26 March 2020
EMA/225105/2020
Human Medicines Division

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

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/030

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On 19.12.2019, the MAH submitted a completed paediatric study for Bexsero, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

No amendments to the Product Information are being submitted as part of this procedure.

2. Scientific discussion

2.1. Information on the development program

Bexsero (rMenB+OMV NZ) vaccine was first registered in the European Union (EU), through the centralized procedure on 14 January 2013, and has received marketing authorization in twelve additional (non-EU) countries. The current therapeutic indication in the rMenB+OMV NZ Summary of Product Characteristics (SmPC) is for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *N meningitidis* serogroup (or group) B.

The MAH stated that (V102_19) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Bexsero (rMenB+OMV NZ) was used as a comparator in this study. Standard formulation of Bexsero was used in this study.

The licensed rMenB+OMV NZ vaccine (volume 0,5 ml) contains 50 µg of recombinant Neisserial Heparin Binding Antigen (NHBA) fusion protein (also referred to as recombinant protein [rp]287-953), 50 µg ofrecombinant Neisseria adhesin A (NadA) protein (rp961c), 50 µg of recombinant factor H binding protein (fHbp) fusion protein (rp936-741), 25 µg of Outer Membrane Vesicles (OMV) from *Neisseria meningitidis* serogroup B strain NZ98/254 containing PorA P 1.4 (the immunodominant antigen present in the OMV component), and 1,5 mg of aluminium hydroxide as adjuvant adsorbent.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for study V102_19.

2.3.2. Clinical study

Study V102_19: A Phase II, Randomized, Open-label, Multicenter Study to Assess the Immunogenicity and Safety of GSK Meningococcal MenABCWY Vaccine, and of GSK Meningococcal Group B and MenACWY Conjugate Vaccines Administered Concomitantly in the Same Arm or in 2 Different Arms, or Alone in Healthy Subjects 10 to 25 Years of Age

Description

In study V 102_19, immune responses to an investigational Meningococcal MenABCWY vaccine have been assessed and compared with responses to 2 licensed vaccines, *Menveo* (Meningococcal group A, C, W-135, and Y conjugate vaccine, referred to as MenACWY throughout this document) and ***Bexsero*** (Meningococcal group B vaccine, referred to as rMenB+OMV NZ or **rMenBOMV**) when administered concomitantly (in the same arm or in 2 different arms) or either vaccine alone.

The purpose of the current study was to evaluate whether there is a potential immune interference (possible lymph nodes stress) when MenABCWY (the combination vaccine consisting of MenACWY lyophilized component and rMenB+OMV NZ liquid component) is administered to healthy adolescents and adults following a 2-dose vaccination schedule with doses administered 2 months apart. Bexsero and Menveo were used as comparators in this study.

Methods

Objectives

Primary Objective:

- To assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY at 1 month after the last vaccination

Secondary Objectives:

- Immunogenicity objective: to assess the immune response to 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms at 1 month after the first vaccination
- Safety objective: to assess the safety and tolerability of 2 doses of MenABCWY, rMenB+OMV NZ, or rMenB+OMV NZ and MenACWY administered concomitantly in the same arm or in 2 different arms, and to a single dose of MenACWY

Study design

Study V 102_19 was a Phase II, open-label, randomised, controlled study conducted at 16 centres in the Czech Republic. A total of 500 subjects (10-25 years old at the time of first vaccination) were randomised (1:1:1:1:1) to 5 groups and received vaccinations as follows:

MenABCWY study group: 1 intramuscular (IM) dose of MenABCWY twice, 2 months apart.

rMenBOMV+ACWY_S study group: concomitantly received 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in the same arm (approximately 2.5 cm apart) twice, 2 months apart.

rMenBOMV+ACWY_D study group: concomitantly received 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in 2 different arms twice, 2 months apart.

rMenBOMV study group: 1 IM dose of rMenB+OMV NZ twice, 2 months apart.

MenACWY study group: 1 IM dose of MenACWY once.

Study population /Sample size

Approximately 500 subjects were planned to be randomly assigned at a 1:1:1:1:1 ratio to one of the following 5 study groups, with stratification by age group within each group (10 to 17 years and 18 to 25 years):

Treatments

- MenABCWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) were to receive 1 intramuscular (IM) dose of MenABCWY twice, 2 months apart.
- **rMenBOMV**+ACWY_S: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) were to concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in the same arm (approximately 2.5 cm apart) twice, 2 months apart.
- **rMenBOMV**+ACWY_D: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) were to concomitantly receive 1 IM dose of rMenB+OMV NZ and 1 IM dose of MenACWY in 2 different arms twice, 2 months apart.
- **rMenBOMV**: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) were to receive 1 IM dose of rMenB+OMV NZ twice, 2 months apart.
- MenACWY: Approximately 100 subjects (50 subjects aged 10 to 17 years and 50 subjects aged 18 to 25 years) were to receive 1 IM dose of MenACWY once.

