1-1 Overview of Data Sets Analyzed for Safety – As Treated

	Number (%) of Subjects		
Analysis Set	rMenB+ACWY	rMenB	MenACWY
Enrolled set	252	250	248
Exposed set	249 (99%)	249 (>99%)	246 (99%)
Vaccination 1	249 (99%)	249 (>99%)	246 (99%)
Vaccination 2	234 (93%)	227 (91%)	233 (94%)
Vaccination 3	229 (91%)	219 (88%)	229 (92%)
Vaccination 4	206 (82%)	205 (82%)	207 (83%)
Overall safety set	249 (99%)	249 (>99%)	246 (99%)
Solicited safety set (6h-day7)	240 (95%)	232 (93%)	237 (96%)
Vaccination 1	239 (95%)	230 (92%)	235 (95%)
Vaccination 2	227 (90%)	221 (88%)	230 (93%)
Vaccination 3	218 (87%)	215 (86%)	223 (90%)
Vaccination 4	203 (81%)	200 (80%)	204 (82%)
Unsolicited Safety Set	249 (99%)	249 (>99%)	246 (99%)

Source: Table 14.1.1.1.1.
The percentages presented for each analysis set are relative to the number of subjects enrolled.

Baseline data

All demographic and baseline characteristics were balanced across the vaccine groups. 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. Most of the subjects (92%-93%) were categorized under the race category of 'Other'. More than 99% subjects met study entry criteria (Table 11.2-1).

Table 11.2-1 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.

Efficacy results

Immunogenicity results:

- A total of 750 subjects were enrolled into the study: 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.
- Across vaccine groups, 63%-65% of enrolled subjects were included in the PPS analysis for primary and secondary objectives. Overall, 79%-86% of enrolled subjects were included in the different FAS populations, which were defined based on the different study visits (Table 11.1-1).
- The primary objective of the study was met as the immune responses to rMenB and MenACWY when concomitantly administered (rMenB+ACWY) were noninferior to either rMenB or MenACWY administered alone. 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 (Table 2-3).

Table 2-3 Geometric Mean hSBA Titers and Vaccine Group Ratios Against N meningitidis Serogroup B Strains (for rMenB) and Serogroups A, C, W-135 and Y (for MenACWY) at 1 Month Post 4th Vaccination – Per Protocol Set

			Vaccine Group Ratios (95% CI)
rMenB Strains	**rMenB+ACWY**	**rMenB**	**rMenB+ACWY:rMenB**
H44/76 (fHbp)	**N = 115**	**N = 153**	
1 month post4th vaccination	92 (67-128)	104 (77-141)	0.89 (0.71-1.10)
5/99 (NadA)	**N = 113**	**N = 148**	
1 month post4th vaccination	1850 (1122-3050)	1790 (1128-2842)	1.03 (0.74-1.45)
NZ98/254 (PorA P1.4)	**N = 148**	**N = 158**	
1 month post4th vaccination	39 (29-53)	38 (28-52)	1.01 (0.82-1.25)
M10713 (NHBA)	**N = 131**	**N = 157**	
1 month post4th 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 post4th vaccination	409 (300-556)	165 (122-224)	2.48 (1.97-3.11)
Serogroup C	**N = 157**	**N = 149**	
1 month post4th vaccination	452 (312-655)	421 (294-602)	1.07 (0.83-1.38)
Serogroup W	**N = 144**	**N = 143**	
1 month post4th vaccination	721 (493-1053)	536 (370-776)	1.34 (1.04-1.74)
Serogroup Y	**N = 161**	**N = 156**	
1 month post4th 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.
Abbreviations: CI, confidence interval, GMT, geometric mean titer; hSBA, human serum bactericidal assay; NA, not applicable.
Note: Noninferiority was to be concluded if at 1 month following the 4th vaccination, the lower limits of the 2-sided 95% CI for the between-group ratios of GMTs (rMenB+ACWY versus rMenB alone, and rMenB+ACWY versus MenACWY alone) was >0.5 for all serogroup B indicator strains and all serogroups A, C, W-135 and Y. **Bold** indicates noninferiority criterion met.

Rapporteurs assessment comment:

Study results demonstrate non inferiority of combined rMenB+MenACWY vaccine to either rMenB or MenACWY administered alone. This is shown by lower limits of the 2-sided 95% CIs of > 0.5 for the between ratios of GMTs (rMenB+ACWY vs. rMenB, and rMenB+ACWY vs. MenACWY) after the 4th vaccination for all serogroup B indicator strains and all serogroups A, C, W-135 and Y.

Immune responses following administration of rMenB vaccine:

- At 1 month post 3rd rMenB vaccination (day 151), in vaccine groups rMenB+ACWY and rMenB, 96%-100% of subjects achieved hSBA ≥5 against serogroup B strains H44/76, 5/99, and NZ98/254 and 68%-70% subjects achieved hSBA ≥5 against strain M10713. At 1 month post 4th vaccination (day 331), the percentages in both vaccine groups were 97%-100% for strains H44/76, 5/99, and NZ98/254 and 87% in each vaccine group for strain M10713 (Table 11.4.1-2).

