Amsterdam, 19 June 2025
EMADOC-1700519818-2025334
Committee for Medicinal Products for Human Use (CHMP)

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

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMA/PAM/0000263482

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	21 April 2025	21 April 2025
☐	CHMP Rapporteur AR	26 May 2025	27 May 2025
☐	CHMP comments	10 June 2025	n/a
☐	Updated CHMP Rapporteur AR	12 June 2025	n/a
☒	CHMP outcome	19 June 2025	19 June 2025

Table of contents

1. Introduction

On 28 March 2025, the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

The present submission includes the Clinical Study Report for study 212458 conducted with EU licensed products to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II). Bexsero and Menveo were administered in the study as a comparator vaccine.

Study 212458 was not conducted in accordance with an agreed paediatric investigation plan for Bexsero or Menveo.

A short critical expert overview has also been provided.

The current indications for these vaccines in EU are following:

Bexsero is indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B.

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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 212458, A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Study interventions administered in the study are MenABCWY-2Gen low dose, MenABCWY-2Gen high dose, placebo (saline), MenACWY (Menveo) and MenB (Bexsero). All the interventions were administered via intramuscular injection.

The current vaccine formulation of Bexsero is based on 3 proteins: i) factor H binding protein (fHbp), ii) Neisseria adhesion A (NadA) and iii) Neisseria Heparin Binding Antigen (NHBA) or 287. The fHbp protein has been combined with the accessory protein GNA2091 (936), and the 287 protein has been combined with GNA1030 (953), to create 2 fusion proteins. In addition, the vaccine also contains OMV (with Porin A [porA] antigen) derived from the New Zealand epidemic strain.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number 212458: A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).

Neisseria meningitidis infections causing invasive meningococcal disease (IMD) are an important public health concern worldwide due to the substantial morbidity and mortality they cause, as well as the transmissibility of these infections. Ninety percent of meningococcal meningitis and septicaemia are caused by only 5 *N. meningitidis* serogroups: A, B, C, W and Y.

In January 2013, a centralised marketing authorisation in European Union (EU) was granted for Bexsero for use in individuals from 2 months of age and older against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* group B.

In March 2010, a centralised marketing authorisation in European Union (EU) was granted for Menveo for use in individuals from 11 years of age and older against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* groups A, C, W135 and Y. In April 2012, an extension of indication was granted to include children from 2 to 10 years of age inclusive.

GSK is currently developing a MenABCWY combination vaccine intended to protect against IMD caused by all 5 meningococcal serogroups.

2.3.2. Clinical study

Study number 212458: A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).

Description

The early clinical development plan consisted of a seamless Phase I/II study. The study was conducted at 54 sites in Australia, Belgium, Brazil, Finland, Poland, Sweden, Turkey and United States. The first-time-in-human, Phase I part of this study was conducted in healthy adults in a dose-escalating fashion with 2 formulations of the investigational MenABCWY-2Gen vaccine, and was served as a safety lead-in to the Phase II study part.

The Phase I safety lead-included 4 study groups (randomised 3:1), with a staggered enrolment (16 participants initially followed by 16 participants later) of a total of 32 participants.

Study groups	Study intervention(s)	Blinding
ABCWY low dose	MenABCWY-2Gen in a 0,1-month schedule	Observer-blinded
ABCWY high dose	MenABCWY-2Gen in a 0,1-month schedule	
Placebo low dose	NaCl in a 0,1-month schedule	
Placebo high dose	NaCl in a 0,1-month schedule	

The Phase II part of the study was conducted in 2 parts: The 'formulation and schedule- finding' part (hereafter referred to as Phase II FSF) was conducted in healthy adolescents and young adults and was designed to select the vaccine formulation and schedule to be tested in Phase III. The 'blood sourcing' part (hereafter referred to as Phase II Sourcing) was conducted in healthy adults to collect sufficient serum samples for the development of assays to be used in the MenABCWY-2Gen vaccine clinical development program. Phase II FSF assessed the safety, the effectiveness and the immunogenicity of the above 2 formulations of the investigational MenABCWY-2Gen vaccine, while Phase II Sourcing assessed the safety. Bexsero (rMenB+OMV NZ, hereafter referred to as MenB, 0,6-months schedule) and Menveo (hereafter referred to as MenACWY; single dose) were administered as control vaccines for assessing the response to serogroups B and ACWY, respectively.

