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Assessment Report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/001095/P46/047

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	29 April 2024	29 April 2024
☐	CHMP Rapporteur Assessment Report	03 June 2024	03 June 2024
☐	CHMP members comments	17 June 2024	17 June 2024
☐	Updated CHMP Rapporteur Assessment Report	20 June 2024	19 June 2024
☒	CHMP adoption of conclusions:	27 June 2024	27 June 2024

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1. Introduction

On 26/03/2024 the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH submitted a phase 3B, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GlaxoSmithKline's (GSK) experimental meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with a meningococcal ACWY vaccine. The study has not been conducted according to an agreed paediatric investigation plan (PIP) for Menveo.

The submitted study, MENABCWY-019, is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The licenced Menveo is a vaccine approved in the European Union as of March 15 2010 and is indicated for use in 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. Menveo may be given as a booster dose in subjects who have previously received primary vaccination with Menveo, other conjugated meningococcal vaccine or meningococcal unconjugated polysaccharide vaccine. The need for and timing of a booster dose in subjects previously vaccinated with Menveo is to be defined based on national recommendations. Menveo contains meningococcal serogroups A, C, W-135 and Y oligosaccharides, conjugated to Cross Reactive Material (CRM197), a nontoxic - *Corynebacterium diphtheriae* mutant.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 213171: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GlaxoSmithKline's (GSK's) meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with meningococcal ACWY vaccine.

In this study Menveo was used as an active comparator to an experimental pentavalent MenABCWY vaccine. Only results relevant to Menveo will be described in this report.

2.3.2. Clinical study

213171: A phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of GlaxoSmithKline's (GSK's) meningococcal ABCWY vaccine when administered in healthy adolescents and adults, previously primed with meningococcal ACWY vaccine.

Description

Methods

Study design

This multi-center, observer-blind study was conducted at 65 centers in 4 countries (Argentina, Australia, Canada, US). The study was set up to assess immunological noninferiority of the experimental (2-dose) MenABCWY vaccine to the licenced Menveo in participants already primed with a MenACWY vaccine. For analysis of the two co-primary endpoints, the population was further split into two groups, "Family 1" and "Family 2."

Assessor's comment:

It is unclear when and how patients were selected for either "family 1" or "family 2." However, selection for these two families was performed for the comparison of Menveo for the experimental MenABCWY vaccine (i.e. the co-primary endpoints). As the comparison of Menveo to an experimental vaccine is of limited value for the SmPC for Menveo, the issue is not further pursued.

Study participants

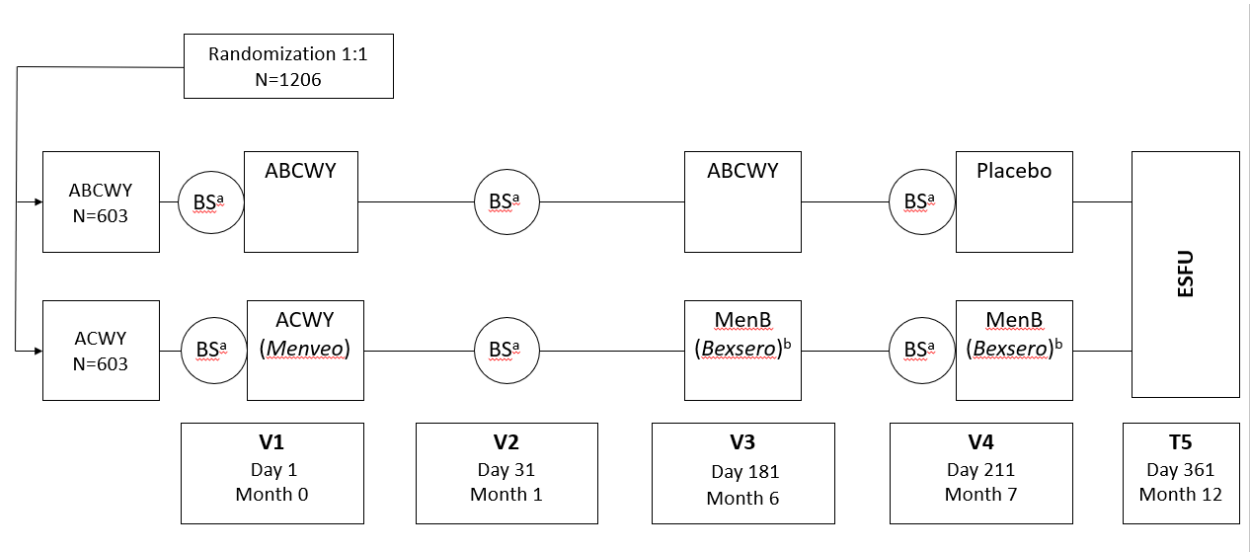
The study was conducted in healthy males and females 15 through 25 years of age, with a history of a previous MenACWY vaccination at an age of 10 years or older, with an interval of at least 4 years and not more than 6 years between the previous MenACWY vaccine and enrolment.

