Amsterdam, 25 April 2025
EMADOC-1700519818-1860215
Committee for Medicinal Products for Human Use (CHMP)

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

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMA/PAM/0000246239

Note

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

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1. Introduction

On 17 January 2025, the MAH submitted a completed paediatric study for Menveo and Bexsero, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

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.

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

2. Scientific discussion

2.1. Information on the development program

The MAH stated that MENB REC 2ND GEN-045, study V72_79: Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine Bexsero (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine Menveo (GSK3536820A) to Healthy Subjects 16-18 Years of Age, is a stand-alone study.

Study V72_79 had not been conducted according to an agreed paediatric investigation plan (PIP). Co-administration of Menveo with Bexsero is approved in the EU [Menveo SmPC, 2024; Bexsero SmPC, 2017], based on information obtained in infants aged 3 to 13 months. However, no data was available on the concomitant use of Bexsero and Menveo in adolescents. GSK was requested by US Centre for Biologics Evaluation and Research (CBER) to assess the concomitant use of Bexsero with a second dose of Menveo in individuals 16 years through 18 years of age, as a post-marketing commitment safety and immunogenicity study. The results of this study are presented in the clinical study report (CSR) of study V72-79.

2.2. Information on the pharmaceutical formulation used in the study

Both Menveo and Bexsero are commercially available. The planned dosing schedule for each study intervention is summarized in Table .

Table 1: Administration and Laterality

Type of contact and timepoint	Study group	Treatment name	Laterality*
Visit 1 (Day 1)	MenB+MenACWY	MenB	Left
		MenACWY	Right
	MenB	MenB	Left
		Placebo	Right
	MenACWY	MenACWY	Left
		Placebo	Right
Visit 3 (Day 61)	MenB+MenACWY	MenB	Left
	MenB	MenB	Left
	MenACWY	MenB	Left
Visit 4	MenB+MenACWY	Placebo	Left

(Day 91)	MenB	MenACWY	Left
	MenACWY	MenB	Left

*Laterality is defined due to multiple vaccinations at different visits; non-dominant arm is the preferred arm for injection, when applicable. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study V72_79: Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine Bexsero (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine Menveo (GSK3536820A) to Healthy Subjects 16-18 Years of Age

The submitted clinical study report (CSR) presents all of the study endpoints, except for the secondary endpoint related to immune response for A, C, W and Y serogroups using electrochemiluminescence (ECL) assay.

2.3.2. Clinical study

V72_79: Safety and Immunogenicity Study of GSK Meningococcal Group B Vaccine Bexsero (GSK3536829A) when Administered Concomitantly with GSK Meningococcal MenACWY Conjugate Vaccine Menveo (GSK3536820A) to Healthy Subjects 16-18 Years of Age

Description

Study V72_79 is a Phase 3B, randomised, observer-blind, multicentre study to assess the safety and demonstrate the non-inferiority of the antibody responses of MenB and MenACWY vaccines when concomitantly administered compared to either alone in healthy participants 16 to 18 years of age.

The design of the study is presented in Figure 1. Participants were randomised to one of the 3 parallel treatment arms in a 1:1:1 ratio to receive the concomitant MenB and MenACWY vaccines (MenB+MenACWY group) or MenB vaccine + Placebo (MenB group) or MenACWY vaccine + Placebo (MenACWY group).

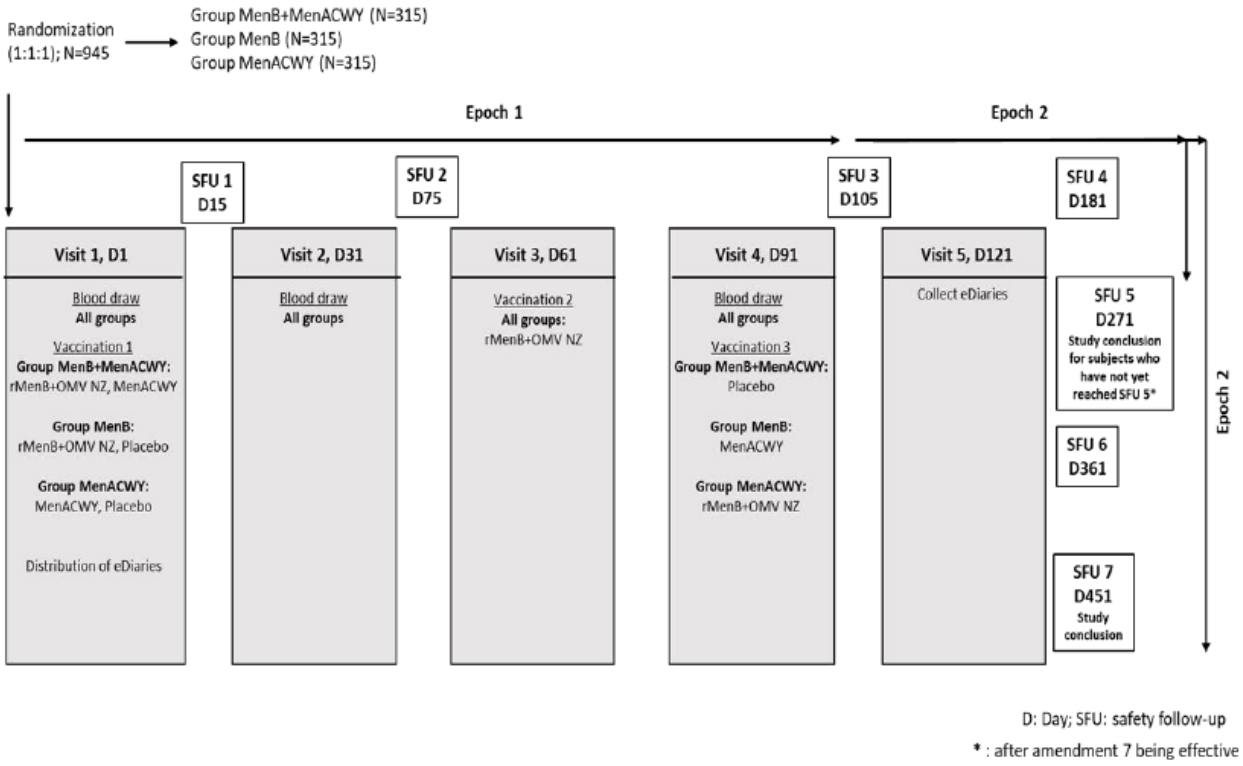


Figure 1: Design of the study

Assessor's comment

Healthy subjects between 16 and 18 years of age received either MenACWY (Menveo), MenB (Bexsero), MenACWY+MenB concomitantly or placebo at visit 1, 3 and 4 (day 1, day 61 and day 91 respectively). Information regarding immunogenicity of the concomitantly administered vaccines will be compared to the immunogenicity when administered sequentially.