After completing all prerequisite procedures prior to the first vaccination, subjects were allocated a study group and treatment number and blood samples were drawn. At Visit 1 (Day 1), subjects received their first dose of study vaccine(s).

The subjects were observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis. Solicited adverse events (AEs) were recorded during this 30-minute period. The subjects/parent(s) or legally acceptable representative (LAR) were given a diary card and were trained on how to self-measure local solicited AEs and body temperature.

The second dose of study vaccine(s) was administered at Visit 3 (Day 61), with the exception of the MenACWY group who only received a single dose at Visit 1.

To test for immune response within the serogroups, blood samples were collected at Visit 1 (Day 1), Visit 2 (Day 31), and Visit 4 (Day 91), with the exception of the MenACWY group who only had blood drawn at Visit 1 and Visit 2.

Paper diary (pDiary, referred to as Subject Diary hereafter) reminder calls to the subject/subject's parent(s)/LAR(s) about completion of the Subject Diary were performed 3 and 5 days (±1 day) after each vaccination (i.e., Day 4 and Day 6 after the first vaccination and accordingly after the second vaccination). Safety follow-up calls were made to the subject by a healthcare professional to collect relevant safety information on Day 15 and Day 75.

Test vaccine, dose, mode of administration and lot number: All vaccines used were developed and manufactured by GSK. The study vaccines specific to this study were:

- MenABCWY obtained by extemporaneous mixing of lyophilized MenACWY powder in a vial with rMenB+OMV NZ supplied in a prefilled syringe
- rMenB+OMV NZ as suspension for injection in a prefilled syringe

- MenACWY conjugate vaccine obtained by extemporaneous mixing of the lyophilized MenA powder component in a vial with the MenCWY liquid components.

The lot numbers used were DSR0141992 and DSR0141993.

Duration of study: For each subject (except for subjects randomized to the MenACWY study group), the duration of study was approximately 3 months, with vaccination at Day 1 and Day 61 followed by a 30-day follow-up period. For subjects randomized to the MenACWY study group, the duration of study was approximately 2 months; with vaccination at Day 1 followed by a 30-day follow-up period.

Outcomes/endpoints

Primary Endpoints

- Immune responses against *Neisseria meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by serum bactericidal assay using human complement (hSBA), 1 month after the last vaccination in all study groups
- hSBA geometric mean titers (GMTs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled). Percentage of subjects with hSBA titers ≥ the lower limit of quantitation (LLOQ) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- Percentage of subjects with a 4-fold increase in hSBA titers against N. *meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA geometric mean ratios (GMRs) against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the last vaccination against baseline (Day 1)

*Serogroup B strains tested are M14459 (factor H binding protein; fHbp), 96217 (Neisserial adhesin A; NadA), NZ98/254 (PorA), and M07-0241084 (Neisseria heparin binding antigen; NHBA); these were pooled to estimate the effect of immune interference due to stress to lymph nodes.

Note: A 4-fold rise is defined as:

a. for individuals whose pre-vaccination titers were < the limit of detection (LOD), the post-vaccination titers had to be ≥4-fold the LOD or ≥ the LLOQ, whichever was greater;

b. for individuals whose pre-vaccination titers were ≥ the LOD and < the LLOQ, the post-vaccination titers had to be at least 4 times the LLOQ; and

c. for individuals whose pre-vaccination titers were ≥ the LLOQ, the post-vaccination titers had to be at least 4 times the pre-vaccination titer.

The ratios of GMTs between study groups were analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.

b. Other unknown interference in the MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.

c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV and MenACWY, rMenBOMV+ACWY_D versus rMenBOMV and MenACWY, and MenABCWY versus rMenBOMV and MenACWY study groups, by serogroup A, C, W-135, Y, and B test strains.

Secondary Endpoints

Immunogenicity Endpoints

- Immune responses against *N. meningitidis* serogroup B* test strains and *N. meningitidis* serogroups A, C, W-135, and Y, as measured by hSBA, 1 month after the first vaccination in all groups (except for subjects in the MenACWY group)
- hSBA GMTs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMTs against all of *N. meningitidis* serogroup B test strains (pooled)
- Percentage of subjects with hSBA titers ≥ the LLOQ against each of the
- *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- Percentage of subjects with a 4-fold increase in hSBA titers against
- *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA GMRs against each of the *N. meningitidis* serogroup B test strains and against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after the first vaccination against baseline (Day 1)

*Serogroup B strains tested are M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA), and M07-0241084 (NHBA).

Note: A 4-fold rise is defined in the same way as described for the primary endpoints.