The purpose of this partially blinded Phase II FSF was to assess the safety, effectiveness and immunogenicity of the MenABCWY-2Gen vaccine in healthy adolescents and young adults (10-25 years). It included 5 study groups with a staggered enrolment of initial 45 participants in a 3:1:3:1:1 ratio for safety lead-in, followed by the remaining participants in 1:1:1:1:1 ratio to receive the investigational or control vaccines. Blood samples were collected to assess the immune responses.

Phase II FSF included 5 study groups, a staggered enrolment was planned (45 participants for safety lead-in and 955 participants thereafter).

tudy groups	Study intervention(s)	Blinding
MenABCWY-2Gen low dose_06	MenABCWY-2Gen low dose in a (0,6-months) schedule	Observer-blinded
	NaCl	
MenABCWY-2Gen low dose_02	MenACWY-2Gen low dose in a (0,2-months) schedule	
	NaCl	
MenABCWY-2Gen high dose _06	MenABCWY-2Gen high dose in a (0,6-months) schedule	
	NaCl	
MenABCWY-2Gen high dose _02	MenABCWY-2Gen high dose in a (0,2-months) schedule	
	NaCl	
Control	MenACWY	Open label
	MenB in a (0,6-months) schedule	

The Phase II Sourcing was observer blinded and included 2 groups (randomised 1:1), with a parallel enrolment of a total of 226* participants:

Additionally, the Phase II sourcing part included 4 more groups (randomised 1:1:1:1), with a parallel enrolment of a total of 240 participants.

Study groups	Study intervention(s)	Blinding
MenABCWY-2Gen low dose_01*	MenABCWY-2Gen low dose in a (0,1-month) schedule	Observer-blinded**
MenABCWY-2Gen high dose_01*	MenABCWY-2Gen high dose in a (0,1-month) schedule	
MenABCWY-2Gen low dose_02	MenABCWY-2Gen low dose in a (0,2-month) schedule	
MenABCWY-2Gen high dose_02	MenABCWY-2Gen high dose in a (0,2-month) schedule	
MenABCWY-2Gen low dose_06	MenABCWY-2Gen low dose in a (0,6-month) schedule	
MenABCWY-2Gen high dose_06	MenABCWY-2Gen high dose in a (0,6-month) schedule	

Assessor´s comment: Bexsero and Menveo were used as a control only in Phase II FSF part. Therefore we focus only on this study part in present report.

Methods

Study participants

Inclusion Criteria: The study enrolled male or female healthy participants with age at time of vaccination between 18 and 40 years for Phase I, 10 and 25 years for Phase II FSF and 18 and 50

years for Phase II Sourcing. Participants were either unprimed or had received a single previous dose of MenACWY vaccine.

Exclusion Criteria: Exclusion criteria essentially consisted of current, or previous, confirmed or suspected disease caused by *N. meningitidis*, household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection within 60 days of enrollment, previous vaccination with any group B meningococcal vaccine. Pregnant or lactating female participants or female participants planning to become pregnant or planning to discontinue contraceptive precautions were also excluded from the study.

Treatments

The timepoints for the collection of blood samples and the vaccination schedule in each study group are presented in the table below.

Groups					
	Observer-blinded				Open-label
Visits	**MenABCWY-2Gen low dose group (0,6-month schedule)**	**MenABCWY-2Gen low dose group (0,2-month schedule)**	**MenABCWY-2Gen high dose group (0,6-month schedule)**	**MenABCWY-2Gen high dose group (0,2-month schedule)**	**Control**
Visit 1 (Day 1), Month 0	MenABCWY-2Gen low dose; Pre-vaccination Blood sample	Placebo	MenABCWY-2Gen high dose; Pre-vaccination Blood sample	Placebo	MenB and MenACWY; Pre-vaccination Blood sample
Visit 2 (Day 31), Month 1	Post-vaccination1 Blood sample	Pre-vaccination Blood sample	Post-vaccination1 Blood sample	Pre-vaccination Blood sample	Post-vaccination1 Blood sample
Visit 3 (Day 121) Month 4	Placebo	MenABCWY-2Gen low dose	Placebo	MenABCWY-2Gen high dose	-
Visit 4 (Day 181) Month 6	MenABCWY-2Gen low dose	MenABCWY-2Gen low dose	MenABCWY-2Gen high dose	MenABCWY-2Gen high dose	MenB
Visit 5 (Day 211), Month 7	Post-vaccination2 Blood sample	Post-vaccination2 Blood sample	Post-vaccination2 Blood sample	Post-vaccination2 Blood sample	Post-vaccination2 Blood sample
Visit 6 (Day 541)	Blood sample	Blood sample	Blood sample	Blood sample	Blood sample

For each participant, the duration of the Phase II FSF was approximately 18 months.