Treatments

Participants were randomized in a 1:1 ratio into one of two study groups.

- **ABCWY**: Participants received 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0,6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
- **ACWY**: Participants received 1 dose of MenACWY vaccine (Menveo) at Visit 1 (Day 1) (single dose) and 2 doses of MenB (Bexsero) vaccine at Visit 3 (Day 181) and Visit 4 (Day 211).

Figure 1: Study groups



ACWY = Menveo; BS = blood sample; ESFU = extended safety follow-up; MenB = Bexsero; N = number of participants; T = telephone contact; V = visit a Insufficient blood volume may lead to test cancellation and

jeopardize the statistical power. Hence, every effort must be made to collect blood volume as per protocol requirements. b Bexsero is given for compliance with standard of care.

Objective(s), outcomes, and endpoints

Table 1 presents the outcomes and objectives of the study.

Table 1: Objectives and endpoints (only those relevant for Menveo shown).

Objectives	**Endpoints**
Primary	
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 1, first co-primary endpoint): To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	The percentages of participants with a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the second vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 2, second co-primary endpoint): To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	The percentages of participants with a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1), relative to baseline (Day 1, Month 0).
Safety To evaluate the safety and reactogenicity of the MenABCWY and MenACWY vaccines.	• The frequencies and percentages of participants with solicited administration site events (i.e., injection site pain, erythema, swelling, induration) and solicited systemic events (i.e., fever [body temperature ≥38.0°C/ 100.4°F], nausea, fatigue, myalgia, arthralgia, headache) during the 7 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group).

	• The frequencies and percentages of participants 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 vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).
Secondary	
Immunological non-inferiority: MenABCWY vs. MenACWY	

To assess the immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W, and Y, at pre-vaccination and 1 month after the first and last MenABCWY vaccinations and 1 month after the MenACWY vaccination.	• The percentages of participants with hSBA titers ≥LLOQ against serogroups A, C, W, and Y:
	  • at baseline (Day 1, Month 0) and at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group, and
	  • at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1).
	• The GMTs against serogroups A, C, W, and Y:
	  • at baseline (Day 1, Month 0) and at 1 month after the first (Day 31, Month 1) and the last (Day 211, Month 7) vaccinations for the ABCWY group, and
	  • at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1).
	• The GMRs against serogroups A, C, W, and Y:
	  • at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group as compared to baseline (Day 1, Month 0) and at 1 month after the MenACWY vaccination (Day 31, Month 1) for the ACWY group as compared to baseline (Day 1, Month 0).

AESI = adverse event of special interest; CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; GMR = geometric mean ratio; hSBA = human

serum bactericidal assay; LLOQ = lower limit of quantitation; N. meningitidis = Neisseria meningitidis; SAE = serious adverse event

Assessor's comment:

As this assessment focuses on potentially relevant information of Menveo, the primary objective to demonstrate non-inferiority of a new experimental MenABCWY compared to MenACWY is of limited relevance. The study planned to further evaluate the safety and reactogenicity of MenACWY in healthy participants.

The within MenACWY group 4-fold rise (reported as part of the primary outcome) as well as percentage of participants with hSBA titers ≥LLOQ and GMTs may provide supportive information on the booster response in healthy adolescents.

Sample size

Considering that approximately 10% of the selected participants might withdraw or not be evaluable for the immunogenicity objectives, the target sample size to be analyzed will be 270 participants per group and 603 participants per group for the first co-primary (Family 1) and the second (family 2) co-primary objectives respectively.

