14 December 2023
EMA/8739/2024
Human Medicines Division

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

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/001095/P46/046

Note

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

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1. Introduction

On the 28th of March 2023, the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

During the procedure the MAH informed the EMA that the study report for study V72_72 was republished due to modifications to the MenACWY hSBA LOQ values.

A short critical expert overview has also been provided.

Menveo (MenACWY vaccine) is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W-135 and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MENB REC 2ND GEN-038 (V72_72) is a standalone study.

Study MENB REC 2ND GEN-038 (V72_72) has not been conducted as part of an agreed paediatric investigation plan (PIP). In this study, submitted as part of this procedure, Menveo, further referred to as MenACWY, was used:

- as a negative control to assess test-based vaccine effectiveness of MenB-containing vaccines
- as a comparator for demonstrating non-inferiority of a 2-dose series of the investigational vaccine, MenABCWY, versus a single dose of MenACWY, in terms of immune response to meningococcal serogroups A, C, W and Y.
- to confirm that reactogenicity and safety to healthy subjects have been assessed, as per vaccination schedule.

For the current procedure, only results related to Menveo (MenACWY) will be assessed and discussed.

During the current procedure, the MAH republished the clinical study report due to a change to the limits of quantitation (LOQs) of the Men A, C, W and Y agar-overlay hSBA. The assessment presented in this report will take into consideration version 02 of the CSR.

2.2. Information on the pharmaceutical formulation used in the study

Menveo consists of powder and solution for injection. Menveo is a quadrivalent meningococcal serogroups A, C, W-135 and Y oligosaccharide vaccine, conjugated to Corynebacterium diphtheriae CRM197 carrier protein. Menveo should be injected intramuscularly as a single dose (0.5 mL) into the deltoid area.

Menveo is commercially available. According to the protocol, the commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

MENB REC 2ND GEN-038 (V72_72) study: A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults. Menveo was used as one of the active comparator vaccines in the study.

2.3.2. Clinical study

MENB REC 2ND GEN-038 (V72_72)

Description

The primary purpose of the MENB REC 2ND GEN-038 (V72_72) study was to evaluate the vaccine effectiveness of the Meningococcal Group B (Bexsero) and the combined Meningococcal Serogroups A, B, C, W, and Y (MenABCWY) vaccine by measuring the bactericidal serum activity against a large panel of epidemiologically relevant invasive disease strains of *Neisseria meningitidis* (*N. meningitidis*) serogroup B using an endogenous complement human serum bactericidal assay (enc-hSBA). This was evaluated when Meningococcal Group B vaccine was administered in a 3-dose (0,2,6-months) or a 2-dose (0,6-months; 0,2-months) schedule and when the combined MenABCWY vaccine was administered in a 2-dose (0,6-months) schedule (Figure 1). In addition, safety of the vaccines administered as per the vaccination schedule to healthy subjects were also assessed.

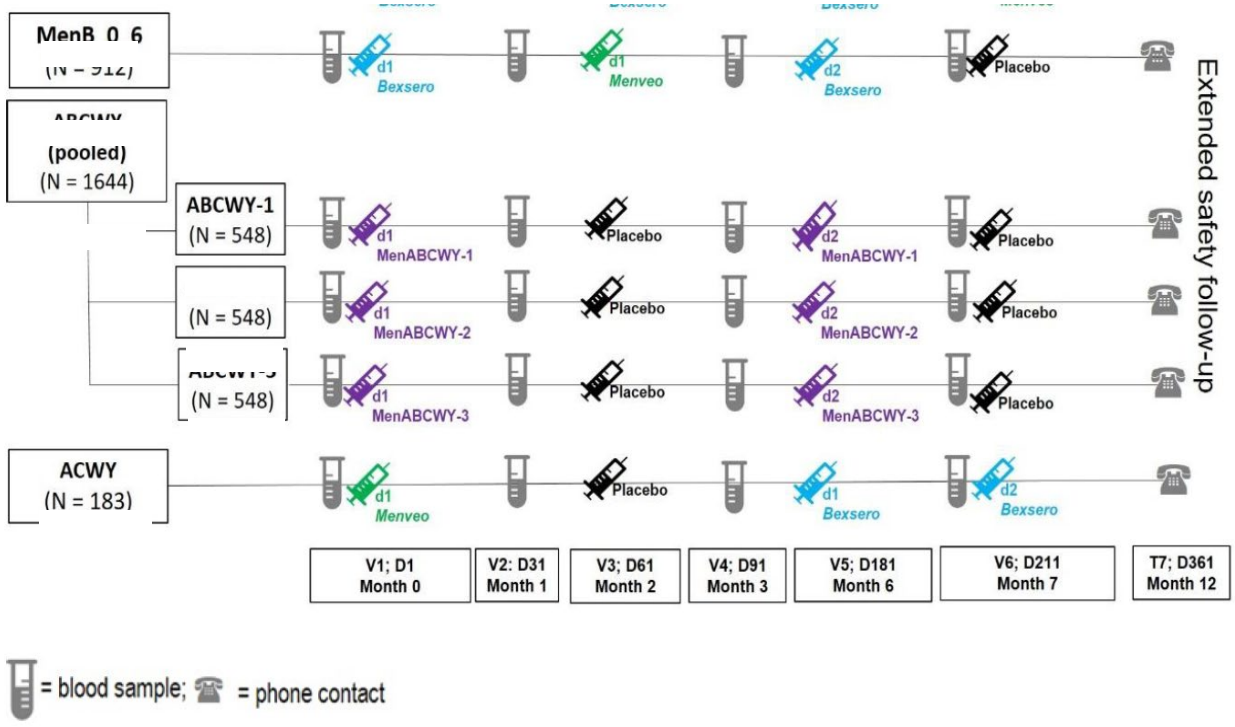

Figure 1 Study design overview. N = number of subjects; d = dose; V = visit; D = day; T=Telephone call

Assessor's comment

Healthy subjects between 10-25 years of age received either MenACWY (Menveo), rMenB+OMV NZ (Bexsero), MenABCWY (combination vaccine based on Menveo and Bexsero) or placebo at visit 1, 3, 5 and 6 (day 1, 61, 181 and 211). Only results on MenACWY will be assessed. Participants in the ACWY-group, MenB_0_2_6 and MenB_0_6 received a single dose of MenACWY at visit 1, 6 and 3, respectively.

Data from the ACWY group will be discussed for immunogenicity since the immune response to MenA, C, W and Y one month after the Menveo vaccination was only assessed in this study group and not in the others receiving MenACWY. Data from the MenB_0_6 group and the ACWY group will be discussed for safety. It is regretted that solicited AEs were not collected after vaccination 4 (Day 211). As a result, only limited safety data is collected for the Menveo dose administered to the MenB_0_2_6 group.

The design of the study will be described below, however, no assessment of the adequacy of the trial design is provided as the trial was not designed to assess Menveo. The assessment performed for the current procedure focusses on deriving useful information on Menveo that might impact the SmPC and/or RMP.

Methods

Study participants

Healthy males and females between 10 and 25 years of age at the time of the first vaccination were included. Subjects who were either unvaccinated with MenACWY vaccine or have received a single previous dose of MenACWY vaccine could participate in the study, if they have received the vaccination at least 4 years prior to informed consent and assent as applicable (with the exception of meningococcal C vaccination, if the last dose of MenC was received at ≤24 months of age).

Exclusion criteria included current or previous, confirmed or suspected disease caused by *N. meningitidis*, contact with and/or intimate exposure to an individual with confirmed *N. meningitidis* infection within 60 days of enrolment, previous MenB vaccination, history of hypersensitivity to components of the vaccine, a known or suspected disorder of the immune system, neuroinflammatory or neurological conditions, pregnancy.

Assessor's comments

MenACWY is indicated for children (from 2 years of age), adolescents and adults. MenACWY can also be administered as a booster dose. In this study, healthy subjects of 10-25 of age were included. Not all subjects were naïve for MenACWY. This is consistent with the current use according to the SmPC.