Objectives

Primary objectives:

- To demonstrate the superiority of the effectiveness of the MenABCWY-2Gen (low and high dose) when administered at 0,2- or 0,6-months schedule, compared to the MenB vaccine administered at 0,6-months schedule.

- To demonstrate the immunological non-inferiority of the MenABCWY-2Gen (low and high dose) administered at 0,2- or 0,6-months schedule compared to the MenACWY vaccine (single dose).
- To evaluate the safety and reactogenicity of the MenABCWY-2Gen (low and high dose), the MenB vaccine and the MenACWY vaccine.

Secondary objectives:

- To describe the distribution of participants by percentages of serogroup B invasive disease strains killed using endogenous complement human serum bactericidal assay (enc-hSBA) at 1 month after the last vaccination of the MenABCWY-2Gen (low and high dose) administered at 0,2 and 0,6-months schedule and of the MenB vaccine administered at 0,6-months schedule.
- To assess the immune response to the MenABCWY-2Gen (low and high dose) administered at 0,2 and 0,6-months schedule and to the MenB vaccine administered at 0,6-months schedule against serogroup B indicator strains.
- To assess the immune response to the MenABCWY-2Gen (low and high dose) administered at 0,2 and 0,6-months schedule and to the MenACWY vaccine (single dose) against serogroups A, C, W and Y.

Outcomes/endpoints for Phase II FSF part

Objectives	Endpoints
Phase II – Formulation and Schedule-finding	
Primary	
To demonstrate the superiority of the effectiveness of the MenABCWY-2Gen vaccine (low and high dose) when administered at 0,2- or 0,6-months schedule, compared to the MenB vaccine administered at 0,6-months schedule.	The percentages of samples with bactericidal serum activity using enc-hSBA against a panel of 110 randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains at 1 month after the last vaccination (Day 211, Month 7) in all groups.
To demonstrate the immunological non-inferiority of the MenABCWY-2Gen vaccine (low and high dose) administered at 0,2- or 0,6-months schedule compared to the MenACWY vaccine (single dose)†.	The percentages of participants achieving a 4-fold rise** in hSBA titres against serogroups A, C, W and Y at 1 month after the • last MenABCWY-2Gen vaccination (Day 211, Month 7) for the ABCWY groups and, • MenACWY vaccination (Day 31, Month 1) in the Control group, relative to Day 1, Month 0 in MenABCWY low dose_06, MenABCWY high dose_06 and Control groups and relative to 3 months pre-first MenABCWY-2Gen vaccination (Day 31, Month 1) in MenABCWY low dose_02 and MenABCWY high dose_02 groups.
To evaluate the safety and reactogenicity of the MenABCWY-2Gen vaccine (low and high dose), the MenB vaccine and the MenACWY vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at:

Objectives	Endpoints
	• Day 1, Day 121 and Day 181 in the MenABCWY low dose_06, MenABCWY low dose_02, MenABCWY high dose_06 and MenABCWY high dose_02 groups, and • Day 1 and Day 181 in the Control group. • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at: • Day 1, Day 121 and Day 181 in the MenABCWY low dose_06, MenABCWY low dose_02, MenABCWY high dose_06 and MenABCWY high dose_02 groups, and • Day 1 and Day 181 in the Control group. • The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 541).

Abbreviations: AE, Adverse event; SAE, Serious adverse event; AESI, Adverse event of special interest; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentrations; enc-hSBA, endogenous complement human serum bactericidal assay; GMT, geometric mean titre; GMR, geometric mean ratio; hSBA, human serum bactericidal assay; LOD, limit of detection; LLOQ, lower limit of quantitation.

**For the serogroup A C, W, Y and serogroup B evaluations, the 4-fold rise (for serogroup B - per each indicator strain) is defined as:

-a post-vaccination hSBA titre ≥16 for participants with a pre-vaccination hSBA titre <4,
-a post-vaccination hSBA titre ≥4 times the LLOQ for participants with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
-a post-vaccination hSBA titre ≥4 times the pre-vaccination hSBA titre for participants with a pre-vaccination hSBA titre ≥LLOQ.

† The primary objective of immunological NI of the MenABCWY-2Gen vaccine to MenACWY will be evaluated only in participants without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in participants with and without previous MenACWY vaccination (primed/unprimed).

Sample size

The number of participants planned was 32 for Phase I, 1000 for Phase II FSF and 466* for Phase II Sourcing.