The current submission presents all of the study endpoints, except for the secondary endpoint related to immune response for A, C, W and Y serogroups using electrochemiluminescence (ECL) assay.

Methods

Study participants

Key criteria for inclusion in the study included:

- Males or females between, and including, 16 to 18 years of age
- Previous vaccination with one dose of quadrivalent meningococcal conjugate vaccine (MenACWY, Menveo or Menactra) at least 4 years prior to informed consent and assent as applicable (according to the subject's age).
- Healthy subjects as established by medical history and clinical examination before entering into the study
- Women of childbearing potential who were not pregnant or breastfeeding

Prior to receipt of the second and third study vaccination, subjects had to be evaluated to confirm that they were eligible for subsequent vaccination. If subjects did not meet any of the original inclusion criteria listed above, they did not receive additional vaccinations.

Key criteria for exclusion from the study included:

- Previous vaccination with any group B meningococcal vaccine at any time prior to informed consent and assent as applicable (according to the subject's age).
- Previous vaccination with two doses of quadrivalent meningococcal conjugate vaccine (MenACWY, Menveo, Menactra or MenQuadfi).
- Current or previous, confirmed or suspected disease caused by *N. meningitidis* or contact to an individual with any laboratory-confirmed N. meningitidis infection within 60 days prior to enrolment.
- Progressive, unstable or uncontrolled clinical conditions
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws
- Abnormal function of the immune system
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines

Treatments

Participants were randomised to one of the 3 parallel treatment arms in a 1:1:1 ratio to receive the concomitant MenB and MenACWY vaccines (MenB+MenACWY group) or MenB vaccine + Placebo (MenB group) or MenACWY vaccine + Placebo (MenACWY group). The planned dosing schedule for each study intervention is summarized in Table 1. An overview of the different treatments is given in Table .

Table 2: Treatments administered

Study Treatment Name:	***Bexsero***	***Menveo****		**Placebo**
Vaccine(s)/ Product(s) name	MenB	MenA lyo	MenCWY liquid	Placebo (NaCl)
Presentation	Suspension for injection_Suspension for suspension for injection in a syringe	Powder for solution for injection in a vial	Solution for solution for injection in a vial	Solution for injection in a syringe
Vaccines 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 (16.7-33.3 µg)	MenC(5 µg)-CRM197 (7.1-12.5 µg); MenW-135(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

Product Category	Combination Product	Biological Product	Combination Product
Route of Administration	Intramuscular use	Intramuscular use	Intramuscular use
Administration site:			
Location	Deltoid	Deltoid	Deltoid
Number of doses:	2	1	1
Volume to be administered**	0.5 mL	0.5 mL	0.65 mL*****
Packaging and Labelling	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	GSK	GSK

* The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.
** Refer to the SPM for the volume after reconstitution, if applicable.
*** Menveo commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL). For Menveo formulation, as the study is also being conducted in the US, US approved specifications are MenA lyo: MenA=10µg,CRM197=12.5 µg - 33 µg; Potassium dihydrogen phosphate; sucrose and MenCWY liquid: MenC=5µg,CRM197=6.25 µg - 12.5 µg ; MenW=5µg,CRM197=3.3 µg - 10 µg ; MenY=5µg,CRM197=3.3 µg - 10 µg ; Sodium chloride; Sodium dihydrogen phosphate monohydrate; Disodium phosphate dihydrate; water for injections q.s. 0.5 mL.
***** The volume of the saline pre-filled syringe may be between 0.6mL and 0.8 mL. The full volume is to be injected.

Assessor's comments

MenACWY and MenB are 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 and Bexsero respectively.

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 a different placebo volume will not have an impact on study outcomes, and given that the unblinded personnel responsible for preparing and/or delivering injections were not involved in the analysis, this issue is not further pursued.

Objective(s)

Primary immunogenicity objectives:

- To demonstrate the non-inferiority of the antibody response to MenB given concomitantly with MenACWY to healthy subjects 16-18 years of age compared to MenB administered alone, as measured by serum bactericidal assay using human complement (hSBA) Geometric Mean Titres (GMTs) against *N. meningitidis* serogroup B indicator strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M07-0241084* (NHBA), at one month after the second vaccination with MenB. * *As indicated in the Protocol, the NHBA indicator strain M07-0241084 was changed to M13520 during the study before clinical testing started.*
    - Criterion: Non-inferiority was demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group

ratio of human Serum Bactericidal Assay (hSBA) GMTs (MenB with MenACWY versus MenB alone) was >0.5.

- To demonstrate the non-inferiority of the antibody response to MenACWY given concomitantly with MenB to healthy subjects 16-18 years of age compared to MenACWY administered alone, as measured by hSBA GMTs against each of the *N. meningitidis* serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.
    - Criterion: Non-inferiority was demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (MenB with MenACWY versus MenACWY alone) was >0.5.

Secondary immunogenicity objectives:

- *To assess the non-inferiority of the responses to MenACWY when given concomitantly with MenB to healthy subjects 16-18 years of age compared to MenACWY administered alone as measured by Enzyme-Linked Immunosorbent Assay (ELISA)* Geometric Mean Concentration (GMCs) against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY. * ELISA was replaced with electrochemiluminescence (ECL) assay*
    - *Criterion: Non-inferiority was demonstrated if for each of the four A, C, W and Y strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of ECL GMCs (MenACWY with MenB versus MenACWY alone) was >0.5.*
- To assess the immune response to MenB in healthy subjects 16-18 years of age against *N. meningitidis* serogroup B test strains M14459 (fHbp), 96217 (NadA), NZ98/254 (PorA) and M13520* (NHBA), at one month after the first and the second vaccination with MenB.
- To assess the immune response to MenACWY in healthy subjects 16-18 years of age against each of the serogroups A, C, W and Y, at one month after the (study) vaccination with MenACWY.

Assessor's comments

Results regarding the secondary objective of the immune response as measured by ECL are not available. This is not an issue given that the value of the additional information this assessment would provide is questioned as the ECL assay will measure all IgGs and not focus on functional antibodies.

The primary immunogenicity objectives of GMT ratio are appropriate for the purpose of this study since it is a continuous outcome and likely more sensitive to small differences than the dichotomized responder analysis (% with hSBA >LLOQ). However, the non-inferiority margin is very wide, with the lower limit of the 2-sided 95% confidence interval of the between-group ratio of concomitant versus sequential administration being >0.5. A non-inferiority margin of 0.67 would have been preferred.