Assessor's comment:

The target sample size for Family 1 is 270 per group out of 603 randomized to ABCWY. The target sample size to be analysed is mentioned to be 270 participants per group for the first co-primary objective. It is unclear how and when patients were selected to be analysed for "family 1", at visit 4. However, this is not further pursued.

Randomisation and blinding (masking)

Approximately 1206 participants will be randomized in a 1:1 ratio to achieve 1084 evaluable participants (at least 542 per group, Figure 1). All eligible participants will be centrally randomized using Interactive Voice Response System (IVRS). Before the study is initiated, login information and directions for the IVRS will be provided to each study center. The system's randomization algorithm will use a minimization procedure accounting for country.

Data will be collected in an observer-blind manner, i.e., participants, investigators, and teams responsible for assessment of any study endpoints will be blinded to the administered vaccine(s)/product. Study vaccine(s)/product will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint (i.e., reactogenicity, safety, immunogenicity). The laboratory in charge of the laboratory testing will be blinded to the treatment, subject and visit number, and codes will be used to link the subject, visit and study (without any link to the treatment attributed to the subject) to each sample.

Statistical Methods

Assessor's comment:

The statistical hypotheses are not relevant for this procedure, however, for a proper interpretation and understanding of the study they are described below.

Analysis sets

The *full analysis set* was all participants who received at least 1 dose of the study intervention. The allocation in a group is done in function of all administered interventions

The *per protocol set* consisted of participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data (FAS) minus participants with protocol deviations that lead to exclusion from the PPS) differed for visit 1 and visit 2.

Hypotheses

Co-primary objective 1 (family 1): non-inferiority of MenABCWY 1 month after second dose vs 1 month after single dose of MenACWY for each strain

The first co-primary immunogenicity objective is to demonstrate the immunological non-inferiority of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the N. meningitidis serogroups A, C, W, and Y, at 1 month after the **second** MenABCWY vaccination and **1 month after the MenACWY vaccination** (single dose).

The primary immunogenicity analysis will be performed for the PPS. The primary immunological noninferiority of the MenABCWY vaccine, compared to MenACWY vaccine, will be demonstrated if the lower limit (LL) of the 2-sided 95% CI for the group difference in percentages of participants achieving a 4-fold rise (refer to Section 6.6) in hSBA titers is above −10%, for each serogroup.*Co-primary objective 2 (familiy 2)*: non-inferiority of MenABCWY 1 month after first dose and 1 month after single dose of MenACWY for each strain

The second co- primary immunogenicity objective is to demonstrate the immunological NI of the antibody response to MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with MenACWY, as measured by percentage of participants with 4-fold rise in hSBA titer against each of the N. meningitidis serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination and **1 month after the MenACWY** vaccination (single dose).For each of the serogroups A, C, W, Y the percentages of participants with 4-fold rise (refer to Section 6.6), and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method (Clopper, 1934) will be calculated for each vaccine group, at 1 month after the first vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1). The standardized asymptotic CIs between group differences in percentages will be derived using the method of Miettinen and Nurminen (Nurminen, 1985). The secondary immunological non-inferiority analysis will be performed for the PPS.

- For the serogroups A, C, W, Y and for each of the serogroup B indicator strains evaluation the *4-fold rise* is defined as:
  a post-vaccination hSBA titer ≥16 for participants with a pre-vaccination hSBA titer
- a post-vaccination hSBA titer ≥16 for participants with a pre-vaccination hSBA titer <4;
- a post-vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥limit of detection (LOD) but <LLOQ; and,
- a post-vaccination hSBA titer ≥4 times the pre-vaccination titer for participants with a pre-vaccination hSBA titer ≥LLOQ.

Secondary objective: immune responses

The immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against N. meningitidis serogroups A, C, W, and Y, at pre-vaccination (Day 1, Month 0) and 1 month

after the first and last MenABCWY vaccinations and 1 month after the single MenACWY vaccination will be demonstrated using logarithmically transformed (base 10) hSBA titers and percentages of participants with hSBA titers ≥LLOQ:

- at baseline (Day 1, Month 0) and at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group, and
- at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1).

Testing strategy and multiplicity control

Family 1 will be tested first, testing for non-inferiority after the second dose of MenABCWY versus MenACWY for each of the 4 strains, and family 2, testing non-inferiority after the first dose of MenABCWY versus MenACWY for each of the 4 strains, will only be tested if the hypothesis in family one is successfully demonstrated.