Table 11.4.1-2 Number (%) of Subjects With hSBA ≥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%)

Strains	Number (%) of Subjects (95% CI)		Vaccine Group Differences (95% CI)
	rMenB+ACWY	rMenB	rMenB+ACWY - rMenB
	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%)
M10713 (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).
Abbreviations: CI, confidence interval; hSBA, human serum bactericidal assay.
[a] 6 months after 3rd vaccination is referred as pre 4th vaccination.
Note: For calculation of percentages, all decimals are rounded off to the nearest number.

- The hSBA GMTs increased across all strains in both the vaccine groups after the 3rd and after the 4th rMenB vaccination with similar titers in the rMenB+ACWY group compared with those in rMenB group at each of the time points assessed post 3rd and 4th vaccination (Table 11.4.1-3).

Table 11.4.1-3 Geometric Mean hSBA Titers and Geometric Mean Ratios Against Serogroup B Strains at Baseline, 1 Month Post 3rd, Pre 4th and 1 Month Post 4th Vaccination – Full Analysis Set

Strains/Serogroups	GMT/GMR (95% CI)		Vaccine Group Ratios (95% CI)
	rMenB+ACWY	rMenB	rMenB+ACWY:rMenB
H44/76 (fHbp)			
Baseline	1.03 (0.99-1.08) N=162	1.02 (0.98-1.07) N = 198	-
1 month post 3rd vaccination	116 (100-135) N = 149	129 (113-147) N=199	0.90 (0.78-1.04)
Pre 4th vaccination[a]	7.71 (5.91-10) N = 126	8.31 (6.53-11) N = 187	-
1 month post 4th vaccination	122 (98-151) N = 141	126 (104-154) N = 188	0.96 (0.79-1.18)
1 month post 4th vaccination/pre 4th vaccination	17 (13-22) N = 109	16 (12-20) N = 178	1.06 (0.83-1.35)
5/99 (NadA)			
Baseline	1.09 (0.99-1.21) N=157	1.07 (0.97-1.17) N=192	-
1 month post 3rd vaccination	891 (752-1055) N = 137	935 (803-1088) N = 188	0.95 (0.81-1.12)
Pre 4th vaccination[a]	130 (105-160) N = 135	108 (89-130) N = 186	-
1 month post 4th vaccination	1404 (1016-1939) N = 143	1262 (934-1706) N = 183	1.11 (0.82-1.51)
1 month post 4th vaccination/pre 4th vaccination	9.60 (6.99-13) N = 118	12 (8.86-16) N = 169	0.81 (0.60-1.11)
NZ98/254 (PorA P1.4)			
Baseline	1.06 (1.01-1.12) N=191	1.07 (1.02-1.12) N=206	-
1 month post 3rd vaccination	32 (26-39) N = 181	33 (27-40) N = 205	0.95 (0.78-1.17)
Pre 4th vaccination[a]	3.17 (2.40-4.17) N = 169	2.95 (2.26-3.85) N = 200	-
1 month post 4th vaccination	37 (30-45)	36 (30-44)	1.02 (0.84-1.24)

Strains/Serogroups	GMT/GMR (95% CI)		Vaccine Group Ratios (95% CI)
	rMenB+ACWY	rMenB	rMenB+ACWY:rMenB
	N = 181	N = 196	
1 month post 4th vaccination/pre 4th vaccination	11 (8.35-15) N = 155	12 (9.39-16) N = 195	0.91 (0.68-1.20)
M10713 (NHBA)			
Baseline	1.88 (1.51-2.34) N = 182	1.59 (1.29-1.96) N = 203	-
1 month post 3rd vaccination	9.09 (6.57-13) N = 168	10 (7.50-14) N = 206	0.90 (0.65-1.23)
Pre 4th vaccination[a]	2.50 (1.89-3.30) N = 147	2.46 (1.89-3.20) N = 194	-
1 month post 4th vaccination	18 (14-24) N = 161	17 (13-22) N = 194	1.09 (0.83-1.43)
1 month post 4th vaccination/pre 4th vaccination	5.99 (4.20-8.54) N = 130	6.75 (4.90-9.29) N = 187	0.89 (0.63-1.26)

Source: Table 14.2.1.5.13 (for baseline and 1 month post 3rd vaccination); Table 14.2.1.5.3 (for pre 4th and post 4th vaccination).
Abbreviations: CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, human serum bactericidal assay.
[a] 6 months after 3rd vaccination is referred as pre 4th vaccination.

- At 1 month after the 4th rMenB vaccination, the percentages of subjects with 4-fold increase in titers over pre 4th vaccination ranged from 92%-95% in both vaccine groups against strains H44/76 and 5/99; whereas for strain NZ98/254 the percentages were 81% and 79% and for strain M10713 the percentages were 58% and 60%, in rMenB+ACWY and rMenB vaccine groups, respectively.
- The immune responses following administration of rMenB vaccine were similar between the rMenB+ACWY and rMenB groups at each of the timepoints assessed post 3rd and 4th vaccination (Table 11.4.1-2; Table 11.4.1-3).