The ratios of GMTs between study groups were analyzed to evaluate effect of treatment as described below:

a. Immune interference due to stress to lymph nodes (lymph-node effect) in rMenBOMV+ACWY_S versus rMenBOMV+ACWY_D study groups, on the pooled B strains, and individually by serogroup A, C, W-135, Y, and B test strains.

b. Other unknown interference in MenABCWY versus rMenBOMV+ACWY_S study groups, by serogroup A, C, W-135, Y, and B test strains.

c. The difference in immune response compared to control groups in rMenBOMV+ACWY_S versus rMenBOMV, rMenBOMV+ACWY_D versus rMenBOMV, and MenABCWY versus rMenBOMV study groups, by serogroup B test strains.

Safety Endpoints

- Solicited local and systemic AEs in all study groups: occurrence of solicited local and systemic AEs during the 7 days (including the day of vaccination) after each vaccination (Day 1 to Day 7 and Day 61 to Day 67 [Day 1 to Day 7 only for subjects in the MenACWY group])
- Unsolicited AEs in all study groups: occurrence of unsolicited AEs during the

- 30 days (including the day of vaccination) after each vaccination (Day 1 to Day 31 and Day 61 to Day 91 [Day 1 to Day 31 only for subjects in the MenACWY group])
- Serious adverse events (SAEs), medically attended AEs, AEs leading to withdrawal, and adverse events of special interest (AESIs), in all study groups from informed consent signature to Visit 4 (Day 91)

Statistical Methods

Primary immunogenicity endpoints (1 month after the last dose)

- hSBA geometric mean titer: As titer results were not normally distributed, summary statistics were calculated using log-transformed titer results. The anti-logarithm of the summary statistics was presented. Unadjusted summaries included the number of subjects with non-missing titer results, GMT, geometric standard deviation (GSD), 80% confidence interval (CI) for GMT, minimum, and maximum. Adjusted summaries were calculated at baseline using an analysis of variance (ANOVA) model (which included study group and center as fixed effects), and at Analysis Visit (AVISIT) 4 (1 month after last dose) using an Analysis of Covariance (ANCOVA) model (which included study group, center, and strain [only the ANCOVA model fitted to pooled serogroup B test strains] as fixed effects, and baseline log-transformed titer with centering at zero as continuous covariate). Both the ANOVA and ANCOVA models were fitted to individual serogroups A, C, W-135, Y and the individual serogroup B test strains, as well to the pooled serogroup B test strains only. The adjusted GMT, standard error (SE), and 80% CI from the ANOVA and ANCOVA models were presented.
- hSBA geometric mean ratios: The GMR was summarized by study group atAVISIT 4 for each serogroup (A, C, W-135, Y) and the 4 individual serogroup B test strains. Unadjusted summaries included the number of subjects with non-missing titer results at AVISIT 4, GMR (at AVISIT 4 only), GSD of the difference in log- transformed titer results at AVISIT 4 and baseline, 80% CI for GMR, minimum, and maximum. Adjusted summaries at baseline were calculated using an ANOVA model, and at AVISIT 4 using an ANCOVA model. The adjusted GMT, SE, and 80% CI from the ANOVA and ANCOVA models were presented. Ratio was calculated by dividing antibody titer from AVISIT4 (1 month after last dose) with baseline antibody titer.
- Percentage of subjects with titers above LLOQ and percentage of subjects with a 4-fold increase in hSBA titer: The percentage of subjects with titers above the LLOQ and percentage of subjects with a 4-fold increase in hSBA titer along with the associated 2-sided 80% Clopper-Pearson CIs were computed by study group at baseline and AVISIT 4. In addition, differences in percentages of subjects with titers above the LLOQ and percentage of subjects with a 4-fold increase in hSBA titer and their 2-sided 80% CIs between selected study groups were calculated using the method of Miettinen and Nurminen.

Secondary immunogenicity endpoints (1 month after the last dose): The analyses described above for the respective primary endpoints was repeated using AVISIT 2 (1 months from primary dose) instead of AVISIT 4. The MenACWY study group was not included in the secondary analyses as subjects in the MenACWY group received single dose of vaccine and analyzed as primary immunogenicity endpoints.

Safety: All safety analyses were run descriptively.

Results

Recruitment/ Number analysed

A total of 520 subjects were enrolled and screened for inclusion in the study. Of these 520 subjects, 20 subjects were screen failures and 500 subjects were randomly assigned to one of the study groups. Of these 500 subjects, 100, 104, 100, 94, and 102 subjects were randomly assigned to MenABCWY, rMenBOMV+ACWY_S, rMenBOMV+ACWY_D, rMenBOMV, and MenACWY study groups, respectively and all randomized subjects (500) completed the study.