Outcomes/endpoints

Primary immunogenicity endpoints:

- Co-primary endpoints for Group MenB+MenACWY and Group MenB are the hSBA GMTs for MenB against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M13520) at one month after the second vaccination with MenB (Visit 4, Month 3).

- Co-primary endpoints for Group MenB+MenACWY and Group MenACWY are the hSBA GMTs against each of the four serogroups A, C, W and Y with MenACWY at one month after the study vaccination of MenACWY (Visit 2, Month 1).

Secondary immunogenicity endpoints

- *The immune response to MenACWY when administered with/without MenB at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as ECL GMCs.*
- The **immune response to MenB** when administered with/without MenACWY was evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B test strains M14459, 96217, NZ98/254 and M13520* in both MenB+MenACWY and MenB Groups as following:
    - GMTs at one month after first and second vaccination with MenB and Geometric Mean Ratio (GMRs) at one month after the first (Visit 2, Month 1) and the second (Visit 4, Month 3) MenB vaccination compared to the baseline at Visit 1, Day 1/Month 0.
    - The percentage of subjects with hSBA titres ≥Lower Limit of Quantitation (LLOQ) for each and all serogroup B test strains, one month after the first (Visit 2, Month 1) and second (Visit 4, Month 3) vaccination.
    - The percentage of subjects with fourfold increase in hSBA titres relative to baseline (Visit 1, Day 1/Month 0) is defined as:
        - For a pre-vaccination titre < limit of detection (LOD), a post-vaccination titre (Visit 2, Month 1 and Visit 4, Month 3) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater,
        - For a pre-vaccination titre ≥LOD but <LLOQ, a post-vaccination titre (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the LLOQ,
        - For a pre-vaccination titre ≥ LLOQ, a postvaccination titre (Visit 2, Month 1 and Visit 4, Month 3) of at least fourfold the prevaccination titre (for Groups MenB+MenACWY and MenB).
    - The ratio of GMTs (MenB when administered with MenACWY [Group MenB+MenACWY] versus MenB when administered alone [Group MenB]), one month after the first vaccination (Visit 2, Month 1).
- The **immune response to MenACWY** when administered with/without MenB at baseline (i.e. prevaccination, Visit 1, Day 1/Month 0) and at one month after the first vaccination (Visit 2, Month 1; Groups MenB+MenACWY and MenACWY) will be assessed for the serogroups A, C, W and Y as:
    - The percentage of subjects with hSBA titres ≥LLOQ, for each serogroup.
    - GMRs at one month after first vaccination compared to baseline
    - The percentage of subjects with four-fold increase in hSBA titres relative to baseline (Visit 1, Day 1/Month 0) is defined as:

- For a pre-vaccination titre < LOD, a postvaccination titre (Visit 2, Month 1) of ≥ fourfold the LOD or ≥ LLOQ, whichever is greater,
- For a pre-vaccination titre ≥LOD but <LLOQ, a post-vaccination titre (Visit 2, Month 1) of at least fourfold the LLOQ,
- For a pre-vaccination titre ≥ LLOQ, a postvaccination titre (Visit 2, Month 1) of at least fourfold the pre-vaccination titre (for Groups MenB+MenACWY and MenACWY).

Sample size

The target sample size is 750 subjects evaluable for immunogenicity (250 subjects per study group). Evaluable subjects mean all subjects included in the set for the primary statistical analysis. Considering that approximately 20% of the enrolled subjects might withdraw or not be evaluable for immunogenicity, the target sample size to be enrolled is 945 subjects (315 subjects per study group). These sample sizes were calculated based on the standard deviations from corresponding treatments in the mentioned studies, the non-inferiority margin of 0.5 and the expected ratio GMR of the GMTs (or GMCs) of 0.9.

Randomisation and blinding (masking)

Subjects will be randomised in the source data base for internet randomization system (SBIR) system to one of the 3 parallel treatment arms in a 1:1:1 ratio. The randomisation algorithm will use a minimisation procedure accounting for centre.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccines recipient and those responsible for the evaluation of any study endpoint (e.g. safety and reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by qualified healthcare professional who will not participate in any of the study clinical evaluations.

Statistical Methods

Analysis sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	**Description**
Enrolled	All subjects who sign informed consent
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full Analysis	All subjects who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data
Per Protocol	All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion

Analysis of immunogenicity

The primary analysis will be based on the Per Protocol Set of immunogenicity for the primary and secondary (non-inferiority) immunogenicity objective. If, in any study group, the percentage of enrolled or vaccinated subjects with serological results excluded from the per-protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set (FAS) will be performed to complement the per protocol analysis. Supportive analyses using the FAS will also be performed for the primary immunogenicity endpoints.

Endpoint	Statistical Analysis Methods
Primary	**Within group assessment** • For Group MenB+MenACWY and Group MenB: hSBA GMTs for MenB against each of the four serogroup B test strains (M14459, 96217, NZ98/254 and M07-0241084*) at one month after the second vaccination for MenB (Visit 4) will be calculated. • For Group MenB+MenACWY and Group MenACWY: hSBA GMTs against each of the four serogroups A, C, W and Y for MenACWY at one month after the study vaccination of MenACWY (Visit 2) will be calculated. **Between group assessment** • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenB when administered alone [Group MenB], at one month after the second vaccination of MenB will be calculated. • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenACWY when administered alone [Group MenACWY], at one month after the (study) vaccination of MenACWY will be calculated.
Secondary	**Within groups assessment** • ELISA GMCs against each of the four serogroups A, C, W and Y at one month after the (study) vaccination of MenACWY for Groups MenB+MenACWY and MenACWY. The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with hSBA titres ≥LLOQ for each and all serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. • hSBA GMTs against each of the four serogroup B test strains at baseline and one month after first vaccination with MenB for Groups MenB+MenACWY and MenB. • hSBA GMRs (compared to baseline) against each serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and against serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. • The percentage of subjects (and 2-sided 95% Clopper-Pearson CIs) with fourfold increase in hSBA titres relative to baseline for each serogroup B test strains at one month after the first and second vaccination for Groups MenB+MenACWY and MenB; and for serogroups A, C, W and Y at one month after the (study) vaccination for Groups MenB+MenACWY and MenACWY. **Between group assessment** • For all four serogroups A, C, W and Y, non-inferiority of the responses to MenACWY when given with MenB compared to MenACWY administered alone will be assessed in terms of ELISA GMCs. • The ratio of hSBA GMTs between Group MenB+MenACWY versus Group MenB when administered alone at one month after the first vaccination, will be calculated. • Between group differences (Group MenB+MenACWY vs Group MenB; and Group MenB+MenACWY vs Group MenACWY), at one month after the first and the second vaccination (as applicable) will be calculated, as well as their associated 95% CIs.