Immune responses following administration of MenACWY vaccine:

- At 1 month post 3rd MenACWY vaccination (day 151) as well as at 1 month post 4th MenACWY vaccination (day 331), 96%-100% of subjects in vaccine groups rMenB+ACWY and MenACWY achieved hSBA ≥8 across serogroups A, C, W, and Y (Table 11.4.1-4).

Table 11.4.1-4 Number (%) of Subjects With hSBA ≥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);
Abbreviations: CI, confidence interval; hSBA, human serum bactericidal assay.
[a] 6 months after 3rd vaccination is referred as pre 4th vaccination.
Note: For calculation of percentages, all decimals are rounded off to the nearest number.

- The hSBA GMTs increased across all serogroups in both the vaccine groups after the 3rd and after the 4th MenACWY vaccination with higher or similar titers in the rMenB+ACWY group compared with those in MenACWY group at each of the timepoints assessed post 3rd and 4th vaccination (Table 11.4.1-5).

Table 11.4.1-5 Geometric Mean hSBA Titers and Geometric Mean Ratios Against ACWY Serogroups at Baseline, 1 Month Post 3rd, Pre and Post 4th Vaccination – Full Analysis Set

Strains/Serogroups	GMT/GMR (95% CI)		Vaccine Group Ratios (95% CI)
	rMenB+ACWY	MenACWY	rMenB+ACWY:MenACWY
Serogroup A			
Baseline	2.05 (1.97-2.15) N = 211	2.08 (1.99-2.17) N = 206	-
1 month post 3rd vaccination	303 (242-379) N = 214	136 (108-169) N = 210	2.23 (1.78-2.81)
Pre 4th vaccination	20 (15-28) N = 194	15 (11-20) N = 197	-
1 month post 4th vaccination	329 (269-403) N = 197	132 (108-161) N = 203	2.50 (2.04-3.07)
1 month post 4th vaccination/pre 4th vaccination	16 (13-21) N = 192	8.75 (6.69-11) N = 196	1.87 (1.43-2.45)
Serogroup C			
Baseline	2.16 (1.98-2.35) N = 206	2.09 (1.92-2.27) N = 204	-
1 month post 3rd vaccination	388 (320-469) N = 208	416 (345-502) N = 204	0.93 (0.77-1.13)
Pre 4th vaccination	31 (23-41) N = 190	43 (32-57) N = 187	-
1 month post 4th vaccination	331 (268-409) N = 193	311 (252-384) N = 194	1.06 (0.86-1.32)
1 month post 4th vaccination/pre 4th vaccination	11 (8.86-14) N = 185	7.79 (6.25-9.71) N = 178	1.41 (1.13-1.76)
Serogroup W			
Baseline	2.33 (2.13-2.55) N = 194	2.31 (2.11-2.52) N = 196	-
1 month post 3rd vaccination	347 (282-427) N = 178	298 (244-364) N = 188	1.17 (0.95-1.43)
Pre 4th vaccination	48 (37-63) N = 165	47 (36-62) N = 176	-
1 month post 4th vaccination	576 (458-723) N = 179	428 (342-537) N = 184	1.34 (1.07-1.69)
1 month post 4th vaccination/pre 4th vaccination	13 (10-16) N = 155	9.44 (7.52-12) N = 161	1.34 (1.06-1.69)
Serogroup Y			
Baseline	2.06 (1.95-2.17) N = 213	2.16 (2.05-2.28) N = 210	
1 month post 3rd vaccination	226 (182-282) N = 215	283 (228-351) N = 214	0.80 (0.64-1)
Pre 4th vaccination	39 (30-50) N = 197	42 (32-54) N = 201	-
1 month post 4th vaccination	377 (304-466) N = 199	363 (294-448) N = 204	1.04 (0.84-1.29)
1 month post 4th vaccination/pre 4th vaccination	9.75 (8-12) N = 197	8.97 (7.36-11) N = 201	1.09 (0.89-1.33)

Source: Table 14.2.1.5.12 (for baseline and 1 month post 3rd vaccination); Table 14.2.1.5.2 (for pre 4th and post 4th vaccination).
Abbreviations: CI, confidence interval, FAS, full analysis set; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, human serum bactericidal assay.
Note: 6 months post 3rd vaccination is referred as pre 4th vaccination.

- At 1 month after the 4th MenACWY vaccination, the percentages of subjects with at least 4-fold increase in titers ranged from 71%-90% in both vaccine groups against all serogroups, A, C, W, and Y. The percentages were similar in both vaccine groups except for serogroup A in which the

percentages were higher in rMenB+ACWY vs MenACWY at pre- and post 4th vaccination (Table 14.2.1.4).

- The immune responses following administration of MenACWY vaccine were higher or similar in the rMenB+ACWY group compared with those in the MenACWY group at each of the timepoints assessed post 3rd and 4th vaccination (Table 11.4.1-4; Table 11.4.1-5, Table 14.2.1.4).