Subjects could participate in the study, if they have received a previous MenACWY vaccination at least 4 years prior to informed consent. It is unclear why this timeframe of 4 years was chosen as a considerable percentage of subjects has a persistent immune response 5 years after vaccination with Menveo (as stated in the SmPC). This indicates that these participants might have a higher baseline hSBA titer and the vaccine will most likely act as a booster dose. The MAH was requested to elaborate on this. The MAH indicated that participants with a previous history of MenACWY vaccination were included to ensure adequate representation of US adolescents and young adults that have been vaccinated according to ACIP recommendations. The timeframe of at least 4 years between primary and booster vaccination reflects the US prescribing information. Of the population enrolled in the MenACWY group, only 13% (22 out of 177) has received MenACWY vaccination at least 4 years previous. The results in participants without previous vaccination with MenACWY are included in the report. As expected, the results in the group without the previous ACWY vaccination are slightly reduced compared to the total population, however, they do not substantially alter the conclusions of the report with regard to MenACWY vaccination.

A similar question remains for the meningococcal C vaccination. The MAH stated that participants were eligible in case MenC vaccine was received at ≤ 24 months of age. It can be agreed that MenC vaccination has been and still is standard of care in multiple countries. This might in part explain the

rather high percentage of participants achieving hSBA ≥LLOQ at baseline considering the MAH considers these participants "ACWY-naïve".

Treatments

The 3651 participants were randomized (5:5:3:3:3:1 ratio) to one of the 6 parallel study groups (Figure 1) to receive different treatment schedules. An overview of the different treatments is given in Table 1.

Table 1 Treatments administered

Study Treatment Name:	*Bexsero*	MenABCWY#		*Menveo**		Placebo
Vaccine(s)/Product(s) name	rMenB+OMV NZ	MenACWY lyo	rMenB+OMV NZ	MenA	MenCWY	NaCl
Vaccines/ product formulation†:	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from N. meningitidis, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA(10 µg)-CRM197; MenC(5 µg)-CRM197; MenW135(5 µg)-CRM197; MenY(5 µg)-CRM197	NHBA fusion protein (50 µg) adsorbed on aluminium hydroxide; NadA protein (50 µg) adsorbed on aluminium hydroxide; fHBP fusion protein (50 µg) adsorbed on aluminium hydroxide; OMV from N. meningitidis, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL	MenA(10 µg)-CRM197 (16.7–33.3 µg)	MenC(5 µg)-CRM197 (7.1–12.5 µg); MenW135(5 µg)-CRM197(3.3–8.3 µg); MenY(5 µg)-CRM197 (5.6–10 µg); water for injections q.s. 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections
Route of Administration	Intramuscular use	Intramuscular use		Intramuscular use		Intramuscular use
Product category	***Combination***	***Combination***		***Biological***		***Combination***
Type	***Study; Control***	***Study***		***Control***		***Additional***
Number of doses to be administered:						
• MenB_0_2_6 group	3	-		1		-
• MenB_0_6 group	2	-		1		1
• ABCWY-1 group	-	2		-		2
• ABCWY-2 group	-	2		-		2
• ABCWY-3 group	-	2		-		2
• ACWY group	2	-		1		1
Volume to be administered	0.5 mL	0.5 mL		0.5 mL		0.65 mL**

OMV = Outer Membrane Vesicles; SPM = Study procedure manual; CRM 197 = Corynebacterium diphtheriae cross reacting material-197; fHbp = factor H binding protein; GSK = GlaxoSmithKline; NaCl = sodium chloride; NHBA = Neisserial heparin binding antigen; NZ = New Zealand

† The composition per dose is presented here

** Menveo commercial formulation consisting of a MenA lyophilised component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL) by a qualified healthcare professional.*

 # MenABCWY formulation consisting of MenACWY lyo (lyophilised component) and of MenB liquid component, to be reconstituted together before administration (0.5 mL) by a qualified healthcare professional. Both the manufacture and the final composition of the MenB component of the MenABCWY are identical to that of the commercial Bexsero. However, to ensure a consistent reconstitution procedure and to reduce the risk of under-dosing the MenB component, the filling weight has been increased from a nominal 0.609 g presents in commercial Bexsero to 0.640g in the MenB component, used to reconstitute MenABCWY.

*** The volume of the saline pre-filled syringe may be between 0.6ml and 0.8 mL. The full volume is to be injected.*

All injections were administered intramuscularly as a single dose into the deltoid area of the non-dominant arm.

Assessor's comments

MenACWY is administered as a single dose of 0.5 mL. Composition and vaccination regimen used in the study is similar to composition and posology described in the SmPC for Menveo.

The volume to be administered for vaccines is 0.5 mL whereas the volume to be administered for placebo is 0.65 mL. It is not understood why different volumes were chosen. However, considering that the unblinded personnel responsible for preparing and/or delivering injections were not involved in the analysis, this issue was not further pursued.

Objective(s)

Assessor's comments

Note that only objectives and endpoints relevant for evaluating the response to MenACWY are listed.

Primary objective:

- To evaluate the safety and reactogenicity of the MenACWY vaccine.

Secondary objective:

- To assess the immune response to MenACWY (single dose) vaccine against *N. meningitidis* serogroups A, C, W and Y, at pre-vaccination (Day 1, Month 0) and 1 month after the MenACWY vaccination.

Outcomes/endpoints

Primary safety endpoints

- The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.
- The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.
- The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).

Secondary immunogenicity endpoints

- The percentage of subjects with hSBA titres ≥ LLOQ for serogroups A, C, W and Y at baseline (Day 1, Month 0) and at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
- The percentage of subjects with 4-fold rise in hSBA titres at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
- hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y at baseline (Day 1, Month 0) and at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).
- hSBA GMRs against *N. meningitidis* serogroups A, C, W and Y at 1 month after the single MenACWY vaccination in the ACWY group (Day 31, Month 1) as compared to baseline (Day 1, Month 0).
- The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at baseline (Day 1, Month 0) and at 1 month after the MenACWY vaccination in the ACWY group (Day 31, Month 1).

Assessor's comments

Safety endpoints taken along in the study are in line with the Guideline on clinical evaluation of vaccines. Local and systemic solicited adverse events are well chosen, based on the SmPC.

The immune response following MenACWY vaccination was determined as the percentage of subjects with hSBA titres ≥ LLOQ, percentage of subjects with a 4-fold rise in hSBA titres, hSBA GMTs and hSBA GMRs and total IgG at one month after vaccination. This is considered acceptable. An hSBA titre of 1:4 is considered a surrogate of protection. As all LLOQs for the assays fall above 1:4, this is considered a conservative measure and will highlight potential protection.

Sample size

Approximately 3651 healthy adolescents and young adults aged 10-25 years were planned to be enrolled into the study. Of the planned subjects, a subset was planned to receive MenACWY:

- MenB_0_2_6 group: Approximately 912 subjects were planned to receive MenACWY vaccine at visit day 211 (month 6);
- MenB_0_6 group: Approximately 912 subjects were planned to receive MenACWY vaccine at visit day 61 (month 2);
- MenACWY group: Approximately 183 subjects were planned to receive MenACWY vaccine at visit day 1 (month 0).

Assessor's comments

The study was not powered to study MenACWY as MenACWY was used only as an active comparator vaccine in the study. The numbers are adequate to determine immunogenicity and the reactogenicity profile.

Randomisation and blinding (masking)

Allocation of the subject to a study group/a treatment number at the investigator site was performed using a randomisation system on internet (SBIR). The randomisation algorithm used a minimisation procedure accounting for study, region (US and ex-US countries), previous MenACWY vaccination (Yes/No), and age category (10-17 years of age and 18-25 years of age). Minimisation factors had equal weight in the minimisation algorithm.

Data was collected in an observer-blind manner; the participants and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and effectiveness) will all be unaware of which vaccine/product was administered. A minimum number of study site personnel responsible for preparing and / or delivering the injections were to be unblinded.

Assessor's comments

The randomisation procedure is based on a minimisation procedure accounting for the factors study, region (US and ex-US countries), previous MenACWY vaccination (Yes/No), and age category (10-17 years of age and 18-25 years of age). It is unclear why minimisation was applied for this sizable trial as this procedure is mainly applied in case stratification is not possible due to many prognostic factors for small trials (Guideline on adjustment for baseline covariates in clinical trials). Minimisation does not guarantee balance within combinations of prognostic factors. However, as adequacy of trial design was not the focus of this procedure, this issue is not further pursued.