*The NHBA indicator strain M07-0241084 may be subject to change during the study, before clinical testing starts. In this case, this change will be documented in the clinical report.

The endpoints related to primary immunogenicity objective were achieved if all non-inferiority hypotheses were demonstrated simultaneously.

The statistical hypotheses and analyses are based on the common assumption that the logarithmically (base of 10) transformed hSBA titres are normally distributed.

Non-inferiority of concomitant MenB with MenACWY to MenB

The null (not non-inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} \leq \log_{10}(0.5) \text{ versus}$$

$$H_{1,i}^{MenB}: \mu_{A,MenB,i} - \mu_{B,MenB,i} > \log_{10}(0.5),$$

where i=1,…,4 is an index over the 4 serogroup B strains M14459, 96217, NZ98/254 and M13520, and $\mu_{A,MenB,i}$ and $\mu_{B,MenB,i}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the i^{th} serogroup B strain at one month after the second vaccination in Groups MenB+MenACWY and MenB respectively.

Non-inferiority of concomitant MenB with MenACWY to MenACWY

The null (inferiority) and the alternative (non-inferiority) hypotheses are:

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} \leq \log_{10}(0.5) \text{ versus}$$

$$H_{0,j}^{MenACWY}: \mu_{A,MenACWY,j} - \mu_{C,MenACWY,j} > \log_{10}(0.5),$$

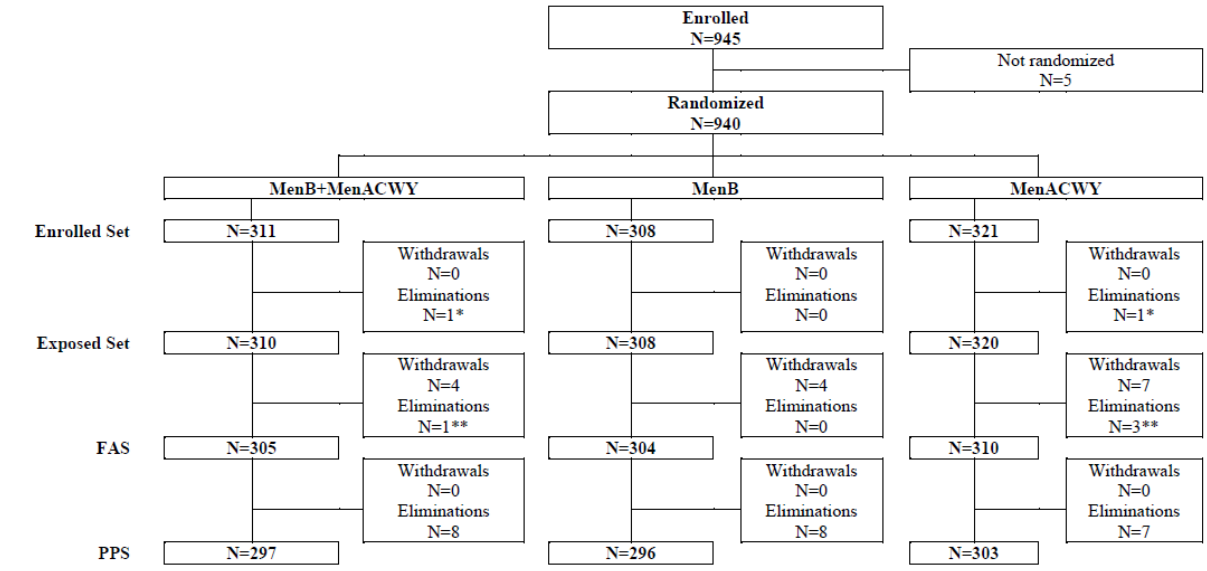
where j=1,…,4 is an index over the 4 serogroups A, C, W and Y, and $\mu_{A,MenACWY,j}$ and $\mu_{C,MenACWY,j}$ are the population means of the logarithmically (base of 10) transformed hSBA titers for the j^{th} MenACWY serogroup at one month after the first vaccination in Groups MenB+MenACWY and MenACWY respectively.

The 8 hypotheses associated with the primary objective were tested simultaneously, to control for the type I error rate. The testing of the hypotheses was done simultaneously on all the strains and serogroups.

Results

Participant flow

A total of 945 participants were enrolled in the study (Figure 2); 879 (93.7%) completed the study and 59 (6.3%) were withdrawn from the study (Table). The most common reasons for study withdrawal were Lost to follow-up (28 [3.0%] participants) and Consent withdrawal (20 [2.1%] participants); Table).



FAS = full analysis set; PPS = per protocol set; N = number of participants
* The participant(s) did not receive any study intervention after enrollment.
** No biological sample obtained
Source: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.4 (02OCT2024 11:35 GMT)

Figure 2: Study disposition flowchart, as enrolled

Table 3: Summary of study completion with reasons for withdrawal As Treated - Exposed Set

	MenB+MenACWY N=310		MenB N=308		MenACWY N=320		Total N=938	
	n	%	n	%	n	%	n	%
Completed the study	297	95.8	284	92.2	298	93.1	879	93.7
Withdrawn from the study	13	4.2	24	7.8	22	6.9	59	6.3
Primary reason for withdrawal :								
Adverse Event Requiring Expedited Reporting	0	0.0	0	0.0	1	0.3	1	0.1
Consent Withdrawal, Not Due To A (S)ae	5	1.6	9	2.9	6	1.9	20	2.1
Lost To Follow-Up	6	1.9	13	4.2	9	2.8	28	3.0
Migrated / Moved From The Study Area	0	0.0	0	0.0	1	0.3	1	0.1
Other	1	0.3	2	0.6	3	0.9	6	0.6
Protocol Deviation	1	0.3	0	0.0	2	0.6	3	0.3

Completed = number of participants who completed the last study visit/contact
Withdrawn = number of participants who did not complete their last visit/contact
N = number of participants; n/% = number / percentage of participants in a given category

Assessor's comments

The participant flow is comparable for all three groups, with withdrawal being low (in total ~6%). Of the randomised participants who were withdrawn, "lost to follow-up" was listed as the most prominent reason for withdrawal followed by "consent withdrawal not due to a (S)AE" in all three groups.

Recruitment

The study was conducted at 52 centres in 2 countries: 48 centres in the United States (US), and 4 in Italy. Study period was between 25 August 2020 (first participant first visit) and 21 November 2023 (Last participant last visit). Database lock date: 24 September 2024.