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Percentages of Subjects With Four-fold Increase in hSBA Titers and Vaccine Group Differences, from Pre-fourth Vaccination (Day 301) to Post-fou
Vaccination (Day 331) by Serogroup
- 1 Month Post dose 4, Booster response
Full Analysis Set

Strain: Serogroup A

	rMenB+ACWY	MenACWY
Seroresponse - Pre-fourth vaccination < LLOQ		
Number	63	62
Percentage	98%	83%
95% Conf Int	91.6%-99.96%	72.2%-90.4%
N	64	75
Seroresponse - Pre-fourth vaccination >= LLOQ		
Number	109	78
Percentage	85%	64%
95% Conf Int	77.8%-90.8%	55.2%-73.0%
N	128	121
Overall Seroresponse		
Number	172	140
Percentage	90%	71%
95% Conf Int	84.4%-93.5%	64.6%-77.6%
N	192	196
Seroresponse - Pre-fourth vaccination < LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		16%
95% Conf Int		6.9%-26.2%
Seroresponse - Pre-fourth vaccination >= LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		21%
95% Conf Int		10.1%-31.2%
Overall Seroresponse (rMenB+ACWY vs. MenACWY)		
Difference		18%
95% Conf Int		10.5%-25.9%

Strain: Serogroup C

	rMenB+ACWY	MenACWY
Seroresponse - Pre-fourth vaccination < LLOQ		
Number	22	20
Percentage	96%	100%
95% Conf Int	78.1%-99.89%	83.2%-100.0%
N	23	20
Seroresponse - Pre-fourth vaccination >= LLOQ		
Number	140	117
Percentage	86%	74%
95% Conf Int	80.2%-91.3%	66.5%-80.7%
N	162	158
Overall Seroresponse		
Number	162	137
Percentage	88%	77%
95% Conf Int	81.9%-92.0%	70.1%-82.9%
N	185	178
Seroresponse - Pre-fourth vaccination < LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		-4%
95% Conf Int		-21.3%-12.4%
Seroresponse - Pre-fourth vaccination >= LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		12%
95% Conf Int		3.7%-21.1%
Overall Seroresponse (rMenB+ACWY vs. MenACWY)		
Difference		11%
95% Conf Int		2.8%-18.5%

Strain: Serogroup W

	rMenB+ACWY	MenACWY
Seroresponse - Pre-fourth vaccination < LLOQ		
Number	11	5
Percentage	100%	71%
95% Conf Int	71.5%-100.0%	29.0%-96.3%
N	11	7
Seroresponse - Pre-fourth vaccination >= LLOQ		
Number	127	131
Percentage	88%	85%
95% Conf Int	81.8%-93.0%	78.4%-90.3%
N	144	154
Overall Seroresponse		
Number	138	136
Percentage	89%	84%
95% Conf Int	83.0%-93.5%	77.9%-89.7%
N	155	161
Seroresponse - Pre-fourth vaccination < LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		29%
95% Conf Int		-3.2%-64.9%
Seroresponse - Pre-fourth vaccination >= LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		3%
95% Conf Int		-4.8%-11.0%
Overall Seroresponse (rMenB+ACWY vs. MenACWY)		
Difference		5%
95% Conf Int		-3.0%-12.2%

Strain: Serogroup Y

	rMenB+ACWY	MenACWY
Seroresponse - Pre-fourth vaccination < LLOQ		
Number	15	11
Percentage	83%	100%
95% Conf Int	58.6%-96.4%	71.5%-100.0%
N	18	11
Seroresponse - Pre-fourth vaccination >= LLOQ		
Number	146	151
Percentage	82%	79%
95% Conf Int	75.1%-87.0%	73.0%-85.0%
N	179	190
Overall Seroresponse		
Number	161	162
Percentage	82%	81%
95% Conf Int	75.6%-86.9%	74.4%-85.8%
N	197	201
Seroresponse - Pre-fourth vaccination < LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		-17%
95% Conf Int		-39.7%-11.7%
Seroresponse - Pre-fourth vaccination >= LLOQ (rMenB+ACWY vs. MenACWY)		
Difference		2%
95% Conf Int		-6.1%-10.2%
Overall Seroresponse (rMenB+ACWY vs. MenACWY)		
Difference		1%
95% Conf Int		-6.6%-8.9%

Rapporteurs assessment comment:

Of note, immunogenicity against especially serogroup A and to a limited extent against W and C appears to be more pronounced with the combined vaccine as compared to MenACWY given alone, as reflected in GMT ratios obtained after the 3rd and 4th vaccination, at pre 4th/post 4th vaccination and subjects reaching a 4fold increase from pre 4th to post 4th vaccination with the combined vaccine compared to MenACWY alone (tables 2.3, 11.4.1-5, 14.2.1.4). This observation may speak for the production of cross-reactive Ab induced by MenB component in the vaccine combination.

Safety results

- Across vaccination groups, any solicited AEs were reported in 62%-87% subjects after the 1st vaccination, 57%-81% subjects after the 2nd vaccination, 56%-79% subjects after the 3rd vaccination, and 54%-84% subjects after the 4th vaccination. The percentages of subjects with

solicited local and systemic AEs were higher in the rMenB+ACWY and rMenB groups than those in MenACWY group (Table 2-4).