Statistical Methods

Analysis sets

Enrolled Set = Subject/ Subject for whom parent(s)/LAR's agreed to participate in a clinical study after completion of the informed consent process, who meet screening/eligibility criteria and randomized and/or received study intervention or undergone an invasive procedure.

Exposed Set = All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.

Full Analysis Set = All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data.

Per Protocol Set = All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.

Solicited Safety Set = All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data beyond 30 minutes post vaccination.

Unsolicited Safety Set = All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.

Analysis of primary safety endpoints:

Analyses were conducted on the Solicited Safety Set (solicited local and systemic AEs and other solicited AEs), Unsolicited Safety Set (unsolicited AEs), and Overall Safety Set. The safety analyses were descriptive.

Analysis of secondary immunogenicity endpoints:

Immunogenicity of the MenACWY vaccine against serogroups A, C, W and Y was evaluated by serum bactericidal assays using exogenous source of human complement (hSBAs), using indicator strains representing serogroups A, C, W and Y. To this end, whole blood was drawn from the MenACWY group at pre-vaccination (Visit 1, month 0) and Visit 2 (month 1) for the bactericidal assays (enc-hSBA and/ or hSBA(s) and ELISA (or equivalent).

The hSBA titres at both time points were logarithmically transformed (base10) to fulfil the normal distribution assumption. For each *N. meningitidis* serogroup A, C, W and Y, the GMTs and GMRs (postvaccination/baseline) were obtained from an Analysis of Variance (ANOVA) with factors for vaccine group, region (US/ex-US), age category (10-17 YoA/18-25 YoA), and previous MenACWY vaccination (y/n), and then exponentiating the log-transformed means and their 95% CIs.

An Enzyme-Linked Immunosorbent Assay (ELISA) was used to evaluate the serotype-specific IgG responses to A, C, W, and Y at baseline and month 1. The total IgG were analysed in a comparable way as described above for hSBA titres. Since total IgG is measured as concentration instead of titer, the resulting geometric mean of the concentrations is abbreviated as GMC.

To assess the percentage of subjects with 4-fold rise in hSBA titres, the 4-fold rise is defined as:

- a post-vaccination hSBA titre ≥4 times the LOD or ≥LLOQ, whichever is greater, for subjects with a pre-vaccination hSBA titre <LOD
- a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
- a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

For each *N. meningitidis* A, C, W and Y and for each (individual response) the percentages of subjects with hSBA titres ≥LLOQ and of subjects with 4- fold rise and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method were calculated.

Analyses were based on the Full Analysis Set (FAS).

Assessor's comments

In previous studies, efficacy of Menveo has been inferred by measuring the generation of serogroup-specific anti-capsular antibodies with bactericidal activity. Serum bactericidal activity (SBA) was measured using human serum as the source of exogenous complement (hSBA). The hSBA 1:4 is considered a surrogate of protection. As LLOQ is often higher than 1:4, as is the case in this study, this is considered a conservative surrogate.

For determining the 4-fold rise in hSBA titers, note that different cut offs (LLOQ) were used as compared to previous assays employed in the clinical development of Menveo. The MAH confirmed that a different quantitative hSBA assay, the MenACWY agar-overlay hSBA assay, was used compared to the assay used during the initial application, the manual (tilt) hSBA assay.

Direct comparisons of immune responses between the present study and older studies should be avoided or at least interpreted with caution.

During the course of the current procedure the MAH republished the clinical study report due to a change to the limits of quantitation for the MenA, C, W and Y agar-overlay hSBA. Based on the validation of the agar-overlay hSBA in 2020 using LSOP 9000064782 version 02, dilution linearity led to other LLOQ values for Men A, C, W and Y. Based on the validation of dilutional linearity for version 07, the LLOQ increased. As the LLOQ of the assay increased and remained well above the correlate of protection (CoP), no clinical impact is expected based on changes in the LLOQs.

Results

Participant flow

A total of 3657 subjects were enrolled (Figure 2), and 3638 subjects were randomized and received at least 1 dose of study vaccination.

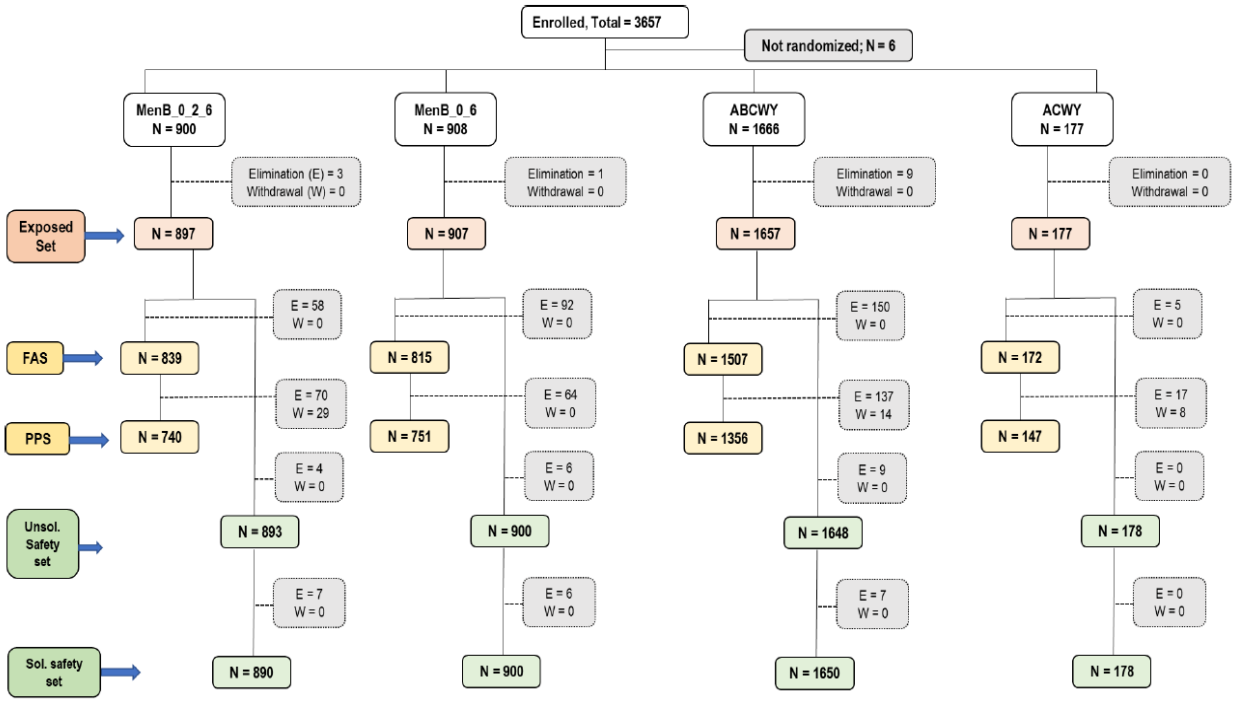

Figure 2 Subject disposition flowchart of each treatment arm. FAS, full analysis set; PPS, per protocol set

In the ACWY group 163/178 completed the study, 15 withdrawn from the study due to consent withdrawal not due to an (S)AE (n=7), lost to follow-up (n=4), an adverse event requiring expedited reporting (n=1), protocol deviation (n=1), migrated/moved away from study area (n=1) or another reason (n=1).

In the MenB_0_6 group, where also the safety effects of MenACWY administration is evaluated, 811/906 completed the study, 95 where withdrawn from the study due to consent withdrawal not due to an (S)AE (n=38), lost to follow-up (n=36), protocol deviation (n=8), migrated/moved away from study area (n=7), an adverse event requiring expedited reporting (n=2), an unsolicited non-serious adverse event (n=2) or a solicited adverse event (n=2).

Overall, 478 out of 3638 (13.1%) subjects in the Exposed Set had received a previous MenACWY vaccination. Of which n=22 in the ACWY group (8 subjects of 10-17 years of age and 14 subjects of 18-25 years of age) and n=119 in the MenB_0_6 group (68 subjects of 10-17 years of age and 51 subjects of 18-25 years of age).