A total of 496/500 (99.2%) subjects were included in the full analysis set (FAS)1 and FAS3, 396/398 (99.5%) subjects were included in the FAS2, and

395/398 (99.2%) subjects were included in the FAS4. A total of

483/500 (96.6%) subjects were included in the per protocol set (PPS)1 and PPS3, 388/398 (97.5%) subjects were included in the PPS2, and 387/398 (97.2%) subjects were included in the PPS4.

Baseline data

Gender distributions were similar across the vaccination groups (male 43.6% to 53.8% and female 46.2% to 56.4%). All subjects were white. Age, height, and weight of the all randomized subjects were similar across the study groups: overall mean ± SD (range) age, height, and weight were 17.1±4.45 years (10 to 25 years), 168.51±12.763 cm (133.0 to 197.0 cm), and 63.5±16.271 kg (27.6 to 105.0 kg), respectively. A total of 250 (50.0%) subjects were 10 to 17 years of age and 250 (50.0%) subjects were 18 to 25 years of age.

Table 11.2 Demographics and Baseline Characteristics (All Randomized Set)

	MenABCWY N=100	rMenBOMV +ACWY_S N=104	rMenBOMV +ACWY_D N=100	rMenBOMV N=94	MenACWY N=102	Total N=520
Age (years)						
n	100	104	100	94	102	520
Mean	17.1	16.9	17.1	17.4	17.1	17.1
SD	4.34	4.28	4.49	4.64	4.57	4.45
Median	17.0	18.0	18.0	17.0	18.0	17.5
Min, max	10, 25	10, 25	10, 25	10, 25	10, 25	10, 25
Age strata, n (%)						
10 – 17 years	53 (53.0)	50 (48.1)	48 (48.0)	49 (52.1)	50 (49.0)	250 (50.0)
18 – 25 years	47 (47.0)	54 (51.9)	52 (52.0)	45 (47.9)	52 (51.0)	250 (50.0)
Sex, n (%)						
Male	53 (53.0)	56 (53.8)	51 (51.0)	41 (43.6)	53 (52.0)	254 (50.8)
Female	47 (47.0)	48 (46.2)	49 (49.0)	53 (56.4)	49 (48.0)	246 (49.2)
Race, n (%)						
White	100 (100.0)	104 (100.0)	100 (100.0)	94 (100.0)	102 (100.0)	500 (100.0)
Height (cm)						
n	100	104	100	94	102	500
Mean	169.73	168.44	168.07	169.06	167.29	168.51
SD	12.844	14.221	12.492	12.236	11.943	12.763
Median	169.00	170.00	170.00	170.25	167.75	169.00
Min, max	138.0, 194.0	133.0, 197.0	135.0, 191.0	136.0, 193.0	136.0, 193.0	133.0, 197.0
Weight (kg)						
n	100	104	100	94	102	500
Mean	63.53	63.48	64.72	62.54	63.17	63.50
SD	15.276	17.203	16.535	15.975	16.494	16.271
Median	65.00	62.90	64.05	60.00	62.00	62.95
Min, max	29.1, 99.9	27.6, 101.0	29.4, 98.0	31.0, 105.0	29.2, 105.0	27.6, 105.0
BMI (kg/m^2)						
n	100	104	100	94	102	500
Mean	21.79	21.99	22.58	21.59	22.24	22.04
SD	3.565	3.849	4.069	3.691	3.854	3.812
Median	21.20	21.30	22.51	20.98	21.84	21.62
Min, max	15.1, 29.7	15.1, 30.5	15.3, 31.3	14.6, 30.1	14.4, 29.9	14.4, 31.3

Source: Table 14.1.3.6.
Abbreviations: BMI, body mass index (calculated as [weight in kg/height in meters^2]).

Efficacy results

Immunogenicity

Primary Objectives (one month after the last vaccination)

- One month after the last vaccination, the GMTs against pooled serogroup B strains, serogroup B test strain M14459 and strain 96217, and serogroups A, C, W-135, and Y were similar between the rMenBOMV+ACWY_S and rMenBOMV+ACWY_D study groups. The GMTs against serogroup B test strain NZ98/254 and strain M07-0241084 were lower for the rMenBOMV+ACWY_S study group compared with the rMenBOMV+ACWY_D study group.

Table 11.4 Summary of GMT and GMR of hSBA Against Pooled Serogroup B Strains, Serogroup B Test Strains, and Serogroups A, C, W-135, Y at 1 Month after Last Vaccination (Per Protocol Set 1)