Table 2-4 Numbers (%) of Subjects With At Least One Solicited Local and Systemic AE Reported From 6 Hours Through Day 7 After Each Vaccination – Solicited Safety Set

	Number (%) of Subjects		
Vaccine Group	**rMenB+ACWY**	**rMenB**	**MenACWY**
1st Vaccination	**N = 239**	**N = 230**	**N = 235**
Any	203 (85%)	200 (87%)	146 (62%)
Local	179 (75%)	181 (79%)	96 (41%)
Systemic	171 (72%)	174 (76%)	129 (55%)
2nd Vaccination	**N = 227**	**N = 221**	**N = 230**
Any	183 (81%)	177 (80%)	132 (57%)
Local	162 (71%)	157 (71%)	94 (41%)
Systemic	153 (67%)	150 (68%)	109 (47%)
3rd Vaccination	**N = 218**	**N = 215**	**N = 223**
Any	172 (79%)	167 (78%)	124 (56%)
Local	154 (71%)	154 (72%)	82 (37%)
Systemic	138 (63%)	133 (62%)	106 (48%)
4th Vaccination	**N = 203**	**N = 200**	**N = 204**
Any	165 (81%)	167 (84%)	111 (54%)
Local	140 (69%)	149 (75%)	79 (39%)
Systemic	137 (67%)	134 (67%)	96 (47%)

Source: Table 14.3.1.1.
Abbreviation: AE, adverse event.
Note: S1 is administration site for rMenB vaccine and S2 is administration site for MenACWY vaccine for group rMenB+ACWY. Total values are provided 1 for any solicited AEs and solicited systemic AEs.

- Across vaccination groups, the solicited local AEs were reported in 41%-79% subjects after the 1st vaccination, 41%-71% subjects after the 2nd vaccination, 37%-72% subjects after the 3rd vaccination, and 39%-75% subjects after the 4th vaccination (Table 2-4). Tenderness was the most common solicited local AE reported after each vaccination with the incidence being higher after rMenB vaccination compared with that after the MenACWY vaccination (Table 12.2.3-1, 12.2.3-4, below). Most of the reported solicited local AEs after either dose of vaccine were mild to moderate in intensity with onset from 6 hours to day 3 after vaccination.

Table 12.2.3-1 Numbers (Percentage) of Subjects Reported Solicited Local and Systemic AEs and Other Indicators of Reactogenicity From 6 Hours Through Day 7 After 1st Vaccination – Solicited Safety Set

Vaccination 1		Number (%) of Subjects				
		rMenB+ACWY			rMenB	MenACWY
		rMenB	ACWY	Total[a]		
Solicited Local AEs		**N = 239**	**N = 239**	**N = 239**	**N = 230**	**N = 234**
Tenderness	Any	155 (65%) N = 238	114 (48%) N = 238	162 (68%)	159 (70%) N = 227	73 (31%)
	Severe	31 (13%) N = 238	17 (7%) N = 238	36 (15%)	35 (15%) N = 227	2 (1%)
Erythema (mm)	Any	91 (38%) N = 238	48 (20%) N = 238	101 (42%)	102 (45%) N = 227	44 (19%) N = 232
	Severe (>50)	0 N = 238	0 N = 238	0	1 (<1%) N = 227	0 N = 232
Swelling (mm)	Any	76 (32%) N = 238	28 (12%) N = 238	82 (34%)	86 (38%) N = 229	22 (9%) N = 233
	Severe (>50)	0 N = 238	0 N = 238	0	0 N = 229	0 N = 233
Induration (mm)	Any	106 (44%) N = 238	37 (15%) N = 238	111 (46%)	102 (44%) N = 229	22 (9%) N = 233
	Severe (>50)	0 N = 238	0 N = 238	0	0 N = 229	0 N = 233
Solicited Systemic AEs			**N = 239**		**N = 229**	**N = 234**
Change in eating habits	Any		53 (22%) N = 238		47 (21%) N = 227	34 (15%) N = 232
	Severe		1 (<1%) N = 238		2 (1%) N = 227	0 N = 232
Sleepiness	Any		69 (29%) N = 238		78 (35%) N = 225	54 (23%) N = 232
	Severe		4 (2%) N = 238		3 (1%) N = 225	0 N = 232
Persistent crying	Any		124 (52%) N = 237		132 (58%) N = 228	85 (36%)
	Severe		10 (4%) N = 237		9 (4%) N = 228	4 (2%)
Vomiting	Any		14 (6%) N = 237		28 (12%) N = 228	23 (10%)
	Severe		0 N = 237		0 N = 228	0
Diarrhea	Any		46 (19%) N = 237		41 (18%) N = 228	42 (18%)
	Severe		1 (<1%) N = 237		1 (<1%) N = 228	2 (1%)