Assessor's comments

In the participant flow 177 subjects were randomised into the MenACWY group. Whereas 178 subjects were in the (un)solicited safety set. It was unclear where this extra subject came from. The MAH stated that the additional subject in the unsolicited safety set was due to one participant who was randomised to the MenB_0_6 group, but received MenACWY vaccine as a first dose. This subject was included and analysed in the safety analyses of the MenACWY group.

In the MenACWY group and the MenB_0_6 group, approximately 10% of participants withdrew during the study. The main reason was consent withdrawal not due to an (S)AE. This is not unexpected in the population studied.

There were 22 subjects in the ACWY group and 119 subjects in the MenB_0_6 group that had received a previous MenACWY vaccination. Thus, majority was naïve for MenACWY.

Recruitment

This study was conducted at 114 centers in 7 countries: 7 in Australia, 12 in Canada, 12 in Czechia, 3 in Estonia, 10 in Finland, 5 in Turkey and 65 in United States (US).

Baseline data

Demographic and other baseline characteristics were generally balanced in the study groups (Table 3). The mean age of subjects who participated in this study was 16.5 (SD, 4.7) years across groups. There was a slightly higher percentage of 10–17-year-olds (59.3%) than 18–25-year-olds (40.6%). Overall, 53.5% of participants in the study were females. A total of 89% of subjects were of White heritage and the majority (93.7%) identified as Not Hispanic or Latino ethnicity. Thirty percent of the enrolled subjects were from US and the rest of the subjects were from Australia, Canada, Czechia, Estonia, Finland and Turkey. Overall, 478 out of 3638 (13.1%) subjects in the Exposed Set had received a previous MenACWY vaccination (of which n=22 in the ACWY group and n=119 in the MenB_0_6 group).

Table 2 Summary of demography and baseline characteristics – Enrolled Set

	MenB_0_2_6 N=900		MenB_0_6 N=908		ABCWY N=1666		ACWY N=177		Not Randomized N=6		Total N=3657	
	Value or		Value or		Value or		Value or		Value or		Value or	
	n	%	n	%	n	%	n	%	n	%	n	%
Age (years) at first vaccination												
n	897		907		1658		177		0		3639	
Mean	16.5		16.5		16.5		16.9				16.5	
Standard Deviation	4.7		4.7		4.7		4.6				4.7	
Median	16.0		16.0		16.0		16.0				16.0	
Minimum	10		9		9		10				9	
Maximum	26		26		26		25				26	
Age group (years)												
10-17	534	59.3	542	59.7	989	59.4	102	57.6	0	0.0	2167	59.3
18-25	366	40.7	366	40.3	677	40.6	75	42.4	0	0.0	1484	40.6
Missing	0	0.0	0	0.0	0	0.0	0	0.0	6	100	6	0.2
Age group (EudraCT)												
Children (2-11 years)	183	20.3	172	18.9	320	19.2	27	15.3	0	0.0	702	19.2
Adolescents (12-17 years)	349	38.8	369	40.6	666	40.0	75	42.4	0	0.0	1459	39.9
Adults (18-64 years)	365	40.6	366	40.3	672	40.3	75	42.4	0	0.0	1478	40.4
Missing	3	0.3	1	0.1	8	0.5	0	0.0	6	100	18	0.5
Region												
US	274	30.4	272	30.0	499	30.0	51	28.8	0	0.0	1096	30.0
ex-US	626	69.6	636	70.0	1167	70.0	126	71.2	0	0.0	2555	69.9
Missing	0	0.0	0	0.0	0	0.0	0	0.0	6	100	6	0.2
Country												
Australia	73	8.1	66	7.3	146	8.8	11	6.2	0	0.0	296	8.1
Canada	51	5.7	63	6.9	108	6.5	7	4.0	1	16.7	230	6.3
Czech Republic	179	19.9	189	20.8	344	20.6	38	21.5	0	0.0	750	20.5
Estonia	28	3.1	40	4.4	54	3.2	5	2.8	0	0.0	127	3.5
Finland	214	23.8	191	21.0	366	22.0	49	27.7	0	0.0	820	22.4
Turkey	81	9.0	87	9.6	149	8.9	16	9.0	0	0.0	333	9.1
United States	274	30.4	272	30.0	499	30.0	51	28.8	5	83.3	1101	30.1
Sex												
Male	434	48.2	461	50.8	728	43.7	77	43.5	2	33.3	1702	46.5
Female	466	51.8	447	49.2	938	56.3	100	56.5	4	66.7	1955	53.5
Ethnicity												
Hispanic or Latino	55	6.1	41	4.5	95	5.7	6	3.4	0	0.0	197	5.4
Not Hispanic or Latino	842	93.6	854	94.1	1552	93.2	171	96.6	6	100	3425	93.7
Not Reported	3	0.3	13	1.4	19	1.1	0	0.0	0	0.0	35	1.0
Race												
American Indian or Alaska Native	5	0.6	5	0.6	3	0.2	0	0.0	0	0.0	13	0.4
Asian	43	4.8	60	6.6	71	4.3	9	5.1	1	16.7	184	5.0
Black or African American	33	3.7	29	3.2	61	3.7	6	3.4	2	33.3	131	3.6
Native Hawaiian or Other Pacific Islander	3	0.3	1	0.1	3	0.2	0	0.0	0	0.0	7	0.2
White	799	88.8	793	87.3	1498	89.9	161	91.0	3	50.0	3254	89.0
Other	17	1.9	20	2.2	30	1.8	1	0.6	0	0.0	68	1.9

MenB_0_2_6 = Subjects received 3 doses of rMenB+OMV NZ at Months 0, 2 and 6; MenB_0_6 = Subjects received 2 doses of rMenB+OMV NZ at Months 0 and 6 and 1 dose of MenACWY vaccine at Month 2. ABCWY = Subjects received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY = Subjects received 1 dose of MenACWY vaccine at Month 0, one dose of placebo at Month 2 and 1 dose of rMenB+OMV NZ at Month 6.

Not randomized: Subjects who enrolled in the study but withdrew prior to randomization into any study group.
N = number of subjects; n/% = number / percentage of subjects in a given category

Assessor's comments

The majority of subjects in the ACWY group and MenB_0_6 were adolescents between 10-17 years of age (57.6% and 59.7% respectively).

Baseline characteristics were balanced between the ACWY and MenB_0_6 group.

Number analysed

A total of 3333 (91.6 % of the enrolled subjects) subjects were included in the full analysis set (FAS), from which a total of 2994 (89.8%) subjects were included in the per protocol set (PPS). The most common reasons for elimination from PPS were out of window treatment administration (3.5%, overall) and out of window assessment for immunogenicity (3.0%, overall).

A total of 370 subjects (10.2%) withdrew prematurely from the study. The most common reasons for premature withdrawal throughout the study were withdrawal of consent, not due to an (S)AE (4%, overall) and lost to follow-up (3.9%, overall).

For the two groups receiving Menveo that were analysed for efficacy and safety in this procedure; in total 95 (10.5%) and 15 (8.4%) subjects of the MenB_0_6 group and ACWY group respectively, withdrew prematurely from the study. This was most commonly due to withdrawal of consent, not due to an (S)AE (4.2% in the MenB_0_6 group and 3.9% in the ACWY group) and lost to follow-up (4.0% in the MenB_0_6 group and 2.2% in the ACWY group).

Efficacy results

Assessor's comments

As indicated, only results directly relevant for evaluating the response to MenACWY are assessed. For efficacy only the first vaccination of the ACWY group is taken along in the assessment.

Percentage of subjects with hSBA titers ≥ LLOQ

At baseline, the percentages of subjects with hSBA titres ≥ LLOQ against *N. meningitidis* serogroups were: 11.7% for A, 25.9% for C, 12.9% for W, and 13.5% for Y. At 1 month after a single dose of MenACWY vaccine, there was an increase in the percentage of subjects with hSBA titres ≥ LLOQ (ranging from 63.5% to 90.2% across serogroups; Table 4).

Table 3 Percentage of subjects with hSBA titres greater or equal to LLOQ for each serogroup A, C, W and Y at baseline and month 1 in the ACWY-group (Full analysis set).