Assessor's comment:

The statistical co-primary hypotheses are not relevant for this procedure, as the non-inferiority of an experimental vaccine compared to MenACWY is tested – they have been described to aid understanding of the design and rationale of the study.

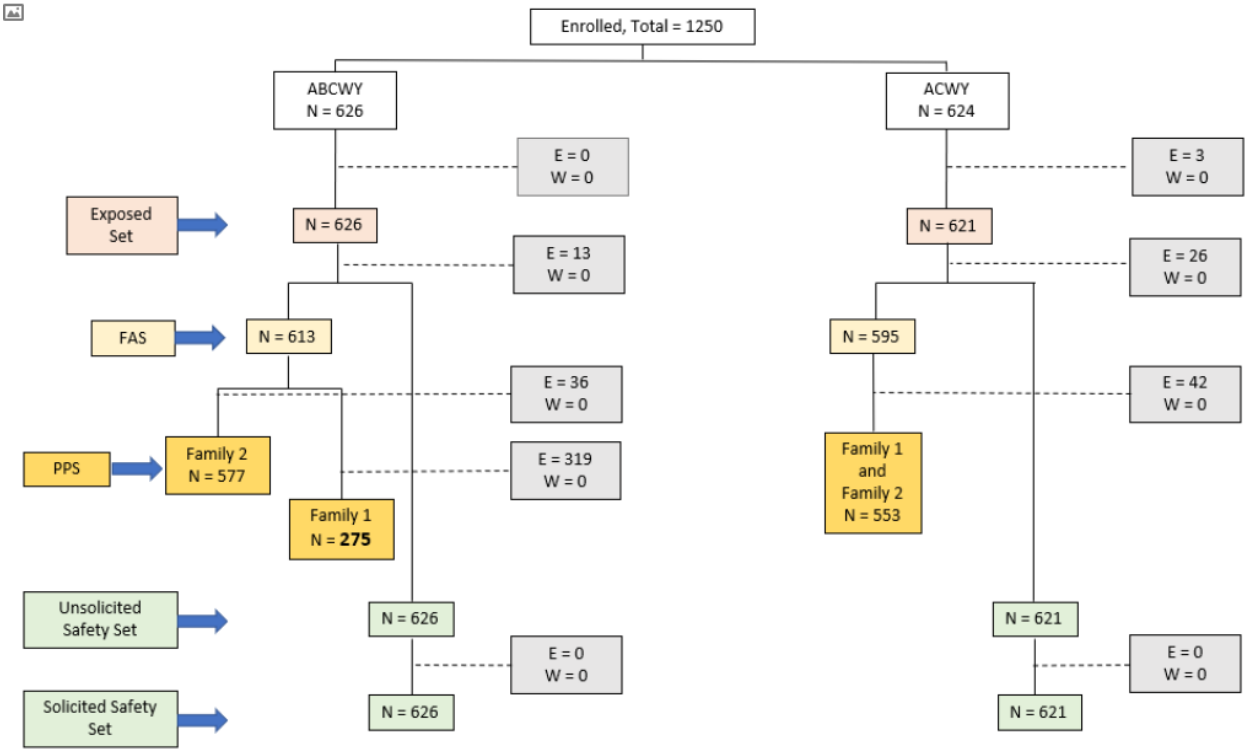
For this assessment no hypothesis will be tested. Descriptive statistics of the 4-fold rise and hSBA titers before and 1 month after a single booster dose will be described.

Results

Participant flow ad numbers analysed

Figure 2 shows the disposition of study participants. A total of 1250 participants were enrolled in the study. Overall, 1247 (99.8%) participants received at least one dose of study vaccine. Of these, a total of 1208 (96.6%) participants were included in the full analysis set (FAS), from which a total of 275 (43.9%) participants were included in the per protocol set (PPS) for Family 1 and 1130 (90.4%) participants were included in the PPS for Family 2.

Figure 2: Disposition of study participants



Abbreviations: E = eliminated; N = number of participants in each vaccine group; W = withdrawal
Source: Table 14.1.1.1, Table 14.1.1.3, Table 14.1.2.1

The most common reason for elimination from PPS for Family 1 subset was lack of immunogenicity results (24.7%) and for Family 2 subset the most common reason for elimination from subset was protocol deviations (2.6%). Table 2 provides an overview of the most common reasons for elimination per randomized group.