Vaccination 1		Number (%) of Subjects		
		rMenB+ACWY	rMenB	MenACWY
Irritability	Any	111 (47%) N = 237	121 (54%) N = 226	87 (37%) N = 233
	Severe	5 (2%) N = 237	11 (5%) N = 226	6 (3%) N = 233
Rash	Any	19 (8%) N = 237	28 (12%) N = 225	18 (8%) N = 233
	Severe	2 (1%) N = 237	0 N = 225	0 N = 233
Fever (≥38°C)	Yes	49 (21%)	54 (24%)	10 (4%) N = 233
Other Indicators of Reactogenicity		**N = 239**	**N = 229**	**N = 233**
Body temperature (°C)	36 - 36.4	19 (8%)	21 (9%)	29 (12%)
	36.5 - 36.9	86 (36%)	83 (36%)	134 (58%)
	37 - 37.4	54 (23%)	45 (20%)	47 (20%)
	37.5 - 37.9	31 (13%)	26 (11%)	12 (5%)
	38 - 38.4	29 (12%)	28 (12%)	8 (3%)
	38.5 - 38.9	11 (5%)	19 (8%)	2 (1%)
	39 - 39.4	5 (2%)	6 (3%)	0
	39.5 - 39.9	3 (1%)	1 (<1%)	0
	≥40	1 (<1%)	0	0
Analgesic/ antipyretic medication used		N = 237	N = 228	N = 227
	Prophylactic	44 (19%)	37 (16%)	32 (14%)
	Therapeutic	82 (35%)	98 (43%)	25 (11%)

Source: Table 14.3.1.2, Table 14.3.1.4.

Abbreviation: AEs, adverse events.

[a] Total = number (%) of subjects that reported solicited local AEs either at rMenB vaccination site and/or at MenACWY vaccination site.

Note: Threshold for erythema, swelling, and induration; Type III: 0 mm, 1-9 mm, 10-25 mm, 26-50 mm, >50 mm.

- Across vaccination groups, the solicited systemic AEs were reported in 55%-76% subjects after the 1st vaccination, 47%-68% subjects after the 2nd vaccination, 48%-63% subjects after the 3rd vaccination, and 47%-67% subjects after the 4th vaccination (Table 2-4). The most common solicited systemic AEs reported after each vaccination across the vaccine groups were persistent crying and irritability (Table 12.2.3-1, Table 12.2.3-4).

Table 12.2.3-4 **Numbers (Percentage) of Subjects Reported Solicited Local and Systemic AEs and Other Indicators of Reactogenicity From 6 Hours Through Day 7 After 4th Vaccination – Solicited Safety Set**

Vaccination 4		Number (%) of Subjects				
		rMenB+ACWY			rMenB	MenACWY
		rMenB	ACWY	Total[a]		
Solicited Local AEs		**N = 203**	**N = 203**	**N = 203**	**N = 200**	**N = 204**
Tenderness	Any	121 (60%)	81 (40%)	126 (62%)	129 (65%)	64 (31%)
	Severe	18 (9%)	5 (2%)	19 (9%)	14 (7%)	3 (1%)
Erythema (mm)	Any	72 (35%)	45 (22%)	73 (36%)	88 (44%) N = 199	37 (18%)
	Severe (>50)	3 (1%)	2 (1%)	4 (2%)	2 (1%) N = 199	2 (1%)
Swelling (mm)	Any	72 (35%)	31 (15%)	75 (37%)	74 (37%)	21 (10%)
	Severe (>50)	3 (1%)	1 (<1%)	3 (1%)	5 (3%)	1 (<1%)
Induration (mm)	Any	79 (39%)	35 (17%)	84 (41%)	93 (47%)	29 (14%)
	Severe (>50)	1 (<1%)	0	1 (<1%)	1 (1%)	1 (<1%)
Solicited Systemic AEs		**N = 203**			**N = 200**	**N = 204**
Change in eating habits	Any	59 (29%)			45 (23%)	40 (20%)
	Severe	1 (<1%)			2 (1%)	2 (1%)
Sleepiness	Any	50 (25%)			37 (19%)	33 (16%)
	Severe	3 (1%)			0	2 (1%)
Persistent crying	Any	84 (41%)			89 (45%)	56 (27%)
	Severe	3 (1%)			6 (3%)	3 (1%)
Vomiting	Any	15 (7%)			14 (7%)	11 (5%)
	Severe	2 (1%)			0	0
Diarrhea	Any	29 (14%)			28 (14%)	23 (11%)
	Severe	2 (1%)			0	1 (<1%)
Irritability	Any	81 (40%)			74 (37%)	57 (28%)
	Severe	5 (2%)			5 (3%)	3 (1%)
Rash	Any	11 (5%)			13 (7%)	6 (3%)
	Severe	0			1 (1%)	1 (<1%)
Fever (≥38°C)	Yes	53 (26%)			46 (23%)	19 (9%) N = 202

Vaccination 4		Number (%) of Subjects		
		rMenB+ACWY	rMenB	MenACWY
Other Indicators of Reactogenicity		**N = 203**	**N = 200**	**N = 202**
Body temperature (°C)	36 - 36.4	13 (6%)	25 (13%)	33 (16%)
	36.5 - 36.9	78 (38%)	68 (34%)	111 (55%)
	37 - 37.4	41 (20%)	30 (15%)	25 (12%)
	37.5 - 37.9	18 (9%)	31 (16%)	14 (7%)
	38 - 38.4	26 (13%)	26 (13%)	11 (5%)
	38.5 - 38.9	22 (11%)	17 (9%)	7 (3%)
	39 - 39.4	3 (1%)	2 (1%)	1 (<1%)
	39.5 - 39.9	1 (<1%)	1 (1%)	0
	≥40	1 (<1%)	0	0
Analgesic/antipyretic medication used		**N = 202**	**N = 200**	**N = 204**
	Prophylactic	26 (13%)	26 (13%)	10 (5%)
	Therapeutic	71 (35%)	67 (34%)	31 (15%)

Source: Table 14.3.1.2, Table 14.3.1.4.