	Number (%) of subjects (95% CI) with >=LLOQ			
	Serogroup A	**Serogroup C**	**Serogroup W**	**Serogroup Y**
Baseline	16 (11.7%) (6.8%-18.3%) n=137	40 (28.8%) (21.4%-37.1%) n=139	18 (12.9%) (7.8%-19.6%) n=140	19 (13.5%) (8.3%-20.2%) n=141
Month 1	120 (90.2%) (83.9%-94.7%) n=133	87 (64.0%) (55.3%-72.0%) n=136	95 (69.3%) (60.9%-76.9%) n=137	112 (80.0%) (72.4%-86.3%) n=140

Abbreviations: CI, confidence interval; hSBA, human serum bactericidal assay; LLOQ, lower limit of quantification. ACWY group: subjects received 1 dose of MenACWY vaccine at Month 0 (and one dose of placebo at Month 2 and 1 dose of rMenB+OMV NZ at Month 6).

Percentage of subjects achieving a 4-fold rise in hSBA titers

At 1 month after the single MenACWY dose, the percentages of subjects with at least a 4-fold rise in hSBA titers against *N. meningitidis* serogroups were: A (85.3%), C (56.7%), W (66.2%), and Y (72.1%; Table 5).

Table 4 Percentage of subjects with 4-fold rise for each serogroup A, C, W and Y at month 1 (Full analysis set).

	Number (%) of subjects (95% CI)			
	Serogroup A	**Serogroup C**	**Serogroup W**	**Serogroup Y**
Overall % of subjects with 4-fold rise	111 (86.0%) (78.8%-91.5%) n=129	76 (56.7%) (47.9%-65.2%) n=134	90 (66.2%) (57.6%-74.1%) n=136	101 (72.1%) (63.9%-79.4%) n=140

Abbreviations: CI, confidence interval.
ACWY group: subjects received 1 dose of MenACWY vaccine at Month 0 (and one dose of placebo at Month 2 and 1 dose of rMenB+OMV NZ at Month 6).

At baseline, the hSBA GMTs against serogroups A, C, W and Y were low, and increased following the vaccination (Table 6). The same pattern was observed for the total IgG; total IgG for serogroup A, C, W and Y at baseline were 2.3, 0.8, 0.6 and 0.9, respectively and increased (to 53.7, 13.8, 8.4 and 14.3, respectively) at month 1.

Table 5 Geometric Mean Titre (GMT) and Geometric Mean Ratio (GMR) for each serogroup A, C, W and Y at baseline and month 1 (Full analysis set).

Time point		**Value (95% CI lower limit – upper limit)**			
		Serogroup A	**Serogroup C**	**Serogroup W**	**Serogroup Y**
Baseline	GMT	12.7 (10.9-14.8) n=137	11.4 (9.1-14.3) n=139	7.4 (6.2-8.9) n=140	9.9 (8.6-11.5) n=141
Month 1	GMT	474.8 (331.3-680.3) n=133	379.0 (204.4-703.0) n=136	194.3 (128.3-294.2) n=137	320.9 (213.8-481.7) n=140
	GMR	31.8 (21.4-47.1) n=129	22.9 (12.8-41.1) n=134	23.2 (15.5-34.7) n=136	25.6 (16.9-38.8) n=140

Abbreviations: CI, confidence interval; GMT, geometric mean titer; GMR, geometric mean ratio.
ACWY group: subjects received 1 dose of MenACWY vaccine at Month 0 (and one dose of placebo at Month 2 and 1 dose of rMenB+OMV NZ at Month 6).

Assessor's comments

The percentage of subjects with hSBA titres greater or equal to LLOQ against serogroups A, C, W and Y were 11.7%, 28.8%, 12.9% and 13.5%, respectively at baseline. The percentages increased at 1 month after the single dose of MenACWY to 90.2%, 64.0%, 69.3% and 80.0%, respectively. The percentages of subjects with at least a 4-fold rise in hSBA titers against *N. meningitidis* serogroups were: A (86.0%), C (56.7%), W (66.2%), and Y (72.1%). The hSBA GMTs against serogroups A, C, W and Y were low, and increased following the vaccination. The same was observed for total IgG.

Based on version 02 of the CSR only minor changes to the results compared to version 01 of the CSR were noted. The changes did not impact the conclusions of the study with regard to MenACWY vaccination as presented. It is noteworthy that even though the LLOQ for the MenA hSBA increased, the number of participants with a 4-fold rise increased for subjects with a pre-vaccination titer ≥LLOQ. This is not considered possible, however, as it only pertains to 1 participant this is not further pursued as it will not change the outcome or the results of this study. Finally, it was not fully understood why there were any changes in GMT or GMR for MenY as no change in LLOQ was reported. However, the

changes were so minor that this is not further pursued. The MAH is strongly encouraged to ensure correct data presentation in case this study will be used in future submissions.

In the SmPC, the percentage of subjects (11-18 years of age) with hSBA ≥ 1:8 is 75%, 85%, 96% and 88% for serogroup A, C, W and Y respectively. For adults, the percentage of subjects (19-55 years of age) with hSBA ≥ 1:8 is 69%, 80%, 94% and 79% for serogroup A, C, W and Y respectively. Although direct comparison between this study and previous studies is difficult, the MAH was requested to discuss the rather low percentage of subjects with a 4-fold rise in hSBA levels for serogroup C and W one month after vaccination. In addition, GMT levels one month after MenACWY vaccination observed in this study are considerably higher (194.3-474.8) when compared to GMTs listed in the SmPC. It is acknowledged that a direct comparison of GMTs data across studies conducted in different populations and time periods should be performed with caution. The MAH indicated that these differences can be attributed to the characteristics of the serology assay used, including different LLOQ and definition used to calculate the 4-fold rise and the use of a different imputation method for calculating the GMTs.

Safety results

Assessor's comments

Note that only (un)solicited AEs following a MenAWCY vaccination in the MenB_0_6 and ACWY group (administered at day 61 and day 1, respectively) were presented by the Applicant in the body text of the report. Only limited safety data was collected after vaccination 4 (Day 211) in the MenB_0_2_6 group that received a MenACWY vaccination at Visit 6, Day 211 (see above).

A total of 3619 (99.5%) and 3618 (99.5%) subjects were included in the Exposed Set for the Unsolicited Safety Set and Solicited Safety Set, respectively. No safety follow-up was the reason for the elimination of a few subjects from both these sets.

In the ACWY group, 177 subjects received a MenACWY vaccination at Visit 1, month 0. In the MenB_0_6 group, 906 subjects received a Men B (Bexsero) vaccination at Visit 1, month 0 followed by a MenACWY vaccination (n=854) at Visit 3, month 2. One participant in the MenB_0_6 group received MenACWY vaccination at Visit 1 and was included and analysed in the safety analyses in the MenACWY group.

Solicited AEs

After MenACWY vaccination

- In the 7 days following the MenACWY vaccination, at least one solicited AE was reported in 53.6% of subjects in the MenB_0_6 group and in 70.8% of subjects in the ACWY group (Table 7)
- In 28.9% of subjects in the MenB_0_6 group and 41.0% of subjects in the ACWY group had at least one local AE (injection site pain, erythema, swelling, induration) and 41.9% and 59.6% of subjects in respective groups had at least one systemic AE (fever, nausea, fatigue, myalgia, arthralgia, headache).
- The most frequently reported solicited local AE was pain (27.6% in the MenB_0_6 group and 37.6% in the ACWY group) in both the groups followed by erythema (3.2% and 6.2%).
- Most of the observed solicited local AEs after the MenACWY vaccination were mild to moderate in severity in both groups. None of the subjects in the ACWY group experienced severe pain and 0.6% (n=5) reported severe pain in the MenB_0_6 group, and other severe solicited local AEs reported by less than or equal to 1.1% of subjects in both the MenACWY group and MenB_0_6 group.

- The most frequently reported solicited systemic AEs were fatigue (28.0% and 43.8%) and headache (27.4% and 38.8%) in the MenB_0_6 and ACWY group, respectively.
- Most of the solicited systemic AEs were mild in severity in both groups. Less than or equal to 2.2% of subjects had severe systemic AEs across the 2 groups. After the MenACWY vaccination, 12 (1.5%) subjects in the MenB_0_6 group and 3 (1.7%) subjects in the ACWY group had fever (temperature ≥ 38°C).

Table 6 Summary of solicited adverse events within 7 days following MenACWY vaccination (Solicited safety set).