Table 2: Overview of Analysis Sets - As Randomized

	ABCWY N=626 N (%)	**ACWY N=624 N (%)**	**Total N=1250 N(%)**
Exposed set	626 (100.0)	621 (99.5)	1247 (99.8)
Did not receive at least one dose of study intervention	0 (0)	3 (0.5)	3 (0.2)
Full analysis set (FAS)	613 (97.9)	595 (95.4)	1208 (96.6)
Did not have post-vaccination immunogenicity data	13 (2.1)	26 (4.2)	39 (3.1)
Did not receive at least one dose of study intervention	0	3 (0.5)	3 (0.2)
Per protocol analysis set at Visit 2 (PPS)	577 (92.2)	553 (88.6)	1130 (90.4)
Participant doesn't have any immunogenicity results at visit	9 (1.4)	11 (1.8)	20 (1.6)
Participant has a protocol deviation that leads to exclusion from the PP population	17 (2.7)	15 (2.4)	32 (2.6)
Participant has a protocol deviation of temperature excursion	10 (1.6)	14 (2.2)	24 (1.9)
Participant has a visit that was out of window	0 (0)	2 (0.3)	2 (0.2)
Participant withdrew from the study	0 (0)	0 (0)	0 (0)
Per protocol analysis set at Visit 4 (PPS)	274 (43.8)		274 (21.9)
Participant doesn't have any immunogenicity results at visit	309 (49.4)		309 (24.7)
Participant has a protocol deviation that leads to exclusion from the PP population	19 (3.0)		19 (1.5)
Participant has a protocol deviation of temperature excursion	5 (0.8)		5 (0.4)
Participant has a visit that was out of window	6 (1.0)		6 (0.5)

Participant withdrew from the study	0 (0)		0 (0)

Derived from table 14.1.1.1 in the study report. N = Number of participants in each vaccine group. Exposed set - all participants who received at least 1 dose of study vaccines. Full analysis set - all participants who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data. Per protocol analysis set - all participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data (in the Full Analysis Set) minus participants with protocol deviations that lead to exclusion from the PPS. As randomized is based on randomized participants analyzed on an intent-to-treat basis. Participants are only included in the exclusions from the Per Protocol Set once at each visit, prioritizing the categories in the order they are displayed.

Assessor's comment:

For this assessment, we focus on descriptive immunogenicity within the ACWY group. In total 624 subjects have been randomized to the MenACWY group, 621 of them have been exposed, of which 595 have been included in the FAS (95% of those randomized). In total 553 subjects were available in the per protocol set (89% of those randomized).

According to Table 2 there is a very high percentage of participants that do not have immunogenicity results at visit 4: 309 (49.4%) for the ABCWY group. As no analysis was performed for the ACWY serotypes in visit 4 of the MenACWY group, the table does not provide the number in the per protocol analysis for visit 4 in the ACWY group. It appears from table 1 "Immunological readout" in the protocol that only a small subgroup of participants in the MenACWY group had blood drawn at day 221. However, the sequence of events in the protocol (table 3) lists that blood should be drawn at visit 4, as does figure 1, the study design overview. It is not understood why this has not been reported, nor it is clear how the participants would have been selected for blooddraw/immunogenicity analyses at visit 4, i.e. whether this was random or concerned a convenient selection. For the assessment of Menveo, the non-inferioirty comparison to an experimental MenABCWY vaccine is of limited relevance . There for the issue is not pursued.

Conduct of the study

The original protocol was amended three times.

Amendment 1 (31 august 2020) concerned the volume of placebo administered and was considered non-substantial.

Amendment 2 (12 February 2020) was considered substantial. A secondary endpoint ("Family 1") was updated to co-primary endpoint in Amendment 2 (dated 12 February 2021) of the protocol. The statistical considerations were revised.

Amendment 3 (1 November 2021) has as a goal to extend the window for the priming MenACWY vaccination prior to enrolment from 4 to 6 years to at least 4 years. This is to increase the pool of potential participants who may benefit from the intervention.