Baseline data

Demographic and other baseline characteristics are presented in Table .

The mean age of subjects who participated in this study was 16.4 (SD 0.7) years old. Overall, 48.47% of participants in the study were females (n=457). Most of the participants in the MenB+MenACWY group (89.0%–97.7%) and the MenB group (85.7%–97.1%) had baseline titre <LLOQ across serogroup B strains). A majority of participants in the MenB+MenACWY group (52.6%–73.5%) and the MenACWY group (53.8%–74.4%) had baseline titre <LLOQ across serogroups A, C, W, and Y.

Table 4: Summary of demography and baseline characteristics As Treated - Exposed Set

	MenB+MenACWY N=310		**MenB N=308**		**MenACWY N=320**		**Total N=938**	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at first vaccination	310		308		320		938	
Mean (Standard deviation)	16.4 (0.7)		16.4 (0.7)		16.5 (0.7)		16.4 (0.7)	
Minimum	15		15		15		15	
Maximum	18		19		19		19	
Age group [EudraCT]								
Adolescents (12-17 years)	286	92.3	283	91.9	288	90.0	857	91.4
Adults (18-64 years)	24	7.7	25	8.1	32	10.0	81	8.6
Country								
Italy	37	11.9	37	12.0	37	11.6	111	11.8
United States	273	88.1	271	88.0	283	88.4	827	88.2
Sex								
Male	154	49.7	170	55.2	157	49.1	481	51.3
Female	156	50.3	138	44.8	163	50.9	457	48.7
Ethnicity								
Hispanic Or Latino	46	14.8	38	12.3	37	11.6	121	12.9
Not Hispanic Or Latino	263	84.8	270	87.7	282	88.1	815	86.9
Not Reported	1	0.3	0	0.0	1	0.3	2	0.2
Race								
American Indian Or Alaska Native	3	1.0	6	1.9	4	1.3	13	1.4
Asian	13	4.2	9	2.9	12	3.8	34	3.6
Black Or African American	60	19.4	50	16.2	61	19.1	171	18.2
Native Hawaiian Or Other Pacific	1	0.3	0	0.0	0	0.0	1	0.1
Islander Other	15	4.8	12	3.9	18	5.6	45	4.8
White	218	70.3	231	75.0	225	70.3	674	71.9
Height (cm; Standard deviation)	170.1 (9.6)		170.6 (9.8)		168.8 (9.6)		169.9 (9.7)	
Weight (kg; Standard deviation)	70.2 (18.0)		70.0 (18.2)		69.0 (18.7)		69.7 (18.3)	
BMI (kg/m^2; Standard deviation)	24.2 (5.4)		24.0 (5.3)		24.1 (5.8)		24.1 (5.5)	
Minimum	14		16		16		14	
Maximum	45		47		56		56	
fHbp								
Not Reported*	3	1.0	3	1.0	320	100.0	326	34.8
< LLOQ	295	95.2	280	90.9	0	0.0	575	61.3
>= LLOQ	12	3.9	25	8.1	0	0.0	37	3.9
NadA								
Not Reported*	3	1.0	2	0.6	320	100.0	325	34.6

	MenB+MenACWY N=310		MenB N=308		MenACWY N=320		Total N=938	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%
< LLOQ	284	91.6	277	89.9	0	0.0	561	59.8
>= LLOQ	23	7.4	29	9.4	0	0.0	52	5.5
NHBA								
Not Reported*	2	0.6	0	0.0	320	100.0	322	34.3
< LLOQ	276	89.0	264	85.7	0	0.0	540	57.6
>= LLOQ	32	10.3	44	14.3	0	0.0	76	8.1
PorA								
Not Reported*	2	0.6	1	0.3	320	100.0	323	34.4
< LLOQ	303	97.7	299	97.1	0	0.0	602	64.2
>= LLOQ	5	1.6	8	2.6	0	0.0	13	1.4
Men A								
Not Reported*	34	11.0	308	100.0	34	10.6	376	40.1
< LLOQ	198	63.9	0	0.0	199	62.2	397	42.3
>= LLOQ	78	25.2	0	0.0	87	27.2	165	17.6
Men C								
Not Reported*	6	1.9	308	100.0	9	2.8	323	34.4
< LLOQ	163	52.6	0	0.0	172	53.8	335	35.7
>= LLOQ	141	45.5	0	0.0	139	43.4	280	29.9
Men W								
Not Reported*	9	2.9	308	100.0	14	4.4	331	35.3
< LLOQ	220	71.0	0	0.0	217	67.8	437	46.6
>= LLOQ	81	26.1	0	0.0	89	27.8	170	18.1
Men Y								
Not Reported*	9	2.9	308	100.0	10	3.1	327	34.9
< LLOQ	228	73.5	0	0.0	238	74.4	466	49.7
>= LLOQ	73	23.5	0	0.0	72	22.5	145	15.5

N = number of participants; n/% = number / percentage of participants in a given category; Body mass index[BMI] = (Weight in kilograms[Kg]) / (Height in meters[m])2

* In the MenACWY group, response against serogroup B strains was not tested and in the Men B group, response against serogroups A, C, W, and Y was not tested.

Age is calculated based on participants first vaccination date.

The LLOQs for serogroup B indicator strains fHbp (M14459), NadA (96217), NHBA (M13520) and PorA (NZ98/254) are 5, 14, 6, and 6, respectively.

The LLOQs for serogroups A, C, W, and Y are 12, 8, 8, and 10, respectively.

Assessor's comments

The baseline data appears well balanced between the vaccine groups.

Number analysed

A total of 938 (99.3%) participants were included in the Exposed Set, 919 (98%) participants were included in the FAS and 896 (97.5%) participants were included in the PPS.

At least one important protocol deviation leading to elimination was reported in 93 (9.8%) participants. The most common important protocol deviations were due to, out of window treatment administration (25 [2.6%]) and out of window assessment (23 [2.4%]; Table).