A thousand (1000) participants are to be enrolled in 5 arms of Phase II of the study, 206 participants for both MenABCWY low dose_06 and MenABCWY high dose_06 arms and 196 participants for MenABCWY low dose_02, MenABCWY high dose_02 and Control arms. It is assumed that 15% of the participants will drop out or will not contribute to an evaluable result for the primary endpoints resulting in about 170 evaluable participants per arm. The power to show both immunological non-inferiority of MenABCWY-2Gen vaccine (low or high dose) when administered at 0,2- or 0,6-m schedules compared to the Control vaccine (single dose) and effectiveness superiority of the MenABCWY-2Gen vaccine (low or high dose) when administered at 0,2- or 0,6-m schedules compared to the Control vaccine.

The actual number of participants enrolled and entered into Exposed Set by receiving at least 1 dose of study intervention are presented in the below table.

	Phase I	Phase II FSF	Phase II Sourcing
Enrolled Set	32	1052	356
Exposed Set	32	1049	356

*At the time of the protocol amendment to which this document refers (Protocol amendment 4), enrolment to MenABCWY low dose_01 and MenABCWY high dose_01 groups was stopped.

Randomisation and blinding (masking)

In Phase II (Formulation and Schedule-finding), the minimisation procedure will account for age category (10-17 years of age and 18-25 years of age) and previous MenACWY vaccination (priming) (Yes and No).

Once a participant identification number is allocated, the randomisation system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR).

Phase II (Formulation and Schedule-finding) partially blinded. Data in the 4 ABCWY groups will be collected in an observer-blind manner. To do so, study intervention(s) 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, efficacy). Data in the Control group will be collected in an open-label manner i.e. study participants, investigator and site staff personnel will be aware of the treatment administered as 2 study interventions are administered at Visit V1.

The laboratory in charge of the laboratory testing will be blinded to the treatment as well as to the subject number. There will be no link between the study intervention groups and the identity of the participant. In addition, for each sample, a different randomly selected subject code will be used at each timepoint. This subject coding will prevent the testing laboratory personnel from linking the consecutive timepoints to a specific subject

Statistical Methods

Primary effectiveness and immunogenicity analyses:

Superiority of effectiveness: The analysis was performed using the Full Analysis Set (FAS). The 97.5% CIs for the difference in percentages between MenABCWY-2Gen groups and the control group was constructed using the method of Miettinen and Nurminen.

Superiority criterion: Superiority of MenABCWY-2Gen vaccine compared to the MenB vaccine would be demonstrated if the lower limit of the 2-sided 97.5% CI for the difference in percentages of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic US N. meningitidis serogroup B invasive disease strains was above 5% in the ABCWY groups compared to the Control group at 1 month after the last vaccination.

Immunological Non-Inferiority: The analysis was performed using the Per Protocol Set (PPS). The 97.5% CIs for the difference in percentages between MenABCWY-2Gen groups and the control group was constructed using the method of Miettinen and Nurminen.

Non-inferiority criterion: Non-inferiority of MenABCWY-2Gen vaccine compared to the MenACWY vaccine would be demonstrated if the lower limit of the 2-sided 97.5% CI for the difference in

percentages of participants achieving a 4-fold rise in hSBA titres was above -10% at 1 month after the last vaccination in the ABCWY groups compared to after the first vaccination in the Control group.

Note: The objectives were tested in a hierarchical manner.

Primary Safety analyses:

The safety analyses were descriptive and were conducted on Exposed Set.

Results

Participant flow

The Phase II FSF part of the study enrolled 1052 participants of which, 1049 (99.7%) participants were included in the Exposed Set. Of these 1049 participants, 1025 (97.7%) participants were included in the Full Analysis Set. A total of 197 participants were included in the Exposed Set of the Control (*Bexsero*/*Menveo*) group, of which 182 (92.4%) participants completed the study.

Recruitment

The study was initiated on 14.06.2021 and completed on 02.02.2024 (last participants last visit). The majority of the study population for Phase II FSF part was recruited in EU. See the table below.

Country, n (%)	Phase I Total, N=32 (%)	Phase II FSF Total, N=1052 (%)	Phase II Sourcing Total, N=356 (%)
Australia	32 (100)		195 (54.8)
Belgium	-	169 (16.1)	-
Brazil	-	147 (14.0)	-
Finland	-	157 (14.9)	-
Poland	-	478 (45.4)	118 (33.1)
Sweden	-	11 (1.0)	24 (6.7)
Turkey	-	7 (0.7)	19 (5.3)
United States	-	83 (7.9)	-

Baseline data

Demographic and baseline characteristics were balanced across study groups in different analysis sets. In the Enrolled Set of Control (*Bexsero*/*Menveo*) group, 24 participants were 2-11 years of age, 55 participants were 12-17 years of age and 119 participants were in the 18-64 years of age category.