Abbreviation: AEs, adverse events.

[a] Total = number (%) of subjects that reported solicited local AEs either at rMenB vaccination site and/or at MenACWY vaccination site.

Note: Threshold for erythema, swelling, and induration; Type III: 0 mm, 1-9 mm, 10-25 mm, 26-50 mm, >50 mm.

- No increase in local and solicited AEs was observed after the concomitant administration of MenACWY and rMenB vaccines compared with administration of each vaccine alone and there was no increase in reactogenicity with the subsequent doses (Table 2-4).

- A total of 74%-79% subjects across vaccine groups experienced any unsolicited AEs with 11%-41% subjects experiencing AEs those were at least possibly related to the study vaccine. The most commonly affected system organ class (SOC) was 'infections and infestations' (64%-71%, across vaccine groups) while the most common unsolicited AE by preferred term (PT) were nasopharyngitis (32%-35) and viral upper respiratory tract infection (29%-35%; Table 12.2.3-5). Most of the unsolicited AEs were mild to moderate in intensity and most of them resolved before study termination.

Table 12.2.3-5 All Unsolicited AEs by System Organ Class and Preferred Term, Reported in at Least 5% of Subjects by Preferred Term, and at Least Possibly Related Unsolicited AEs – Unsolicited Safety Set

System Organ Class Preferred Term	Number (%) of Subjects					
	rMenB+ACWY		rMenB		MenACWY	
	All	At least possibly related	All	At least possibly related	All	At least possibly related
	N = 249	N = 249	N = 249	N = 249	N = 246	N = 246
Any AE	**185 (74%)**	**93 (37%)**	**197 (79%)**	**102 (41%)**	**189 (77%)**	**27 (11%)**
Gastrointestinal disorders	**49 (20%)**	**4 (2%)**	**49 (20%)**	**8 (3%)**	**52 (21%)**	**9 (4%)**
Diarrhea	28 (11%)	4 (2%)	33 (13%)	5 (2%)	29 (12%)	7 (3%)
Dyspepsia	12 (5%)	0	2 (1%)	0	8 (3%)	0
General disorders and administration site conditions	**95 (38%)**	**90 (36%)**	**100 (40%)**	**96 (39%)**	**19 (8%)**	**14 (6%)**
Injection site erythema	29 (12%)	29 (12%)	38 (15%)	38 (15%)	2 (1%)	2 (1%)
Injection site induration	86 (35%)	86 (35%)	86 (35%)	86 (35%)	3 (1%)	3 (1%)
Injection site pain	15 (6%)	15 (6%)	14 (6%)	14 (6%)	0	0
Injection site swelling	42 (17%)	42 (17%)	48 (19%)	48 (19%)	1 (<1%)	1 (<1%)
Infections and infestations	**160 (64%)**	**1 (<1%)**	**176 (71%)**	**3 (1%)**	**173 (70%)**	**4 (2%)**
Bronchiolitis	35 (14%)	0	36 (14%)	0	40 (16%)	0
Candida nappy rash	15 (6%)	0	12 (5%)	0	6 (2%)	0
Conjunctivitis	20 (8%)	0	18 (7%)	0	24 (10%)	0
Gastroenteritis	32 (13%)	1 (<1%)	41 (16%)	0	38 (15%)	1 (<1%)
Nasopharyngitis	81 (33%)	0	87 (35%)	0	78 (32%)	0
Otitis media	12 (5%)	0	2 (1%)	0	9 (4%)	0
Pharyngitis	50 (20%)	0	50 (20%)	0	50 (20%)	0
Rhinitis	14 (6%)	0	13 (5%)	0	19 (8%)	0
Viral rash	13 (5%)	0	14 (6%)	0	13 (5%)	0
Viral upper respiratory tract infection	72 (29%)	0	82 (33%)	1 (<1%)	86 (35%)	1 (<1%)
Metabolism and nutrition disorders	**16 (6%)**	**0**	**7 (3%)**	**0**	**17 (7%)**	**2 (1%)**
Malnutrition	11 (4%)	0	6 (2%)	0	12 (5%)	0
Respiratory, thoracic and mediastinal disorders	**37 (15%)**	**0**	**35 (14%)**	**2 (1%)**	**40 (16%)**	**1 (<1%)**
Bronchial hyperreactivity	17 (7%)	0	12 (5%)	0	15 (6%)	0
Bronchospasm	9 (4%)	0	12 (5%)	2 (1%)	13 (5%)	0
Skin and subcutaneous tissue disorders	**34 (14%)**	**3 (1%)**	**36 (14%)**	**2 (1%)**	**45 (18%)**	**4 (2%)**
Dermatitis atopic	6 (2%)	0	11 (4%)	0	17 (7%)	1 (<1%)
Dermatitis diaper	12 (5%)	0	16 (6%)	0	14 (6%)	0

Source: Table: 14.3.1.12; Table 14.3.1.17.
Abbreviations: AEs, adverse events; PT, preferred term; SOC, system organ class.