Table 5: Summary of important protocol deviations leading to elimination from any analysis As Randomised - Enrolled Set

Category Sub category	MenB+MenACWY N=311			MenB N=308			MenACWY N=321			Not Randomized N=5			Total N=945		
	occ	n	%	occ	n	%	occ	n	%	occ	n	%	occ	n	%
At least one important protocol deviation	39	30	9.6	33	29	9.4	44	34	10.6	0	0	0.0	116	93	9.8
Assessment or time point completion	19	16	5.1	15	15	4.9	17	16	5.0	0	0	0.0	51	47	5.0
Out of window treatment administration	9	9	2.9	6	6	1.9	10	10	3.1	0	0	0.0	25	25	2.6
Out of window assessment	10	9	2.9	8	8	2.6	6	6	1.9	0	0	0.0	24	23	2.4
Assessment not properly performed	0	0	0.0	0	0	0.0	1	1	0.3	0	0	0.0	1	1	0.1
Missed assessment	0	0	0.0	1	1	0.3	0	0	0.0	0	0	0.0	1	1	0.1
Study procedures	8	6	1.9	2	2	0.6	8	6	1.9	0	0	0.0	18	14	1.5
Biological sample specimen procedures	8	6	1.9	2	2	0.6	7	5	1.6	0	0	0.0	17	13	1.4
Other deviation from study procedures	0	0	0.0	0	0	0.0	1	1	0.3	0	0	0.0	1	1	0.1
Excluded medication, vaccine or device	5	5	1.6	7	7	2.3	5	5	1.6	0	0	0.0	17	17	1.8
Vaccine, excluded by the protocol, was administered	4	4	1.3	3	3	1.0	3	3	0.9	0	0	0.0	10	10	1.1
Other excluded medication, vaccine or device deviation	0	0	0.0	3	3	1.0	1	1	0.3	0	0	0.0	4	4	0.4
Medication, excluded by the protocol, was administered	1	1	0.3	1	1	0.3	1	1	0.3	0	0	0.0	3	3	0.3
Eligibility criteria	3	3	1.0	4	4	1.3	8	7	2.2	0	0	0.0	15	14	1.5
Eligibility criteria not met	3	3	1.0	4	4	1.3	8	7	2.2	0	0	0.0	15	14	1.5
Wrong study treatment/administration/dose	4	4	1.3	5	4	1.3	6	6	1.9	0	0	0.0	15	14	1.5
Study treatment not administered per protocol	2	2	0.6	3	3	1.0	6	6	1.9	0	0	0.0	11	11	1.2
Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use	1	1	0.3	1	1	0.3	0	0	0.0	0	0	0.0	2	2	0.2
Other deviations related to wrong study treatment/administration/dose	1	1	0.3	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.1
Wrong study treatment or assignment administered	0	0	0.0	1	1	0.3	0	0	0.0	0	0	0.0	1	1	0.1

N = number of participants
n/% = number / percentage of participants in a given category
occ = number of occurrences = number of important protocol deviations

Assessor's comments

The number of participants in each analysis set is comparable between treatment groups. Protocol deviations leading to elimination were reported in approximately 10% of participants in each treatment group. No differences between treatment groups were identified.

Efficacy results

Primary immunogenicity analysis

Non-inferiority was demonstrated for each of the 4 serogroup B indicator strains, as the LL of the 2-sided 95% CI of the between-group ratio of hSBA GMTs (MenB with MenACWY versus MenB alone) at one month after the second vaccination with MenB (Day 91) was 0.77 (M14459 [fHbp]), 0.75 (96217 [NadA]), 0.76 (M13520 [NHBA]), and 0.73 (NZ98/254 [PorA]) that was above the predefined non-inferiority criterion of LL of 95% CI > 0.5 (Table).

Table 6: Adjusted hSBA GMT and group ratios against each of the four serogroup B test strains at Day 91 Primary objective - Per Protocol Set

			MenB+MenACWY				MenB				MenB+MenACWY / MenB		
					95% CI				95% CI			95% CI	
Men B antigen	Time point		n	value	LL	UL	n	value	LL	UL	value	LL	UL
fHbp	Visit 4 (Day 91)	Number of participants with available results	274				266						
		GMT		16.9	14.4	19.8		18.7	15.9	21.9	0.90	**0.77**	1.06
NadA	Visit 4 (Day 91)	Number of participants with available results	274				267						
		GMT		239.6	202.9	283.0		272.4	231.1	321.0	0.88	**0.75**	1.04
NHBA	Visit 4 (Day 91)	Number of participants with available results	273				266						
		GMT		19.0	15.6	23.1		20.5	16.9	24.9	0.93	**0.76**	1.12
PorA	Visit 4 (Day 91)	Number of participants with available results	273				266						
		GMT		18.8	15.6	22.6		21.3	17.7	25.6	0.88	**0.73**	1.06

N = number of participants with available results
value = GMT value
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
GMT = Geometric Mean Titer
Bold = non-inferiority criterion met
The ratio of GMTs (MenB+MenACWY/MenB) and the corresponding CI is constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study centre included as an independent variable.
Non-Inferiority criterion: Non-inferiority will be demonstrated if for each of the four serogroup B test strains, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus rMenB+OMV NZ alone) is >0.5.

Non-inferiority was demonstrated for serogroups A, C, W, and Y, as the LL of the 2-sided 95% CI of the between-group ratio of hSBA GMTs (MenB with MenACWY versus MenACWY alone) at one month after the vaccination with MenACWY (Day 31) was 0.78 (Men A), 0.86 (Men C), 0.82 (Men W), and 0.84 (MenY), that was above the pre-defined non-inferiority criterion of LL of 95% CI > 0.5 (Table 7)

Table 7: Adjusted hSBA GMT and group ratios against each of the four serogroups A, C, W and Y at Day 31 Primary objective - Per Protocol Set

			MenB+MenACWY				MenACWY				MenB+MenACWY / MenACWY		
					95% CI				95% CI			95% CI	
Serogroup	Time point		n	value	LL	UL	n	value	LL	UL	value	LL	UL
Men A	Visit 2 (Day 31)	Number of participants with available results	290				292						
		GMT		2388.8	1977.2	2886.1		2536.1	2095.7	3069.1	0.94	**0.78**	1.14
Men C	Visit 2 (Day 31)	Number of participants with available results	295				302						
		GMT		2075.9	1602.5	2689.3		1867.6	1438.7	2424.2	1.11	**0.86**	1.44
Men W	Visit 2 (Day 31)	Number of participants with available results	295				303						
		GMT		2299.3	1902.5	2778.9		2305.7	1905.3	2790.4	1.00	**0.82**	1.21
Men Y	Visit 2 (Day 31)	Number of participants with available results	295				303						
		GMT		2897.3	2359.2	3558.3		2802.0	2278.3	3446.2	1.03	**0.84**	1.27

N = number of participants with available results
value = GMT value
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
GMT = Geometric Mean Titer
Bold = non-inferiority criterion met
The ratio of GMTs (MenB+MenACWY/MenACWY) and the corresponding CI is constructed by exponentiating the mean difference and the confidence limits in log10 (titer), using ANOVA with study centre included as an independent variable.
Non-Inferiority criterion: Non-inferiority will be demonstrated if for each of the four serogroups A, C, W and Y, the lower limit of the 2-sided 95% confidence interval of the between-group ratio of hSBA GMTs (rMenB+OMV NZ with MenACWY versus MenACWY alone) is >0.5.