	Number (%) of Subjects With Solicited AEs	
After MenACWY vaccination	**MenB_0_6** Vaccination 2 N=813	**ACWY** Vaccination 1 n=178
Any	436 (53.6%)	126 (70.8%)
Local	235 (28.9%)	73 (41.0%)
Systemic	341 (41.9%)	106 (59.6%)

Abbreviations: AEs, adverse events.
MenB_0_6 = Subjects received 2 doses of rMenB+OMV NZ at Months 0 and 6 and 1 dose of MenACWY vaccine at Month 2; ACWY = Subjects received 1 dose of MenACWY vaccine at Month 0, one dose of placebo at Month 2 and 1 dose of rMenB+OMV NZ at Month 6.

Unsolicited AEs

- In the ACWY group, 29 (16.3%) subjects reported at least one unsolicited AE within the 30 days following the MenACWY vaccination. The most commonly reported unsolicited AEs were classified under the MedDRA SOC of Infections and infestations (3.9%), Gastrointestinal disorders (3.4%), General disorders and administration site conditions (1.7%).
- In the MenB_0_6 group, 88 (10.3%) subjects reported at least one unsolicited AE within in the 30 days following the MenACWY vaccination. The most commonly reported unsolicited AEs were classified under the MedDRA SOC of Infections and infestations (3.5%), Injury, poisoning and procedural complications (1.9%), Gastrointestinal disorders (1.4%).
- Unsolicited AEs assessed as causally related to vaccination by the investigator were reported by 6.2% and 5.6% of subjects in MenB_0_6 and ACWY groups, respectively. The causally related AEs were more frequently reported under the SOC "General disorders and administration site conditions", reported by 3% to 3.4% of subjects in MenB_0_6 and ACWY groups, respectively. The most commonly reported causally related unsolicited AE, by PT, was injection site pain (8 subjects) in the MenB_0_6 group and injection site induration in the ACWY group (2 subjects).
- Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

SAE and deaths reported during entire study period

- During the course of the study, 22 (2.4%) subjects in the MenB_0_6 and 5 (2.8%) subjects in the ACWY group reported at least one SAE. Of which, 2 in the MenB_0_6 group were assessed as possibly related. Nausea, vomiting, pyrexia, headache were reported in 1 subject within 12 hours after MenACWY vaccination in MenB_0_6 group. These events were resolved in 2 days. The other SAE in this group was Colitis ulcerative and was reported 44 days after vaccination 3 (rMenB+OMV NZ vaccine). This event was still ongoing at the end of the study.
- There was 1 reported AESI in the MenB_0_6 group. The aforementioned SAE, Colitis ulcerative, reported after vaccination 3 (rMenB+OMV NZ vaccine) was also identified as an AESI.

- There was 1 fatal unsolicited event (overdose) in the MenB_0_6 group and was considered not related to the administered study vaccinations.

Discontinuations

- There were 4 subjects in the MenB_0_6 and 1 subject in the ACWY group that reported unsolicited events leading to premature withdrawal from the study. Two of the non-serious unsolicited AEs that led to withdrawal in the MenB_0_6 group were assessed as causally related to vaccination by the investigator; one subject reported arthritis and one subject reported pyrexia and injection site hematoma. Arthritis was reported 11 days after Bexsero vaccination (rMenB+OMV NZ). Two subjects in the MenB_0_6 and one subject in the ACWY group experienced at least one SAE that led to withdrawal from the study: two subjects in MenB_0_6 group (overdose, major depression and suicide attempt) and one subject in ACWY group (testis cancer). Overdose was fatal (below). None of the SAEs that led to withdrawal from study were assessed as causally related to vaccination.

Assessor's comments

The most frequently reported solicited local AE was pain followed by erythema. The most frequently reported solicited systemic AE were fatigue and headache. This is in line with the SmPC.

Unsolicited AEs assessed as causally related to vaccination by the investigator were reported by 6.2% and 5.6% of subjects in MenB_0_6 and ACWY groups, respectively. The majority of related unsolicited AEs could be considered reactogenicity events or were events already listed as ADRs in the SmPC. Two AEs, one report of 'Pain in extremity' of a subject in the MenB_0_6 group and one report of 'Back pain' in the ACWY group, referred to events not already included in the SmPC. As these are single cases, no strong conclusions on relatedness can be drawn. In addition, for pain in extremity there is overlap with injection site pain. Therefore, these AEs were not considered new safety signals. Unsolicited events assessed as related to the vaccine were also registered in the MenB_0_2_6 group after MenACWY vaccination (vaccination 4). No new safety events were observed in this group.

In total, approximately 2.5% of subjects in the MenB_0_6 group and the ACWY group, 22 and 5 respectively, reported at least one SAE. Of which one participant reported SAEs which were considered possibly related to MenACWY vaccination by the investigator.

One subject in the MenB_0_6 group reported nausea, vomiting, pyrexia and headache within 12 hours after MenACWY vaccination. These SAEs led to hospitalisation. They were resolved in two days. These PTs are already listed as ADRs in section 4.8 of the SmPC and are therefore not considered new safety signals.

There was 1 fatal event (overdose). It is agreed that this was considered not related to vaccination.

In general, currently no new major safety signals were reported.

2.3.3. Discussion on clinical aspects

The MENB REC 2ND GEN-038 (V72_72) study was conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitidis* serogroups (A, B, C, W and Y). Menveo was used as a comparator vaccine in the study. For this procedure, the immune response to- and safety and reactogenicity of the MenACWY vaccine were assessed.

Immunogenicity of the MenACWY vaccine against serogroups A, B, C, W and Y was evaluated by serum bactericidal assays using exogenous source of human complement (hSBAs), using indicator strains representing serogroups A, C, W and Y. The percentage of subjects with hSBA titres greater or equal to LLOQ against serogroups A, C, W and Y were low respectively at baseline. The percentages increased at 1 month after the single dose of MenACWY to 90.2%, 64.0%, 69.3% and 80.0%, respectively. The percentages of subjects with at least a 4-fold rise in hSBA titers against *N. Meningitidis* serogroups were: A (86.0%), C (56.7%), W (66.2%), and Y (72.1%). The hSBA GMTs against serogroups A, C, W and Y were low, and increased following the vaccination. The same was observed for total IgG. Indicating an immune response as could be expected.

During the current study no new safety signals were reported. The most frequently reported solicited local AE was pain followed by erythema. The most frequently reported solicited systemic AE were fatigue and headache, which is in line with the SmPC. Unsolicited events were reported by 10.3% and 16.3% of subjects receiving a MenACWY vaccination, most of which were mild to moderate in intensity.

Approximately 2.5% of subjects reported at least one SAE. One subject reported SAEs (nausea, vomiting, pyrexia, headache) 12 hours after the MenACWY vaccination, which were assessed as related to the study vaccination. The subject discontinued due to these SAEs. However, as these AEs are already included in the SmPC, this is not considered a new safety signal. There was one fatal event unrelated to the study vaccination.

The MAH considers no changes to the current SmPC of MenACWY are necessary. This can be agreed.

3. Rapporteur's overall conclusion and recommendation

In conclusion, in the current study a single MenACWY vaccination generated an immune response as expected. No new safety signals were observed.

It can be agreed that an update of the SmPC based on the current study is not required.

☒ **Fulfilled**

No regulatory action required.

4. Request for supplementary information

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

Study design:

1. Subjects could participate in the study, if they have received a previous MenACWY vaccination at least 4 years prior to informed consent. It is unclear why this timeframe of 4 years was chosen as a considerable percentage of subjects has a persistent immune response 5 years after vaccination with Menveo (as stated in the SmPC). This indicates that these participants might have a higher baseline hSBA titer and the vaccine will most likely act as a booster dose. The MAH is requested to explain this.

2. Subjects were exempted from study participation when they had received a meningococcal C vaccination of which the last dose was received at ≤24 months of age. The MAH is requested to explain this.

3. For determining the 4-fold rise in hSBA titers, different cut offs (LLOQ) were used as compared to previous assays employed in the clinical development of Menveo. The MAH is requested to indicate whether different assays were used in this study compared to the studies submitted during Menveo approval and to provide comparisons between the assay if available.

4. A total of 177 subjects were randomized into the MenACWY group, whereas 178 subjects were in the (un)solicited safety set. It is unclear where this extra subject came from. The MAH is requested to explain this.