- One subject in the rMenB group had an SAE (anemia at day 35 of the 1st vaccination, leading to hospitalization, recovered after 175 days) that was considered to be at least possibly related to the study vaccine. A total of 2 subjects in the rMenB group and 1 subject in the MenACWY group had AEs leading to premature withdrawal from the study. No deaths were reported in the study.

2.3.3. Rapporteurs discussion on clinical aspects

The study shows non inferiority of combined rMenB+MenACWY vaccine to either rMenB or MenACWY administered alone. This is demonstrated by lower limits of the 2-sided 95% CIs of > 0.5 for the between ratios of GMTs (rMenB+ACWY vs. rMenB, and rMenB+ACWY vs. MenACWY) after the 4th vaccination for all serogroup B indicator strains and all serogroups A, C, W-135 and Y.

When comparing the vaccine groups rMenB+ACWY and rMenB, equally strong and potent immunogenicity against all MenB strains could be demonstrated as shown by the high proportion of subjects reaching hSBA GMTs ≥ 5 (strains H44/76, 5/99, and NZ98/254 (97%-100%), M10713 (87%)) in both vaccine groups after the 4th vaccination.

Of note, increase of immunogenicity over time and in dependency of the number of vaccine doses was slowest for strain M10713 with only 68%-70% subjects achieving hSBA GMTs ≥5 after the 3rd vaccination in both vaccination groups. Furthermore, the percentages of subjects with 4-fold increase in titers after the 4th vaccination (over pre 4th vaccination) ranged from 92%-95% in both vaccine groups against strains H44/76 and 5/99, reached 81% and 79% for strain NZ98/254 but were only 58% and 60% for strain M10713 in rMenB+ACWY and rMenB vaccine groups, respectively. These results indicate that the response against M10713, although overall sufficient for all MenB strains, appears in both the rMenB+ACWY and rMenB vaccine lower as compared to the other strains. This observation is in agreement with results obtained in earlier studies (see e.g. study V72_28), showing a lower immune response against the strain M10713.

Acceptable immune responses against the Men-groups A, C, W and Y were reached with the combined vaccine, which is demonstrated by (1) strong increases of hSBA GMTs ≥8 across all strains already after the 3rd vaccination (96-100% for rMenB+ACWY) and (2) by a comparable proportion of individuals showing an at least 4-fold increase of titers compared to pre-4th vaccination (71-90% range for both vaccine groups; equal or higher proportions in the combined vaccine setup compared to MenACWY given alone), besides the fulfilment of the primary endpoint. Of note, immunogenicity against especially serogroup A and to a limited extent against W and C appears to be more pronounced with the combined vaccine as compared to MenACWY given alone, as reflected in GMT ratios obtained after the 3rd and 4th vaccination, at pre 4th/post 4th vaccination and subjects reaching a 4fold increase from pre 4th to post 4th vaccination with the combined vaccine compared to MenACWY alone (tables 2.3, 11.4.1-5, 14.2.1.4). This observation may speak for the production of cross-reactive Ab induced by MenB component in the vaccine combination.

The proportion of individuals reporting solicited systemic or local AEs was comparable between the combined vaccine and rMenB but higher compared to MenACWY, indicating that especially the rMenB component appears to be more reactogenic, which is in agreement with previous studies. Most of the reported solicited local AEs after either dose of vaccine were mild to moderate in intensity. Tenderness was the most common solicited local AE while persistent crying and irritability was the most common solicited systemic AEs reported after each vaccination across the vaccine groups. Unsolicited AEs belonged mostly to the SOC “infections and infestations”, with infections of the respiratory tract (e.g. nasopharyngitis (33-35%) and bronchiolitis (14%)) occurring relatively often with both the combined and the MenB vaccine.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The results of the study demonstrate non-inferiority of the combined vaccine rMenB+ACWY against the isolated vaccines rMenB or MenACWY. The study demonstrates moreover an acceptable and comparable safety profile of the combined vaccine. Based on the results further regulatory action has to be considered.

Recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

Based on the data submitted, the MAH should provide a description of the additional clarifications requested as part of this procedure (see section "Additional clarifications requested").

Additional clarifications requested

Based on the results obtained in the current study the MAH should discuss addition of information regarding concomitant vaccination to section 4.5 of the SmPC.

MAH´s response:

The Company acknowledges the Assessor's request to provide additional information regarding concomitant vaccination with Men A, C, W, Y in the Summary of Product Characteristics for Bexsero and to this end plans to submit a type II variation later this year.

Assessor's comment:

The response of the MAH is endorsed.