	MenABCWY N=98	rMenBOMV+ACWY_S N=101	rMenBOMV+ACWY_D N=97	rMenBOMV N=90	MenACWY N=97
Pooled Serogroup B Strains					
GMT: baseline[a], n		101	97	90	-
Geometric mean		1.73	1.70	1.79	-
80% CI		(1.61, 1.86)	(1.58, 1.84)	(1.66, 1.94)	-
GMT: one month after last vaccination[b], n		100	97	90	-
Geometric mean		38.48	40.08	42.38	-
80% CI		(34.23, 43.26)	(35.44, 45.33)	(37.31, 48.13)	-
Serogroup B: M14459 (fHbp)					
GMT: baseline, n		101	96	90	97
Geometric mean		2.18	2.03	2.21	2.04
80% CI		(1.92, 2.48)	(1.77, 2.33)	(1.92, 2.55)	(1.78, 2.33)
GMT: one month after last vaccination, n		100	96	90	97
Geometric mean		23.34	23.23	22.87	2.48
80% CI		(20.16, 27.01)	(19.91, 27.10)	(19.52, 26.80)	(2.13, 2.89)
GMR, n		100	95	90	97
Geometric mean		10.90	10.85	10.69	1.16
80% CI		(9.42, 12.62)	(9.30, 12.66)	(9.12, 12.52)	(0.99, 1.35)
Serogroup B: 96217 (NadA)					
GMT: baseline, n		101	95	88	97
Geometric mean		2.84	3.23	4.99	3.67
80% CI		(2.32, 3.47)	(2.61, 4.00)	(4.01, 6.21)	(2.98, 4.54)
GMT: one month after last vaccination, n		100	97	90	96
Geometric mean		102.68	97.54	113.54	4.15
80% CI		(88.24, 119.50)	(83.18, 114.39)	(96.25, 133.93)	(3.54, 4.86)
GMR, n		100	95	88	96
Geometric mean		27.02	25.66	29.87	1.09
80% CI		(23.22, 31.44)	(21.88, 30.10)	(25.32, 35.24)	(0.93, 1.28)
Serogroup B: NZ98/254 (PorA)					
GMT: baseline, n		101	97	90	97
Geometric mean		1.73	1.69	1.74	1.81
80% CI		(1.61, 1.86)	(1.57, 1.83)	(1.60, 1.88)	(1.68, 1.95)
GMT: one month after last vaccination, n		100	97	89	97
Geometric mean		16.39	21.12	20.97	2.15
80% CI		(13.86, 19.39)	(17.71, 25.18)	(17.47, 25.16)	(1.81, 2.57)
GMR, n		100	97	89	97
Geometric mean		9.20	11.85	11.77	1.21
80% CI		(7.78, 10.88)	(9.94, 14.13)	(9.81, 14.12)	(1.01, 1.44)
Serogroup B: M07-0241084 (NHBA)					
GMT: baseline, n		98	96	88	96
Geometric mean		3.86	3.80	3.78	3.62
80% CI		(3.20, 4.65)	(3.13, 4.61)	(3.09, 4.63)	(2.98, 4.40)
GMT: one month after last vaccination, n		100	96	89	95
Geometric mean		18.00	22.59	25.34	4.08
80% CI		(15.35, 21.11)	(19.12, 26.69)	(21.30, 30.13)	(3.45, 4.82)
GMR, n		98	95	87	94
Geometric mean		4.96	6.22	6.98	1.12
80% CI		(4.23, 5.81)	(5.27, 7.35)	(5.87, 8.30)	(0.95, 1.33)

- One month after the last vaccination, the percentages of subjects with hSBA titers ≥LLOQ against serogroup B test strains M14459, 96217, NZ98/254, and M07-0241084; and serogroups A, C, and Y were similar between the rMenBOMV+ACWY_S and rMenBOMV+ACWY_D study groups. The percentages of subjects with hSBA titers ≥LLOQ against serogroup W-135 were lower in the rMenBOMV+ACWY_S study group compared with the rMenBOMV+ACWY_D study group.

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- One month after the last vaccination, the percentages of subjects with a 4-fold increase in hSBA titer against serogroup B test strains M14459, 96217, NZ98/254, and M07-0241084; and serogroups A, C, W-135, and Y were similar between the rMenBOMV+ACWY_S and rMenBOMV+ACWY_D study groups.

Table 11.6 Summary of Percentage of Subjects with hSBA Titer Results ≥ LLOQ Against Serogroup B Test Strains and Serogroups A, C, W-135, Y at Baseline and 1 Month After Last Vaccination (Per Protocol Set 1)