Assessor's comment

Amendment 2 was after the first participant first enrolled (25-January-2021), but within the 1 month timeframe for data collections after the first vaccination for the primary endpoint. Therefore the amendment is not expected to influence the results.

Baseline data

Demographic and baseline characteristics were comparable across study groups in the Enrolled Set. The mean age of participants who participated in this study was 17.2 (SD, 2.58) years across groups. There was a higher percentage of adolescents (15 to 17-year-olds) (71.3%) than adults (18 to 25-

year-olds) (28.5%). Overall, 53.4% of participants in the study were females. A total of 75.3% of participants were of White heritage and the majority (70.3%) identified as Not Hispanic or Latino ethnicity. The majority of the enrolled participants were from US (58.5%) and the rest of the participants were from Argentina, Australia, and Canada.

Efficacy results

Co-primary endpoints

For the percentages of participants with 4-Fold Rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, and Vaccine Group differences for both co-primary endpoints are presented in Table 3.

Table 3: Percentages of Participants with 4-Fold Rise in hSBA titers against N. meningitidis serogroups A, C, W, and Y, 1 month after second vaccination for ABCWY group (Day 211) and 1 month after single MenACWY vaccination dose for the ACWY group (Day 31, PPS).

		ABCWY Day 221 ("Family 1")		ABCWY Day 31 ("Family 2")		**ACWY Day 31**		ABCWY (day 221) – ACWY (day 31)	ABCWY (day 31) - ACWY (day 31)
Serogroup	**Four-fold increase**	N	n (%)	N	n (%)	**N**	**n (%)**	% difference (95%CI)	
A	Four-fold increase, overall	169	161 (95.3)	509	471 (92.5)	505	480 (95.0)	0.2 (-4.38, 3.50)	-2.5 (-5.59, 0.47)
	Four-fold increase, pre < LOD	120	120 (100.0)	370	364 (98.4)	356	349 (98.0)		
	Four-fold increase, LOD ≤ pre < LLOQ	0	0	0	0	3	3 (100.0)		
	Four-fold increase, pre ≥ LLOQ	49	41 (83.7)	139	107 (77.0)	146	128 (87.7)		
C	Four-fold increase, overall	181	171 (94.5)	570	536 (94.0)	546	513 (94.0)	0.5 (-4.14, 3.98)	0.1 (-2.76, 2.94)
	Four-fold increase, pre < LOD	63	63 (100.0)	197	194 (98.5)	198	194 (98.0)		
	Four-fold increase, LOD ≤ pre < LLOQ	11	11 (100.0)	42	41 (97.6)	39	39 (100.0)		
	Four-fold increase, pre ≥ LLOQ	107	97 (90.7)	331	301 (90.9)	309	280 (90.6)		
W	Four-fold increase, overall	181	173 (95.6)	565	533 (94.3)	544	511 (93.9)	1.6 (-2.73, 4.89)	-0.4 (-2.41, 3.25)
	Four-fold increase, pre < LOD	104	104 (100.0)	351	345 (98.3)	354	341 (96.3)		
	Four-fold increase, LOD ≤ pre < LLOQ	3	3 (100.0)	8	7 (87.5)	11	10 (90.9)		
	Four-fold increase, pre ≥ LLOQ	74	66 (89.2)	206	181 (87.9)	179	160 (89.4)		

		ABCWY Day 221 ("Family 1")		ABCWY Day 31 ("Family 2")		**ACWY Day 31**		ABCWY (day 221) – ACWY (day 31)	ABCWY (day 31) - ACWY (day 31)
Serogroup	**Four-fold increase**	N	n (%)	N	n (%)	**N**	**n (%)**	% difference (95%CI)	
Y	Four-fold increase, overall	180	171 (95.0)	567	531 (93.7)	537	507 (94.4)	0.6 (-3.93, 3.91)	-0.8 (-3.62, 2.09)
	Four-fold increase, pre < LOD	99	99 (100.0)	333	326 (97.9)	330	318 (96.4)		
	Four-fold increase, LOD ≤ pre < LLOQ	4	4 (100.0)	21	20 (95.2)	21	19 (90.5)		
	Four-fold increase, pre ≥ LLOQ	77	68 (88.3)	213	185 (86.9)	186	170 (91.4)		