Sensitivity analyses (to include possible imbalance in the baseline titre among groups) of adjusted hSBA GMT and between-group GMT ratios as well as analyses using the FAS showed similar results.

Secondary immunogenicity analysis

The immune response indicated no specific differences between groups regarding GMR, percentages of participants with 4-fold rise and ≥LLOQ (Table 8) at Day 91 (1 month after second dose of MenB vaccine) against each of the MenB indicator strains

Table 8: Number and percentages of participants with hSBA titres greater than or equal to LLOQ and group differences against each and all serogroup B strains at baseline, Day 31 and at Day 91 Secondary objective - Per Protocol Set

			MenB+MenACWY				MenB				MenB+MenACWY - MenB		
					95% CI				95% CI			95% CI	
Men B antigen	Time point		n	%	LL	UL	n	%	LL	UL	%	LL	UL
fHbp	Baseline	Number of participants with available results	296				293						
		% of subjects with hSBA titers >=LLOQ	10	3.4	1.6	6.1	25	8.5	5.6	12.3	-5.15	-9.28	-1.40
	Visit 2 (Day 31)	Number of participants with available results	294				294						
		% of subjects with hSBA titers >=LLOQ	95	32.3	27.0	38.0	132	44.9	39.1	50.8	-12.59	-20.30	-4.72
	Visit 4 (Day 91)	Number of participants with available results	274				266						
		% of subjects with hSBA titers >=LLOQ	253	92.3	88.5	95.2	246	92.5	88.6	95.3	-0.15	-4.74	4.48
NadA	Baseline	Number of participants with available results	296				294						
		% of subjects with hSBA titers >=LLOQ	22	7.4	4.7	11.0	26	8.8	5.9	12.7	-1.41	-5.97	3.09
	Visit 2 (Day 31)	Number of participants with available results	294				294						
		% of subjects with hSBA titers >=LLOQ	229	77.9	72.7	82.5	252	85.7	81.2	89.5	-7.82	-14.08	-1.60
	Visit 4 (Day 91)	Number of participants with available results	274				267						
		% of subjects with hSBA titers >=LLOQ	273	99.6	98.0	100	266	99.6	97.9	100	0.01	-1.70	1.76
NHBA	Baseline	Number of participants with available results	296				296						
		% of subjects with hSBA titers >=LLOQ	31	10.5	7.2	14.5	41	13.9	10.1	18.3	-3.38	-8.75	1.92
	Visit 2 (Day 31)	Number of participants with available results	294				293						
		% of subjects with hSBA titers >=LLOQ	109	37.1	31.5	42.9	130	44.4	38.6	50.3	-7.29	-15.16	0.66
	Visit 4 (Day 91)	Number of participants with available results	273				266						
		% of subjects with hSBA titers >=LLOQ	230	84.2	79.4	88.4	240	90.2	86.0	93.5	-5.98	-11.70	-0.34
PorA	Baseline	Number of participants with available results	296				295						
		% of subjects with hSBA titers >=LLOQ	5	1.7	0.6	3.9	8	2.7	1.2	5.3	-1.02	-3.78	1.53
	Visit 2 (Day 31)	Number of participants with available results	294				293						
		% of subjects with hSBA titers >=LLOQ	62	21.1	16.6	26.2	89	30.4	25.2	36.0	-9.29	-16.31	-2.22
	Visit 4 (Day 91)	Number of participants with available results	273				266						
		% of subjects with hSBA titers >=LLOQ	227	83.2	78.2	87.4	226	85.0	80.1	89.0	-1.81	-8.04	4.43
Overall	Baseline	Number of participants with available results	296				292						
		% of subjects with hSBA titers >=LLOQ	3	1.0	0.2	2.9	3	1.0	0.2	3.0	-0.01	-2.08	2.03
	Visit 2 (Day 31)	Number of participants with available results	293				293						
		% of subjects with hSBA titers >=LLOQ	32	10.9	7.6	15.1	59	20.1	15.7	25.2	-9.22	-15.13	-3.39
	Visit 4 (Day 91)	Number of participants with available results	273				266						
		% of subjects with hSBA titers >=LLOQ	197	72.2	66.4	77.4	199	74.8	69.1	79.9	-2.65	-10.09	4.82

n/% = number / percentage of participants with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

The percentages of subjects with hSBA titres >= LLOQ and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint. Comparison is done using the difference in percentages (MenB+MenACWY-MenB).

Overall refers to the Composite Endpoint for which all the individual responses are greater than or equal to LLOQ.

The LLOQs for serogroup B indicator strains fHbp (M14459), NadA (96217), NHBA (M13520) and PorA (NZ98/254) are 5, 14, 6, and 6, respectively.

The immune response against serogroups A, C, W, and Y, in terms of GMR, percentages of participants with 4-fold rise and ≥LLOQ (Table), indicated no specific differences between MenB co-administered with MenACWY versus MenACWY alone at Day 31 (1 month after a single dose of MenACWY vaccine).

Table 9: Number and percentages of participants with hSBA titres greater than or equal to LLOQ and group differences against each serogroups A, C, W and Y at baseline and at Day 31 Secondary objective - Per Protocol Set

			MenB+MenACWY				MenACWY				MenB+MenACWY - MenACWY		
					95% CI				95% CI			95% CI	
Serogroup	Time point		n	%	LL	UL	n	%	LL	UL	%	LL	UL
Men A	Baseline	Number of participants with available results	267				273						
		% of subjects with hSBA titers >=LLOQ	75	28.1	22.8	33.9	82	30.0	24.7	35.9	-1.95	-9.59	5.73
	Visit 2 (Day 31)	Number of participants with available results	290				292						
		% of subjects with hSBA titers >=LLOQ	289	99.7	98.1	100	290	99.3	97.5	99.9	0.34	-1.30	2.15
Men C	Baseline	Number of participants with available results	294				297						
		% of subjects with hSBA titers >=LLOQ	136	46.3	40.5	52.1	132	44.4	38.7	50.3	1.81	-6.20	9.81
	Visit 2 (Day 31)	Number of participants with available results	295				302						
		% of subjects with hSBA titers >=LLOQ	292	99.0	97.1	99.8	298	98.7	96.6	99.6	0.31	-1.78	2.46
Men W	Baseline	Number of participants with available results	292				292						
		% of subjects with hSBA titers >=LLOQ	80	27.4	22.4	32.9	83	28.4	23.3	34.0	-1.03	-8.30	6.26
	Visit 2 (Day 31)	Number of participants with available results	295				303						
		% of subjects with hSBA titers >=LLOQ	295	100	98.8	100	303	100	98.8	100	0.00	-1.29	1.25
Men Y	Baseline	Number of participants with available results	291				296						
		% of subjects with hSBA titers >=LLOQ	68	23.4	18.6	28.7	68	23.0	18.3	28.2	0.39	-6.45	7.25
	Visit 2 (Day 31)	Number of participants with available results	295				303						
		% of subjects with hSBA titers >=LLOQ	294	99.7	98.1	100	302	99.7	98.2	100	-0.01	-1.59	1.54

n/% = number / percentage of participants with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
The percentages of subjects with hSBA titres >= LLOQ and the corresponding exact 2-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at each timepoint. Comparison is done using the difference in percentages (MenB+MenACWY-MenACWY).
The LLOQs for serogroups A, C, W, and Y are 12, 8, 8, and 10, respectively.