	MenABCWY N=98	rMenBOMV+ ACWY_S N=101	rMenBOMV+ ACWY_D N=97	rMenBOMV N=90	MenACWY N=97
Serogroup B: M14459 (fHbp) (LLOQ: 8.0 titer)					
Baseline					
≥LLOQ, s/n (%)		12/101 (11.9)	10/96 (10.4)	10/90 (11.1)	9/97 (9.3)
80% CI[a]		(7.88, 17.10)	(6.58, 15.59)	(7.02, 16.60)	(5.68, 14.25)
Last vaccination					
≥LLOQ, s/n (%)		86/100 (86.0)	85/96 (88.5)	75/90 (83.3)	12/97 (12.4)
80% CI[a]		(80.50, 90.35)	(83.22, 92.57)	(77.18, 88.31)	(8.21, 17.78)
Serogroup B: 96217 (NadA) (LLOQ: 8.6 titer)					
Baseline					
≥LLOQ, s/n (%)		26/101 (25.7)	29/95 (30.5)	38/88 (43.2)	31/97 (32.0)
80% CI[a]		(20.08, 32.15)	(24.31, 37.38)	(36.03, 50.58)	(25.71, 38.79)
Last vaccination					
≥LLOQ, s/n (%)		99/100 (99.0)	96/97 (99.0)	90/90 (100.0)	32/96 (33.3)
80% CI[a]		(96.17, 99.89)	(96.05, 99.89)	(97.47, 100.00)	(26.96, 40.24)
Serogroup B: NZ98/254 (PorA) (LLOQ: 8.2 titer)					
Baseline					
≥LLOQ, s/n (%)		3/101 (3.0)	2/97 (2.1)	4/90 (4.4)	4/97 (4.1)
80% CI[a]		(1.10, 6.49)	(0.55, 5.39)	(1.95, 8.69)	(1.81, 8.07)
Last vaccination					
≥LLOQ, s/n (%)		76/100 (76.0)	78/97 (80.4)	70/89 (78.7)	5/97 (5.2)
80% CI[a]		(69.66, 81.53)	(74.27, 85.57)	(72.05, 84.23)	(2.53, 9.35)
Serogroup B: M07-0241084 (NHBA) (LLOQ: 8.9 titer)					
Baseline					
≥LLOQ, s/n (%)		30/98 (30.6)	22/96 (22.9)	23/88 (26.1)	23/96 (24.0)
80% CI[a]		(24.49, 37.35)	(17.38, 29.34)	(20.04, 33.09)	(18.32, 30.45)
Last vaccination					
≥LLOQ, s/n (%)		74/100 (74.0)	74/96 (77.1)	72/89 (80.9)	22/95 (23.2)
80% CI[a]		(67.54, 79.71)	(70.66, 82.62)	(74.48, 86.22)	(17.57, 29.64)

Secondary Objectives (one month after the first vaccination)

- One month after the first vaccination, the GMTs against pooled serogroup B strains; serogroup B test strains M14459, 96217, NZ98/254, and M07-0241084; and serogroups A, C, W-135, and Y were similar between the rMenBOMV+ACWY_S and rMenBOMV+ACWY_D study groups.

- One month after the first vaccination, the percentages of subjects with hSBA titers ≥LLOQ against serogroup B test strains M14459, 96217, NZ98/254, and M07-0241084; and serogroups A, C, and, W-135 were similar between the rMenBOMV+ACWY_S and rMenBOMV+ACWY_D study groups. The percentages of subjects with hSBA titers ≥LLOQ against serogroup Y were lower in the rMenBOMV+ACWY_S study group compared with the rMenBOMV+ACWY_D study group.

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- One month after the first vaccination, the percentages of subjects with a 4-fold increase in hSBA titer against serogroup B test strains M14459, 96217, NZ98/254, and M07-0241084; and serogroups C, W-135, and Y were similar between the rMenBOMV+ACWY_S and

rMenBOMV+ACWY_D study groups. The percentages of subjects with a 4-fold increase in hSBA titer against serogroup A were lower in the rMenBOMV+ACWY_S study group compared with the rMenBOMV+ACWY_D study group.

Safety results

Overall, the percentages of subjects with local and systemic reactions were similar in the rMenBOMV+ACWY_S, rMenBOMV+ACWY_D, and rMenBOMV study groups and were lower in the MenACWY study groups compared with other study groups.

Within 1 to 7 days of any study vaccination, the most common local solicited reaction was pain which was reported in subjects after the first vaccination and in subjects after the second vaccination. A total of subjects after the first vaccination and subjects after the second vaccination reported severe pain.

Table 12.1 Overall Summary of Solicited and Unsolicited Adverse Events (Solicited Safety Set and Unsolicited Safety Set)