Abbreviations: hSBA = human serum bactericidal assay; N = number of participants in each vaccine group with available results (which additionally satisfy the baseline (pre) criteria, where applicable); n = number of participants with 4-fold rise in hSBA titer at respective timepoints per vaccine group; NE = not estimable; LOD = limit of detection; LLOQ = lower limit of quantitation. ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7. For participants with a baseline titer less than LOD, a four-fold increase is relative to LOD. For participants with a baseline titer greater than or equal to LOD but less than LLOQ, a four-fold increase is relative to LLOQ

Subgroup analyses of by age group

The primary immunogenicity variables were analyzed for the following subgroups: Gender (Female, Male), Age in years. The 4-fold rise within the MenACWY arm stratified for age group 15 - < 18 and >=18 – 25 are reported here. For the 15-< 18 group the results were 97.5% (95.28; 98.84), 97.6% (95.57; 98.92), 98.2% (96.05; 99.26), 98.57% (96.57; 99.41) for MenACWY, respectively. For the >=18 – 25 group the results were 89.1% (82.93; 93.65), 85.4% (79.01; 90.39), 84.0% (77.51; 89.31), 74.5% (60.37;85.67) for MenACWY, respectively.

Assessor's comment:

As described above, the non-inferiority comparison is of limited relevance for this assessment.

The percentage of participants with a 4-fold rise in the MenACWY group overall is >93.9%, with the lowest four-fold increase compared in the subgroup with pre ≥ LLOQ being 87.7%.

For the subgroup analyses by age, the younger group (15 - < 18) had a higher percentage of participants reporting a 4-fold rise than the older group (>=18 – 25). As the subgroup analyses were not powered, and both groups still showed a considerable response to the booster, this is not further pursued for inclusion in the SmPC.

Secondary endpoints:

A single secondary endpoint relates to the Menveo vaccine. This objective was to assess the immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W, and Y, at pre-vaccination and 1 month after the first and last MenABCWY vaccinations and 1 month after the MenACWY vaccination in terms of

The percentages of participants with hSBA titers ≥LLOQ against serogroups A, C, W, and Y

At baseline, the percentages of participants with hSBA titers ≥LLOQ ranged from 27.7% to 57.7% for the ABCWY group and from 28.8% to 56.2% for the ACWY group. The percentages of participants with hSBA titers ≥LLOQ ranged from 97.9% to 98.9% and from 99.5% to 100% for MenABCWY group at 1 month after first vaccination and last vaccination, respectively. For the ACWY group, the percentages ranged from 96.8% to 99% 1 month after vaccination.

Geometric Mean hSBA Titers and Geometric Mean hSBA Ratios

The hSBA GMTs in the ABCWY group one month after first vaccination ranged from 670.78 to 2945.68 and from 645.24 to 2350.14 one month after last vaccination. For the ACWY group one month after the last (an only Menveo) vaccination ranged from 1282.56 to 2552.27.

GMR's ranging from 43.98 (Men A) to 124.11 (Men Y) against *N. meningitidis* serogroups A, C, W, and Y at one month after MenABCWY first vaccination compared to baseline was observed. Similarly, GMR's ranging from 44.74 (Men A) to 97.66 (Men W) one month after ABCWY last vaccination compared to baseline were observed.

In the ACWY group the GMR's ranged from 76.91 (Men A) to 150.83 (Men W) in hSBA GMTs against *N. meningitidis* serogroups A, C, W, and Y at one month after vaccination compared to baseline was observed.

Results of secondary endpoints were not presented stratified for age group.

Assessor's comment:

The GMT's in the Menveo group for the adolescent booster are comparable to those reported in Table 8 of the SmPC for Menveo, in which bactericidal antibody responses to Menveo booster administered at 3 or 5 years after the primary vaccination with Menveo or ACWY-PS in subjects aged 11-17 years are reported. When the booster was given 5 years after primary vaccination the GMT's ranged from 819 – 2092. The GMT's reported for this study does not provide new information relevant for inclusion in the SmPC.

Safety results

Exposure

A total of 1247 (99.8%) participants were included in the Overall Safety Set (combined Unsolicited Safety Set and the Solicited Safety Set). From the ACWY group, 3 participants were eliminated as they did not receive at least 1 dose of the study intervention. The percentage of patients who were compliant with eDiary reporting after any vaccination was comparable between the randomized groups (ABCWY 98.2%; ACWY 98.4%).