Summary of demography and baseline characteristics Phase II FSF - Enrolled Set

	MenABCWY-2Gen high dose_06 N=238		MenABCWY-2Gen high dose_02 N=194		MenABCWY-2Gen low dose_06 N=241		MenABCWY-2Gen low dose_02 N=181		CONTROL N=198		Total N=1052	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) At Informed Consent												
n	238		194		241		181		198		1052	
Mean	18.7		18.6		18.9		18.6		18.4		18.6	
Standard Deviation	5.0		4.7		4.7		4.6		4.6		4.7	
Median	20.0		20.0		20.0		20.0		19.0		20.0	
Minimum	10		9		10		10		10		9	

	MenABCWY-2Gen high dose_06 N=238		MenABCWY-2Gen high dose_02 N=194		MenABCWY-2Gen low dose_06 N=241		MenABCWY-2Gen low dose_02 N=181		CONTROL N=198		Total N=1052	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Maximum	25		25		26		26		25		26	
Age group												
10-17 years	89	37.4	71	36.6	86	35.7	68	37.6	79	39.9	393	37.4
18-25 years	149	62.6	123	63.4	155	64.3	113	62.4	119	60.1	659	62.6
Age group [EudraCT]												
Children (2-11 years)	30	12.6	23	11.9	26	10.8	19	10.5	24	12.1	122	11.6
Adolescents (12-17 years)	59	24.8	48	24.7	60	24.9	49	27.1	55	27.8	271	25.8
Adults (18-64 years)	149	62.6	123	63.4	155	64.3	113	62.4	119	60.1	659	62.6
Country												
Belgium	38	16.0	36	18.6	37	15.4	26	14.4	32	16.2	169	16.1
Brazil	31	13.0	29	14.9	35	14.5	26	14.4	26	13.1	147	14.0
Finland	36	15.1	36	18.6	35	14.5	31	17.1	19	9.6	157	14.9
Poland	115	48.3	76	39.2	111	46.1	78	43.1	98	49.5	478	45.4
Sweden	1	0.4	2	1.0	3	1.2	3	1.7	2	1.0	11	1.0
Turkey	1	0.4	2	1.0	1	0.4	0	0.0	3	1.5	7	0.7
United States	16	6.7	13	6.7	19	7.9	17	9.4	18	9.1	83	7.9
Sex												
Male	82	34.5	73	37.6	86	35.7	85	47.0	85	42.9	411	39.1
Female	156	65.5	121	62.4	155	64.3	96	53.0	113	57.1	641	60.9

MenABCWY-2 Gen high dose_06 = MenABCWY-2Gen high dose vaccination at Month 0 and Month 6 and Placebo at Month 4; MenABCWY-2Gen high dose_02 = MenABCWY-2Gen high dose vaccination at Month 4 and Month 6 and Placebo at Month 0; MenABCWY-2Gen low dose_06 = MenABCWY-2Gen low dose vaccination at Month 0 and Month 6 and Placebo at Month 4; MenABCWY-2Gen low dose_02 = MenACWY-2Gen low dose vaccination at Month 4 and Month 6 and Placebo at Month 0; CONTROL = rMenB+OMV NZ vaccination at Month 0 and Month 6 and MenACWY vaccination at Month 0;
N = number of participants; n/%= number/percentage of participants in a given category
Only year and month of birth is known. Day of birth have been imputed to be 15 for all the participants. Therefore, age in year here reported may be one year different from the real age of the participant
Source: Table 14.1.3.1B (29NOV2024 7:49 GMT)

Number analysed

Exposure to study interventions by visit Phase II FSF - Exposed Set

MenABCWY-2Gen high dose_06 N=238	MenABCWY-2Gen high dose_02 N=194	MenABCWY-2Gen low dose_06 N=239	MenABCWY-2Gen low dose _02 N=181	CONTROL N=197

Efficacy results

The effectiveness and immunogenicity analysis were evaluated in Phase II FSF.