Number of Subjects With	MenABCWY N=100 n (%)	rMenBOMV +ACWY_S N=104 n (%)	rMenBOMV +ACWY_D N=100 n (%)	rMenBOMV N=94 n (%)	MenACWY N=102 n (%)
Solicited Adverse Events Within 1-7 Days of Vaccination (Solicited Safety Set)					
Any Visit					
Any solicited AE		103 (99.0)	98 (98.0)	94 (100.0)	76 (74.5)
Any solicited local AE[a]		103 (99.0)	98 (98.0)	94 (100.0)	59 (57.8)
Menveo		96 (92.3)	77 (77.0)	-	59 (57.8)
Bexsero/ABCWY[a]		102 (98.1)	97 (97.0)	94 (100.0)	-
Any solicited systemic AE		79 (76.0)	81 (81.0)	74 (78.7)	60 (58.8)
Visit 1					
Any solicited AE		102 (98.1)	97 (97.0)	93 (98.9)	76 (74.5)
Any solicited local AE[a]		101 (97.1)	97 (97.0)	90 (95.7)	59 (57.8)
Menveo		86 (82.7)	47 (47.0)	-	59 (57.8)
Bexsero/ABCWY[a]		100 (96.2)	96 (96.0)	90 (95.7)	-
Any solicited systemic AE		73 (70.2)	66 (66.0)	61 (64.9)	60 (58.8)
Visit 3					
Any solicited AE		98 (94.2)	96 (96.0)	91 (96.8)	-
Any solicited local AE[a]		98 (94.2)	96 (96.0)	90 (95.7)	-
Menveo		89 (85.6)	69 (69.0)	-	-
Bexsero/ABCWY[a]		94 (90.4)	95 (95.0)	90 (95.7)	-
Any solicited systemic AE		65 (62.5)	69 (69.0)	63 (67.0)	-
Unsolicited Adverse Events (Unsolicited Safety Set)					
Any AE		33 (31.7)	35 (35.0)	29 (30.9)	15 (14.7)
AE possibly or probably related to study vaccine(s)		11 (10.6)	13 (13.0)	11 (11.7)	4 (3.9)
AE leading to withdrawal from the study		0	0	0	0
AE leading to withdrawal from the study vaccine(s)		0	0	0	0
AE leading to a medically attended visit		17 (16.3)	14 (14.0)	13 (13.8)	6 (5.9)
Any SAE		2 (1.9)	1 (1.0)	2 (2.1)	0
SAE possibly or probably related to study vaccine(s)		0	0	1 (1.1)	0
SAE leading to withdrawal from the study		0	0	0	0
SAE leading to withdrawal from the study vaccine(s)		0	0	0	0
SAE leading to a medically attended visit		2 (1.9)	1 (1.0)	2 (2.1)	0
SAE leading to death		0	0	0	0
SAE possibly or probably related to study vaccine(s) and leading to death		0	0	0	0

Source: Table 14.3.1.1 and Table 14.3.2.1.
Abbreviations: AE, adverse event; SAE, serious adverse event.
Note: Within 1-7 days of vaccination do not include 30 minutes post-vaccination.
a. Subjects with any solicited local AE within each study group.
b. MenABCWY column contains MenABCWY results, other columns contain results for *Bexsero*.

The most common systemic solicited reactions were fatigue (after the first vaccination and after the second vaccination) and headache (after the first vaccination and after the second vaccination).

Severe fatigue was reported in subjects after the first vaccination and subjects after the second vaccination. Severe headache was reported in subjects after the first vaccination and subjects after the second vaccination. Overall, systemic reactions were mild to moderate in severity and were transient in nature.

Fever (≥38°C) was reported in subjects after the first and second vaccination and none of the subject reported body temperature ≥40°C.

Table 12.3 Summary of Solicited Systemic Adverse Events 1-7 Days Post-vaccination by Visit (Solicited Safety Set)