Efficacy:

5. The MAH is requested to discuss the rather low percentage of subjects with a 4-fold rise in hSBA levels for serogroup C and W one month after MenACWY vaccination.

6. GMT levels one month after MenACWY vaccination observed in this study are considerably higher (194.3-458.7) when compared to GMTs listed in the SmPC. The MAH is requested to also elaborate on this discrepancy.

Safety:

7. Narratives for all SAEs were not provided, which hampers any assessment of relatedness to MenACWY vaccination. The MAH is asked to present all narratives of SAEs occurring in groups receiving a MenACWY vaccination; the MenB_0_2_6, MenB_0_6 group and the ACWY group.

8. A higher percentage of subjects reported a local or systemic solicited event in the ACWY group when compared to the MenB_0_6 group. The MAH is requested to discuss this difference.

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

MAH responses to Request for supplementary information

Question 1

Subjects could participate in the study, if they have received a previous MenACWY vaccination at least 4 years prior to informed consent. It is unclear why this timeframe of 4 years was chosen as a considerable percentage of subjects has a persistent immune response 5 years after vaccination with Menveo (as stated in the SmPC). This indicates that these participants might have a higher baseline hSBA titer and the vaccine will most likely act as a booster dose. The MAH is requested to explain this.

Summary of the MAH's response

Study MENB REC 2ND GEN-038 (V72_72) was a post-approval commitment for rMenB+OMV NZ vaccine in the US and was merged with the Phase 3 study for GSK pentavalent investigational MenABCWY vaccine.

One of the primary objectives of study V72_72 was to demonstrate the non-inferiority of the investigational MenABCWY vaccine versus MenACWY vaccine in vaccine-naïve subjects. However, CBER recommended to enrol a subset of subjects with a prior history of MenACWY primary vaccination to ensure adequate representation of US adolescents and young adults who had been vaccinated according to the ACIP recommendations (Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 | MMWR (cdc.gov)).

Considering this CBER recommendation, the Company decided to include subjects who received a previous MenACWY vaccination within a timeframe of 4 years. This timeframe reflects the US prescribing information regarding the timing of the booster in adolescents and young adults (i.e., "Booster Vaccination Adolescents and Adults Aged 15 through 55 Years: A single booster dose of MENVEO may be administered to individuals aged 15 through 55 years who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of a meningococcal (serogroups A, C, Y, W-135) conjugate vaccine."). Data supporting this timeframe derived from study V59_77, which was submitted in Europe as part of an Article 46 application (EMEA/H/C/001095/P46/039). Study V59_77 data did not provide any new conclusions regarding the persistence of the immune response as already presented in the MenACWY SmPC. Consequently, the Company confirmed that there was no impact on the SmPC and no need to update it. The Agency endorsed the rationale provided by the Company.

It is important to note that the percentage of MenACWY vaccine-primed subjects is only 13% of the enrolled population (22 out of 177) in study V72_72. The majority of subjects enrolled in the study were vaccine-naïve and the non-inferiority analysis was conducted on subjects who were vaccine naïve.

Assessment of the MAH's response

The MAH indicated that participants with a previous history of MenACWY vaccination were included to ensure adequate representation of US adolescents and young adults that have been vaccinated according to ACIP recommendations based on recommendations of CBER. The timeframe of 4 years reflects the US prescribing information. This is acknowledged.

Only 13% of the enrolled population in the MenACWY group (22 out of 177) has received MenACWY vaccination at least 4 years previous. In participants without previous ACWY vaccination, as expected, the results were reduced. In participants without previous ACWY vaccination, the percentage of participants with hSBA ≥LLOQ 1 month after study vaccination was 89.7%, 59.0%, 65.3% and 76.9% for Men A, C, W and Y respectively, compared to 90.2%, 64.0%, 69.3% and 80.0% in the total population. The same holds true for the percentage of participants achieving 4-fold rise being 86.0%, 50.9%, 62.4% and 70.2% in participants without previous ACWY vaccination and 86.0%, 56.7%, 66.2% and 72.1%. All results are slightly reduced, however the 95% CI overlap. This indicates that in participants with a previous vaccination with MenACWY, the current vaccine does act as a booster. However, it does not substantially alter any conclusions regarding MenACWY vaccination.

Conclusion

Issue solved.

Question 2

Subjects were exempted from study participation when they had received a meningococcal C vaccination of which the last dose was received at ≤24 months of age. The MAH is requested to explain this.

Summary of the MAH's response

The Company would like to clarify that, as outlined in the study protocol inclusion criterium mentioned in the clinical study report, subjects who received a dose of MenC vaccine at ≤24 months of age were considered eligible for the enrolment.

Since the study was conducted also outside the US, where MenC vaccination has been the standard of care for a significant period, vaccination with MenC has been included among the group of eligible vaccinations. Subjects who had received the last dose of MenC at ≤24 months of age were considered overall ACWY naïve.

Assessment of the MAH's response

The MAH stated that participants were eligible in case MenC vaccine was received at ≤ 24 months of age. It can be agreed that MenC vaccination has been and still is standard of care in multiple countries. The explanation is accepted.

It is noteworthy that the percentage of participants that have hSBA ≥LLOQ for MenC at baseline is substantially higher compared to MenA, W and Y, being 28.8% for Men C compared to 11.7%, 12.9% and 13.5% for MenA, W and Y respectively. Even in the participants without previous ACWY vaccination, the percentage of participants achieving hSBA ≥LLOQ for MenC was 23.1% compared to 9.2%, 10.7% and 9.0% for Men A, W and Y. This might be explained by participants who did receive MenC vaccination at ≤ 24 months of age. This indicates that even though the MAH considers these participants "ACWY-naïve, this population of previously MenC vaccinated participants should be taken into consideration. However, it does not alter the conclusions of the study.

Conclusion

Issue solved.

Question 3

For determining the 4-fold rise in hSBA titres, different cut offs (LLOQ) were used as compared to previous assays employed in the clinical development of Menveo. The MAH is requested to indicate whether different assays were used in this study compared to the studies submitted during Menveo approval and to provide comparisons between the assay if available.

Summary of the MAH's response

The Company confirms that the different cut-offs (limit of blank [LOB], limit of detection [LOD], lower limit of quantitation [LLOQ] and upper limit of quantitation [ULOQ]) for each of the MenACWY serogroups are associated with different validated human serum bactericidal assay (hSBA) formats that were used in study V72_72 compared to the assay formats used in studies submitted to the Agency in the course of the Menveo vaccine development.

In the Phase 3 study V72_72, functional immunogenicity induced by the Men A, C, W and Y glycoconjugate components of the MenABCWY investigational vaccine and by the licensed Menveo vaccine has been assessed with a newly validated quantitative hSBA format, the MenACWY agar-overlay hSBA.

The MenACWY agar-overlay hSBA format relays on the same principles of the manual (tilt) hSBA, the assay format previously used for clinical testing of Phase 2 and Phase 3 studies submitted in support of Menveo initial marketing authorization application (please refer to Standard Operating Procedure 222582-03 entitled *Determination of antibodies against Neisseria meningitidis bacteria of the serogroups A, C, W-135 and Y in human sera using SBA (serum meningitidis bacteria) of the serogroups A, C, W-135 and Y* submitted to EMA with sequence 0042 in the context of procedure EMEA/H/C/1095/II/018).

The former manual (tilt) hSBA was performed in the Clinical Serology Laboratory, Novartis Vaccines and Diagnostics GmbH in Marburg, Germany. Novartis Vaccines Marburg was acquired by GSK in 2015 and later became part of Nexelis in 2021, which is now part of Q2 Solution.

In an effort to streamline and reduce the number of assay formats across GSK clinical trials with meningitis vaccines, the manual (tilt) hSBA format for Men A, C, W and Y, performed in Marburg, Germany, has been discontinued. The clinical testing of recent and ongoing studies is performed in GSK Laboratory in Wavre, Belgium, using the MenACWY agar-overlay hSBA, which has been validated using the MenA (3125), MenC (C11), MenW (240070) and MenY (860800) immunogenicity reference strains, in compliance with the most recent industry standards for assay validation.