Primary objectives:

- Immunological non-inferiority of MenABCWY-2Gen vaccine compared to MenACWY vaccine: The immunological non-inferiority of the MenABCWY-2Gen high dose and MenABCWY-2Gen low dose (at both 0,6 and 0,2-month schedules) compared to the control (MenACWY) vaccine against serogroups A, C, W and Y at 1 month after the last vaccination in unprimed participants was demonstrated, as the LL of the 2-sided 97.5% CI for the group difference in overall percentages of participants achieving a 4-fold rise in hSBA titres was above the pre-defined criteria of -10% .
- Superiority of the effectiveness of MenABCWY-2Gen vaccine compared to MenB vaccine: The superiority of MenABCWY-2Gen high dose and MenABCWY-2Gen low dose (at both 0,6 and 0,2-month schedules) compared to the MenB vaccine was not demonstrated, as the LL of the 2-sided 97.5% CI for the difference in percentages of samples with bactericidal serum activity using enc-hSBA was below the pre-defined criteria of above 5%.
    - The effectiveness of MenABCWY-2Gen high dose and MenABCWY-2Gen low dose at 0,6-month schedule appeared to be greater compared to the control (MenB) as the percentages of samples with bactericidal activity using enc-hSBA were 91.0% in the MenABCWY-2Gen high dose_06 group, 91.0% in the MenABCWY-2Gen low dose_06 group and 86.4% in the control (MenB) group.
    - Regardless of dose, the effectiveness of MenABCWY-2Gen vaccine was higher with 0,6-month schedule compared to the 0,2-month schedule.

Secondary objectives:

- Distribution of percentages of Men B strains killed using enc-hSBA: The percentage of participants with ≥90% killed strains was 70.7% and 71.2% in MenABCWY-2Gen high dose_06 and MenABCWY-2Gen low dose_06 groups (0,6-month schedule groups), 55.0% and 53.4% in MenABCWY-2Gen high dose_02 and MenABCWY-2Gen low dose_02 groups (0,2-month schedule groups) and 52.3% in the control (MenB) group.
- Immune response to Serogroup B indicator strains: For both formulations of MenABCWY-2Gen vaccine (low or high dose), post 2 doses, the percentage of participants with 4-fold rise in hSBA titres in the 0,6-month schedule groups compared with the control group appeared to be higher for fHbp and NHBA and comparable for NadA and PorA.
- The immune responses to all 7 serogroup B indicator strains were comparable between MenABCWY-2Gen high dose_06 and MenABCWY-2Gen low dose_06 groups.
- Regardless of the dose, overall, the immune response for all the serogroup B indicator strains appeared to be generally better with the 0,6-month schedule compared with the 0,2-month schedule.
- Immune response to A, C, W and Y strains: After 1 dose of MenABCWY-2Gen high dose or MenABCWY-2Gen low dose the percentage of participants with 4-fold rise in hSBA titres were comparable for C and W and appeared to be lower for A and Y compared to single dose of MenACWY.
- The immune responses to all 4 serogroups were comparable between MenABCWY-2Gen high dose_06 and MenABCWY-2Gen low dose_06ngroups (Table below).

	MenABCWY-2Gen high dose_06	MenABCWY-2Gen low dose_06	MenABCWY-2Gen high dose_02	MenABCWY-2Gen low dose_02	Control
Secondary Objective:4-fold rise in hSBA titres	**Endpoint: The percentages of participants achieving a 4-fold rise in hSBA titres against each B indicator strain at 1 month after the last vaccination**				
fHbp, % Overall 95% CI (LL, UL)	80.3 (74.0, 85.7)	80.9 (74.3, 86.4)	72.6 (65.2, 79.2)	57.4 (49.2, 65.3)	67.2 (59.8, 74.1)
NadA, % Overall 95% CI (LL, UL)	74.3 (67.2, 80.5)	81.3 (74.6, 86.9)	71.1 (63.4, 78.0)	73.8 (65.7, 80.8)	80.8 (74.0, 86.5)
NHBA, % Overall 95% CI (LL, UL)	91.6 (86.8, 95.1)	93.1 (88.3, 96.4)	82.9 (76.3, 88.3)	81.3 (74.2, 87.2)	81.3 (74.6, 86.8)
PorA, % Overall 95% CI (LL, UL)	68.9 (61.9, 75.4)	70.9 (63.5, 77.5)	58.6 (50.5, 66.4)	49.3 (40.7, 57.9)	63.4 (55.7, 70.6)
fHbp V1.13, % Overall 95% CI (LL, UL)	80.9 (74.3, 86.5)	77.8 (70.6, 83.9)	63.9 (55.5, 71.7)	59.9 (51.1, 68.1)	61.4 (53.3, 69.0)
fHbp V2, % Overall 95% CI (LL, UL)	75.8 (68.9, 81.9)	70.8 (63.3, 77.6)	58 (49.8, 65.8)	47.9 (39.5, 56.4)	12.9 (8.2, 19.0)
fHbp V3, % Overall 95% CI (LL, UL)	65.9 (58.6, 72.8)	55.1 (47.2, 62.8)	48.7 (40.7, 56.8)	42.5 (34.3, 50.9)	4.3 (1.7, 8.6)
Secondary Objective: 4-fold rise in hSBA titres	**Endpoint: The percentages of participants achieving a 4-fold rise in hSBA titres for serogroups A, C, W and Y at 1 month after the first MenABCWY-2Gen vaccination relative to Day 1, Month 0.**				
MenA, % Overall 95% CI (LL, UL)	78 (71.3, 83.7)	82.4 (75.9, 87.7)		-	92.2 (87.3, 95.7)
MenC, % Overall 95% CI (LL, UL)	62 (54.7, 68.9)	64.8 (57.6, 71.5)	-	-	63.5 (56.0, 70.6)
MenW, % Overall 95% CI (LL, UL)	71.3 (64.4, 77.5)	68 (61, 74.5)	-	-	67.8 (60.5, 74.5)
MenY, % Overall 95% CI (LL, UL)	51.7 (44.6, 58.8)	54.4 (47.1, 61.6)	-	-	62.4 (55, 69.3)