Solicited AEs (7-day post-vaccination period):

During the 7-day follow-up period after any vaccination, at least one solicited event was reported by 88.8% participants in the ABCWY group and 84.1% participants in the ACWY group.

Pain (MenACWY 31.8%), headache (MenACWY 34.6%), and fatigue (MenACWY 37.0%), were the most common solicited adverse events after the first vaccination. From day 1 to day 7 following the first vaccination, prophylactic analgesic/antipyretic medications were taken by 7.1% of participants in ACWY

group, and analgesic/antipyretic medications for the treatment of pain and/or fever was taken by 11.8% of participants in ACWY group.

Severe solicited systemic events were reported in ≤2.9% of participants across study groups. Apart from severe injection pain, other severe solicited administration site events were reported by ≤1.6% of participants across study groups.

Assessor's comment:

The reactogenicity of reported for Menveo is similar to that in the Menveo SmPC. However, in the Menveo SmPC pain fatigue is not listed as a side-effect for those 10-65 years of age.

Please note that the inclusion of fatigue as an ADR table of section 4.8 is currently being evaluated in the SmPC for those 10-65 years of age (line-extension EMEA/H/C/001095/X/0119). Therefore, this is not further pursued in this article 46 procedure.

Unsolicited AEs (30-day post-vaccination period) and SAE's (entire study period):

Unsolicited AEs were reported during the 30 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). During the 30-day post-vaccination period following any vaccination, at least one unsolicited AE was reported by 24.2% of participants in the ACWY group.

The most commonly reported causally related unsolicited AEs, by PT, were lymphadenopathy, dizziness, abdominal pain, diarrhoea, and myalgia. The majority of the AEs that were considered related to vaccination by the investigator happened within the first 7 days. Unsolicited AEs assessed as causally related to vaccination by the investigator were reported by 2.9% and 5.0% of participants in ABCWY and ACWY groups, respectively.

During the entire study period, a total of 18 and 7 participants reported at least 1 SAE in the ABCWY and ACWY groups, respectively. There were no SAEs assessed as causally related to vaccination.

Withdrawals due to Aes/SAEs (throughout the study period):

At least one unsolicited adverse event leading to premature withdrawal from the study within 30 days after vaccination was reported by 0.3% (n=2) and 0.5% (n=3) of participants in the ABCWY and ACWY groups, respectively. For the entire study period, these percentages are 0.6% (n=4) in the ABCWY group, and 1.0% (n=6) in the ACWY group.

2 fatal events were reported (1 participant in ABCWY group and 1 in ACWY group). Both were completed suicides, occurring 75 after the first (MenACWY group) and 83 days (MenABCWY group) after final vaccine administration.

Other significant AEs

In total, 4 participants reported AESIs in the ACWY group (celiac disease, colitis ulcerative, Crohn's disease, and arthritis). Only one AESI was considered new onset (colitis ulcerative), which was reported within 30 days following the second vaccination. There were no AESIs reported in the ABCWY group. None of the AESIs were considered as causally related to vaccination by the investigator.

Assessor's comment:

The new-onset AESI concerned a case of ulcerative colitis reported by a 18-25-year-old subject with a family history of inflammatory GI disease who was enrolled in study MENB REC 2ND GEN-038 (V72_72), with onset of symptoms approximately three months after MenACWY administration.

Upon reviewing the narrative, the assessor agrees with the conclusion of the MAH that this AESI is unlikely related to MenACWY vaccination.

2.3.3. Discussion on clinical aspects

In study MENABCWY-019, 1247 participants aged 15-25 previously primed with a MenACWY vaccine were randomized into two groups. The ABCWY group received an experimental MenABCWY vaccine at 0 and 6 months, and the ACWY group received Menveo at 0 months, and Bexsero at 6 and 7 months.

Menveo was generally tolerated in the study. The safety results were generally found to be in line with the established safety profile of Menveo.

Immunogenicity at 1 month after the booster dose showed results in line with those currently presented in the SmPC.

3. CHMP overall conclusion and recommendation

The study results are in line with the approved product information for Menveo in the EU. No changes to the current SmPC for Menveo are considered necessary following this procedure.

☒ Fulfilled:

No regulatory action required.