As of note, the assay format previously used for testing Menveo Phase 2 and Phase 3 studies relied on F8238 reference strain to measure Men A bactericidal antibodies, which is different from the one used in the current assay (3125).

The information regarding this new assay format was provided to the Menveo EMA Rapporteur in the context of a National Scientific Advice meeting with the Dutch Medicines Evaluation Board (MEB) to discuss the data generated for the planned line extension application for the new 1-vial presentation of Menveo (SA number/case number WAG 23306 case 958685; date of the meeting: 4 October 2022; date of the advice: 31 October 2022).

Assessment of the MAH's response

The MAH confirmed that a different serological assay was used during the current study compared to the studies included in the initial application. This is acknowledged.

During the SA no question regarding the use and or applicability of the assay was posed. If the results of the current study are to be included in future submissions, it is expected that the assay is fully validated. Validation documents are expected to be included in the future submission.

Conclusion

Issue solved.

Question 4

A total of 177 subjects were randomized into the MenACWY group, whereas 178 subjects were in the (un)solicited safety set. It is unclear where this extra subject came from. The MAH is requested to explain this.

Summary of the MAH's response

The extra subject was randomized to the MenB_0_6 group but received MenACWY vaccine as a first dose. For this reason, this subject was included and analysed in the safety analyses in the MenACWY group, therefore the solicited and unsolicited safety set, which is based on the exposed set, included 178 instead of 177 subjects.

Assessment of the MAH's response

The explanation of the MAH is understood and appreciated.

Conclusion

Issue solved.

Question 5

The MAH is requested to discuss the rather low percentage of subjects with a 4-fold rise in hSBA levels for serogroup C and W one month after MenACWY vaccination.

Summary of the MAH's response

The Company acknowledges the observed low percentage of subjects with a 4-fold rise in hSBA levels for serogroup C and W one month after MenACWY vaccination and would like to explain that these differences can be attributed to the characteristics of the serology assay used, including different LLOQ employed to calculate the 4-fold rise in hSBA levels and 4-fold definition. Of note, a more conservative approach was taken in study V72_72 compared to the MenACWY development program studies.

Based on that, the Company believes that these observations do not lead to a different immunological response to the vaccine, which is overall robust. Despite the differences in assay characteristics, the results remain clinically meaningful and consistent across studies. Furthermore, the results are in line with the information outlined in the currently approved SmPC.

Assessment of the MAH's response

It is acknowledged that comparing immunogenicity results across studies conducted in different populations and time periods should be performed with caution. The explanation of the MAH regarding the use of a different assay, leading to differences in the LLOQ to calculate a 4-fold rise, and a different definition of a 4-fold rise can be accepted.

Conclusion

Issue solved.

Question 6

GMT levels one month after MenACWY vaccination observed in this study are considerably higher (194.3-458.7) when compared to GMTs listed in the SmPC. The MAH is requested to also elaborate on this discrepancy.

Summary of the MAH's response

The Company acknowledges the observed difference in GMT levels one month after MenACWY vaccination between study V72_72 and the GMTs reported in the SmPC.

However, the Company would like to clarify that a direct comparison of GMTs data across studies conducted in different populations and time periods should be performed with caution. In addition, study V72_72 data have been generated through serology assays with different characteristics and using a different imputation method for calculating the GMTs.

Despite the above, the GMTs results aligned with the response observed in previous studies detailed in the SmPC. It is important to note that, despite these observations, the immunological response to the vaccine remains robust and is expected to be consistent with the data reported in the SmPC.

Assessment of the MAH's response

Again, it is acknowledged that comparing immunogenicity results across studies conducted in different populations and time periods should be performed with caution. The explanation of the MAH regarding the use of a different assay and different imputation method for calculating GMTs can be accepted.

Conclusion

Issue solved.

Question 7

Narratives for all SAEs were not provided, which hampers any assessment of relatedness to MenACWY vaccination. The MAH is asked to present all narratives of SAEs occurring in groups receiving a MenACWY vaccination; the MenB_0_2_6, MenB_0_6 group and the ACWY group.

Summary of the MAH's response

The Company acknowledges the request and provides the complete narratives of SAEs occurring in groups receiving a MenACWY vaccination (MenB_0_2_6 group, MenB_0_6 group, and ACWY group) as annexes to this document.

Assessment of the MAH's response

It is noted that not all narratives are provided in the annex as narratives already presented in the report were not also included in the annex. However, the fact that the additional narratives were provided is appreciated. It can be agreed, based on these narratives, that the newly provided narratives do not give rise to any new safety signal. None of the SAEs were considered related to MenACWY vaccination, which can be agreed.

Conclusion

Issue solved.

Question 8

A higher percentage of subjects reported a local or systemic solicited event in the ACWY group when compared to the MenB_0_6 group. The MAH is requested to discuss this difference.

Summary of the MAH's response

The Company acknowledges the observed overall higher percentage of subjects reporting a local or systemic solicited event in the ACWY group when compared to the MenB_0_6 group.

It is important to note that the percentages of local and systemic solicited events in the ACWY group are consistent with the data generated during the MenACWY development program studies, which supported its licensure.

There is no biologically plausible reason for the observed difference. Indeed, the study was designed to minimize the potential introduction of reporting bias by ensuring that the study subjects were unaware of which vaccine they received, as it was conducted in a blinded manner.

Overall, the observed data are in line with the data reported in the SmPC.

Assessment of the MAH's response

The fact that the study is blinded and includes placebo injections is appreciated. It can be agreed that the data are in general in line with the data reported in the SmPC.

Conclusion

Issue solved.

Question 9

Critically review the failure of your quality system, including root cause analysis and CAPAs, that caused the need for republishing of the Clinical Study Report.

Summary of the MAH's response

As mentioned in Response to Question 3, the clinical testing of study V72_72 was performed using the Men A, C, W and Y agar-overlay hSBAs. The need for republishing the clinical study report comes from a change to the Men A, C, W and Y agar-overlay hSBA limits of quantitation (LOQs).

As per internal quality control framework, the Company monitors the stability of a validated assay through regular testing (minimum once every 6 months) of a proficiency panel of samples (referred to as "Assay stability monitoring [ASM] test").

In December 2022 and January 2023, ASM tests revealed an excursion of stability of the 4 Men A, C, W and Y agar-overlay hSBAs. There was a trend to underestimate Men A, C, W and Y hSBA titers.

Investigations were launched and duly documented through an unplanned event in quality-controlled system. The Company identified a change to sample preparation introduced in the assay standard operating procedure (SOP) "Measurement of bactericidal activity of human serum antibodies to Neisseria meningitidis A, C, W & Y with the manual agar overlay hSBA" version 06 (LSOP 9000064782 version 06) as the main root cause of the observed trend.

As corrective action, the Company invalidated the laboratory results generated according to this LSOP 9000064782 version 06. These data included dilutional linearity validation data generated in 2022 using a negative non-depleted serum matrix following CBER recommendations, and from which were derived the LOQs used in the version 01 of the CSR for study V72_72. The version 06 was made obsolete. The version 07 of the SOP was issued to re-introduce the sample preparation in use in LSOP 9000064782 version 05 and previous versions. Dilutional linearity validation experiments were repeated leading to an update of Men A, C, W and Y agar-overlay hSBA limits. These new limits, compiled in Table 1, were used to create the version 02 of the CSR for study V72_72.

Of note, the Company would like to clarify that clinical testing of study V72-72 was finalized before effectivity of the LSOP 9000064782 version 06. Impact of the stability excursion only affected the above mentioned dilutional linearity validation data generated in 2022, and in turn, the assay LOQs.

Assessment of the MAH's response

The explanation of the MAH is appreciated. It is acknowledged that sample preparation can affect dilutional linearity.

Based on the validation of the agar-overlay hSBA in 2020 using LSOP 9000064782 version 02, dilution linearity led to other LLOQ values for Men A, C, W and Y. As the LLOQ of the assay increased and remained well above the CoP, no clinical impact is expected based on changes in the LLOQ.

It is noteworthy however, that based on the CSR version 2, not only limits of quantitation for the hSBA were updated, but also for the ECL assay. It is currently unknown why the ECL assay was subjected to an update. Considering that the update of the ECL assay only led to minute changes in IgG results in the Menveo group, this issue is not further pursued.

Conclusion

Issue solved.