CI: Confidence interval; hSBA: human serum bactericidal assay; LL: lower limit; UL: upper limit

Specific results for the Control study arm:

Bexsero

The effectiveness of Bexsero vaccine at 0,6-month schedule against a panel of 110 randomly selected endemic *N. meningitidis* serogroup B strains as measured by the percentage of samples with bactericidal activity using enc-hSBA was 86.4%.

The percentages of strains killed was measured by enc-hSBA against a randomly selected panel of Men B strains. The percentage of participants with ≥90% killed Men B strains at 1 month after the second dose of Bexsero vaccination was 52.3%.

The percentage of participants with hSBA titres ≥LLOQ (lower limit of quantitation) at 1 month after the second dose of Bexsero vaccine in the Control group against each serogroup B indicator strain was 76.5% for fHbp, 86.0% for NadA, 97.2% for NHBA and 76.4% for PorA. The percentage of participants with hSBA titres ≥LLOQ for all serogroup B indicator strains (composite response) was 19.0%.

The percentage of participants with 4-fold rise in hSBA titres at 1 month after the 2nd dose of Bexsero vaccine in the Control group was 67.2% for fHbp, 80.8% for NadA, 81.3% for NHBA and 63.4% for PorA.

At 1 month after the second dose of Bexsero vaccine compared to the baseline, increase in geometric mean antibody titre (GMT) was observed against each serogroup B indicator strain and was 62.0 for fHbp, 109.1 for NadA, 58.2 for NHBA and 30.4 for PorA.

Menveo

The percentage of participants with hSBA titres ≥LLOQ for each serogroup A, C, W and Y in the Control group 1 month after administration of Menveo was 93.0%, 77.9%, 74.5% and 74.2% respectively.

In the Full Analysis Set, the percentage of participants with 4-fold rise in hSBA titres against serogroups A, C, W and Y in the Control group 1 month after administration of Menveo was 92.2%, 63.5%, 67.8% and 62.4% respectively.

At 1 month after vaccination compared to baseline, an increase in hSBA GMTs was observed against each serogroup all serogroups A, C, W and Y in the Control (Bexsero/Menveo) group. The geometric mean ratios (GMR) for serogroups A, C, W and Y were 42.9, 15.6, 12.5 and 13.1, respectively.

Safety results

The Bexsero and Menveo vaccines were tolerated in the study in healthy adolescents and young adults. Pain was the most frequently reported solicited administration-site event, while fatigue and headache were the most frequently reported solicited systemic events. Most of the solicited (administration-site or systemic) events were mild to moderate in intensity and with a mean duration of ≤4 days. The most frequently reported unsolicited adverse events (AE) were under the SOC of 'infections and infestations'. The most frequently reported unsolicited AE was upper respiratory tract infection in the Control (Bexsero/Menveo) group. The most frequently reported unsolicited AEs considered related were injection site reactions. None of the serious adverse events (SAEs) or adverse events of special interest (AESIs) reported throughout the study in the Control (Bexsero/Menveo) group were considered as related to study vaccination by the investigator. There were no fatal AEs or AESIs characterized as exacerbations throughout the study.