Solicited Symptom Visit	MenABCWY N=100 n (%)			rMenBOMV+ACWY_S N=104 n (%)			rMenBOMV+ACWY_D N=100 n (%)			rMenBOMV N=94 n (%)			MenACWY N=102 n (%)		
Maximal Severity	N1	Any	Severe	N1	Any	Severe	N1	Any	Severe	N1	Any	Severe	N1	Any	Severe
Arthralgia															
Any				103	29 (28.2)	3 (2.9)	98	18 (18.4)	2 (2.0)	92	19 (20.7)	1 (1.1)	98	18 (18.4)	0
Visit 1				100	15 (15.0)	2 (2.0)	96	9 (9.4)	1 (1.0)	86	9 (10.5)	0	98	18 (18.4)	0
Visit 3				103	19 (18.4)	1 (1.0)	98	12 (12.2)	1 (1.0)	92	17 (18.5)	1 (1.1)	-	-	-
Fatigue															
Any				104	74 (71.2)	14 (13.5)	100	72 (72.0)	11 (11.0)	94	63 (67.0)	16 (17.0)	100	50 (50.0)	7 (7.0)
Visit 1				102	61 (59.8)	8 (7.8)	100	55 (55.0)	2 (2.0)	92	46 (50.0)	7 (7.6)	100	50 (50.0)	7 (7.0)
Visit 3				104	61 (58.7)	7 (6.7)	100	62 (62.0)	9 (9.0)	94	56 (59.6)	11 (11.7)	-	-	-
Nausea															
Any				103	26 (25.2)	5 (4.9)	98	26 (26.5)	2 (2.0)	93	26 (28.0)	2 (2.2)	99	14 (14.1)	0
Visit 1				101	23 (22.8)	3 (3.0)	97	14 (14.4)	1 (1.0)	85	13 (15.3)	0	99	14 (14.1)	0
Visit 3				102	13 (12.7)	3 (2.9)	98	15 (15.3)	1 (1.0)	93	17 (18.3)	2 (2.2)	-	-	-
Headache															
Any				104	57 (54.8)	9 (8.7)	100	54 (54.0)	6 (6.0)	94	52 (55.3)	6 (6.4)	99	36 (36.4)	4 (4.0)
Visit 1				102	46 (45.1)	4 (3.9)	98	38 (38.8)	3 (3.1)	92	36 (39.1)	4 (4.3)	99	36 (36.4)	4 (4.0)
Visit 3				104	36 (34.6)	5 (4.8)	100	37 (37.0)	3 (3.0)	93	39 (41.9)	2 (2.2)	-	-	-
Myalgia															
Any				103	49 (47.6)	7 (6.8)	99	44 (44.4)	2 (2.0)	94	41 (43.6)	5 (5.3)	99	28 (28.3)	4 (4.0)
Visit 1				101	29 (28.7)	4 (4.0)	97	27 (27.8)	0	87	21 (24.1)	2 (2.3)	99	28 (28.3)	4 (4.0)
Visit 3				103	38 (36.9)	4 (3.9)	99	35 (35.4)	2 (2.0)	94	38 (40.4)	3 (3.2)	-	-	-
Fever[a]					None (<38.0°C)	Any (≥38.0°C)		None (<38.0°C)	Any (≥38.0°C)		None (<38.0°C)	Any (≥38.0°C)		None (<38.0°C)	Any (≥38.0°C)
Any				104	97 (93.3)	7 (6.7)	100	92 (92.0)	8 (8.0)	94	92 (97.9)	2 (2.1)	101	98 (97.0)	3 (3.0)
Visit 1				103	98 (95.1)	5 (4.9)	100	95 (95.0)	5 (5.0)	94	93 (98.9)	1 (1.1)	101	98 (97.0)	3 (3.0)
Visit 3				104	101 (97.1)	3 (2.9)	100	97 (97.0)	3 (3.0)	94	93 (98.9)	1 (1.1)	-	-	-

Source: Table 14.3.1.5.
Abbreviations: N1, number of subjects with non-missing data

The percentages of subjects with unsolicited AEs were similar across the study groups (14.7% to 26.0%). The most commonly reported AE after any vaccination were injection site pain (up to 5.3%) followed by upper respiratory tract infection (up to 5%) and injection site induration (up to 4.8%).

A total of 14 (14.0%), 17 (16.3%), 14 (14.0%), 13 (13.8%), and 6 (5.9%) subjects had at least one unsolicited medically attended AEs in rMenBOMV+ACWY_S, rMenBOMV+ACWY_D, rMenBOMV, and MenACWY study groups, respectively.

No deaths were reported in this study. A total of 2 (1.9%), 1 (1.0%), and 2 (2.1%) subjects had at least one SAEs post-vaccination at any visit in the rMenBOMV+ACWY_S (concussion in both the subjects considered not related to study vaccines), rMenBOMV+ACWY_D (tibia fracture considered not related to study vaccines), and rMenBOMV study groups (lower limb fracture in 1 subject considered not related to study vaccines and syncope in 1 subject considered related to study vaccines), respectively.

No subjects were withdrawn from the study or study vaccine due to AEs. None of the subjects reported an AESI (arthritis) in the study.

2.3.3. **Discussion on clinical aspects**

The purpose of the current study was to evaluate whether there is a potential immune interference (possible lymph nodes stress) when new investigational vaccine MenABCWY (the combination vaccine consisting of MenACWY (Menveo) lyophilized component and rMenB+OMV NZ (Bexsero) liquid component) is administered to healthy adolescents and adults following a 2-dose vaccination schedule with doses administered 2 months apart. Bexsero and Menveo were used as comparators in this study.

The results showed that the highest antibody response against MenB serotypes was archived when rMenB+OMV NZ (Bexsero) was administered alone. Also, if Bexsero and Menveo were administered at the same time, but on different arms, the antibody levels against MenB was comparable as if Bexsero was administered alone.

The safety data did not add any new information about Bexsero safety profile. Interestingly, fever after Bexsero administration was rare (1%) whereas in investigational product it reached to 6 % of recipients to report appearance of fever. The study population was relatively small (Subjects at age 10-17; N= 147) and therefore the chance to detect rare AEs and SAEs is low. No new safety or efficacy concern is raised from this study.

3. CHMP overall conclusion and recommendation

The results of this study indicate no new efficacy or safety concern for Bexsero. This P46 procedure is considered fulfilled.

PAM Fulfilled:

No regulatory action required.