Summary of participants with administration site and systemic solicited events during the 7-days post-vaccination period, following each vaccination and overall Phase II FSF - Exposed Set

		MenABCWY-2Gen high dose_06				MenABCWY-2Gen high dose_02				MenABCWY-2Gen low dose_06				MenABCWY-2Gen low dose_02				CONTROL			
		n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL
Vaccination 1	N	238				194				239				181				197			
	Any adverse event	225	94.5	90.8	97.1	183	58.2	51.0	65.3	217	91.6	87.4	94.8	186	58.2	51.0	65.8	181	91.9	87.1	95.3
	Administration-site adverse event	221	92.9	88.8	95.8	42	21.6	16.1	28.1	217	90.8	86.4	94.1	169	85.5	79.8	90.3	165	83.8	77.9	88.3
	Systemic adverse event	149	62.6	56.1	68.8	100	51.5	44.3	58.8	152	63.6	57.2	69.7	87	48.1	40.6	55.6	118	59.9	52.7	66.8
Vaccination 2	N	224				182				220				170				187			
	Any adverse event	85	37.9	31.6	44.7	154	84.6	78.9	89.5	86	39.1	32.6	45.9	146	85.9	79.7	90.7	156	83.4	77.3	88.4
	Administration-site adverse event	26	11.6	7.7	16.5	153	84.1	77.9	89.1	29	13.2	9.0	18.4	143	84.1	77.8	89.3	155	82.9	76.9	88.0
	Systemic adverse event	72	32.1	26.1	38.7	86	47.3	39.8	54.8	74	33.6	27.4	40.3	95	55.9	48.1	63.5	97	51.9	44.5	59.2

		MenABCWY-2Gen high dose_06				MenABCWY-2Gen high dose_02				MenABCWY-2Gen low dose_06				MenABCWY-2Gen low dose_02				CONTROL			
		n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL	n	%	95% CI LL	UL
Vaccination 3	N	220				176				216				163				0			
	Any adverse event	192	87.3	82.1	91.4	148	84.1	77.8	89.2	195	90.3	85.5	93.9	138	84.7	78.2	89.8	0			
	Administration-site adverse event	187	85.0	79.6	89.4	146	83.0	76.5	88.1	193	89.4	84.5	93.1	135	82.8	76.1	88.2	0			
	Systemic adverse event	128	58.2	51.4	64.8	81	46.0	38.5	53.7	113	52.3	45.4	59.1	85	52.1	44.2	60.0	0			
Any vaccination	N	238				194				239				181				197			
	Any adverse event	233	97.9	95.2	99.3	179	92.3	87.6	95.6	227	95.0	91.4	97.4	167	92.3	87.4	95.7	190	96.4	92.8	98.6
	Administration-site adverse event	232	97.5	94.6	99.1	172	88.7	83.2	92.8	226	94.6	90.6	97.1	160	88.4	82.8	92.7	187	94.9	90.9	97.5
	Systemic adverse event	191	80.3	74.6	85.1	139	71.6	64.8	77.8	181	75.7	69.7	81.0	134	74.0	67.0	80.3	139	70.6	63.7	76.8

MenABCWY-2Gen high dose_06 = MenABCWY-2Gen high dose vaccination at Month 0 and Month 6 and Placebo at Month 4; MenABCWY-2Gen high dose_02 = MenABCWY-2Gen high dose vaccination at Month 4 and Month 6 and Placebo at Month 0; MenABCWY-2Gen low dose_06 = MenABCWY-2Gen low dose vaccination at Month 0 and Month 6 and Placebo at Month 4; MenABCWY-2Gen low dose_02 = MenABCWY-2Gen low dose vaccination at Month 4 and Month 6 and Placebo at Month 0; CONTROL = rMenB+OMV NZ vaccination at Month 0 and Month 6 and MenACWY vaccination at Month 0;

N = number of participants; n/%= number/percentage of participants presenting at least one type of symptom whatever the dose administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

The safety results were found to be in line with the established safety profile of the Bexsero and Menveo vaccines the current European Summary of Product Characteristics.

2.3.3. Discussion on clinical aspects

The present submission includes the Clinical Study Report for study 212458; this was a Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II). EU authorised MenB vaccine Bexsero was administered in the study as a comparator vaccine in Phase II FSF part.

The data set has very limited size for children in this study. Altogether 79 participants in this study were at age below 18: 24 participants were 2-11 years of age, 55 participants were 12-17 years of age. Generally, the Control group, exposed to Bexsero and Menveo, show similar immunogenicity and safety as demonstrated in much larger pivotal trials for Bexsero and Menveo authorisation.

The MAH considers no changes to the current SmPC of Menveo are necessary. This is agreed.

3. CHMP overall conclusion and recommendation

The control group, exposed to Bexsero and Menveo, show similar immunogenicity and safety as demonstrated in much larger pivotal trials for Bexsero and Menveo authorisations. The results of this study does not indicate new efficacy or safety concern.

☒ **Fulfilled:**

No regulatory action required