Assessor's comments

The study met the pre-specified non-inferiority margins of 0.5 for the lower limit of the two-sided 95% CI for the between group ratio of GMTs for all 4 MenB strains and all serogroups. The more conservative non-inferiority margin of 0.67 would also have been met for all comparisons.

Overall, no notable differences are observed in the induced immune response when Bexsero or Menveo are given alone or concomitantly.

It is noted that slight differences in the number of participants with available results for the GMR compared to participants with a 4-fold rise in hSBA titre exist. It is not understood where the differences in these numbers come from as all participants for whom GMR could be determined would be able to attribute to number of participants with a 4-fold rise. However, as overall difference in numbers of participants attributing to results is small (up to maximally n=3), it is not expected to influence overall results. Therefore this is not further pursued.

Safety results

Analysis of safety was performed on the Exposed Set.

A total of 929 (99.0%) participants received at least 1 dose MenB vaccine, 919 (98.0%) received at least 1 dose of MenACWY vaccine, and 927 (98.8%) received at least 1 dose of Placebo. Two doses of MenB vaccine were administered in 901 (96.1%) participants, with 302 (97.4%) participants, 298

(96.8%) participants and 301 (94.1%) participants in the MenB+MenACWY group, MenB group and MenACWY group, respectively.

- At Visit 1 (Day 1), all of the participants in the Exposed Set received the vaccine/placebo as assigned.
- At Visit 3 (Day 61), 302 (97.4%) participants in the MenB+MenACWY group, 298 (96.8%) in the MenB group, and 311 (97.2%) in the MenACWY group received MenB vaccine. In addition, 1 participant in the MenB group received MenACWY vaccine.
- At Visit 4 (Day 91), 301 (94.1%) participants in the MenACWY group received MenB vaccine, 288 (93.5%) in the MenB group received MenACWY vaccine, and 299 (96.5%) in the MenB+MenACWY group received Placebo. In addition, 1 participant in the MenACWY group received Placebo.

The safety follow-up period was 6 months after the last vaccination for participants who did not reach Day 271 (Month 9) at the time of Protocol Amendment 7 (N=673); for rest of the participants (N=265), the safety follow-up period was 12 months after the last vaccination.

Solicited AEs

During the 7-day follow-up period after any vaccination, solicited events were reported in 88.1%–94.8% of participants across study groups (Table).

Table 10: Summary of participants with administration-site and systemic solicited AEs during the 7-day (Day 1-7) period after each vaccination and overall As Treated - Exposed Set

		MenB+MenACWY				MenB				MenACWY			
				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Vaccination at visit 1	N	310				308				320			
	Any adverse event	280	90.3	86.5	93.4	284	92.2	88.6	94.9	207	64.7	59.2	69.9
	Administration-site adverse event : MenACWY	96	31.0	25.9	36.4	0	0.0			106	33.1	28.0	38.6
	Administration-site adverse event : Placebo	0	0.0			78	25.3	20.6	30.6	79	24.7	20.1	29.8
	Administration-site adverse event : rMenB+OMV NZ	248	80.0	75.1	84.3	250	81.2	76.3	85.4	0	0.0		
	Systemic adverse event	174	56.1	50.4	61.7	184	59.7	54.0	65.3	177	55.3	49.7	60.8
Vaccination at visit 3	N	302				299				311			
	Any adverse event	248	82.1	77.3	86.3	240	80.3	75.3	84.6	247	79.4	74.5	83.8
	Administration-site adverse event : MenACWY	0	0.0			1	0.3	0.0	1.8	0	0.0		
	Administration-site adverse event : rMenB+OMV NZ	241	79.8	74.8	84.2	231	77.3	72.1	81.9	238	76.5	71.4	81.1
	Systemic adverse event	157	52.0	46.2	57.7	147	49.2	43.4	55.0	151	48.6	42.9	54.3
Vaccination at visit 4	N	299				288				302			
	Any adverse event	87	29.1	24.0	34.6	106	36.8	31.2	42.7	215	71.2	65.7	76.2
	Administration-site adverse event : MenACWY	0	0.0			42	14.6	10.7	19.2	0	0.0		
	Administration-site adverse event : Placebo	25	8.4	5.5	12.1	0	0.0			0	0.0		
	Administration-site adverse event : rMenB+OMV NZ	0	0.0			0	0.0			206	68.2	62.6	73.4
	Systemic adverse event	77	25.8	20.9	31.1	92	31.9	26.6	37.7	124	41.1	35.5	46.8
Any vaccination	N	310				308				320			
	Any adverse event	291	93.9	90.6	96.3	292	94.8	91.7	97.0	282	88.1	84.1	91.5
	Administration-site adverse event : MenACWY	96	31.0	25.9	36.4	43	14.0	10.3	18.3	106	33.1	28.0	38.6
	Administration-site adverse event : Placebo	25	8.1	5.3	11.7	78	25.3	20.6	30.6	79	24.7	20.1	29.8
	Administration-site adverse event : rMenB+OMV NZ	279	90.0	86.1	93.1	279	90.6	86.8	93.6	254	79.4	74.5	83.7
	Systemic adverse event	225	72.6	67.3	77.5	224	72.7	67.4	77.6	228	71.3	66.0	76.1

N = number of participants
n/% = number / percentage of participants in a given category
95% CI = 95% confidence interval; LL = Lower Limit ; UL = Upper Limit

Solicited administration-site events after administration of the rMenB+OMV NZ vaccine were reported in 90.0% of participants in the MenB+MenACWY group, 90.6% in the MenB group, and 79.4% in the MenACWY group.

- The most frequently reported solicited administration-site event after administration of the rMenB+OMV NZ vaccine was pain (90.0% of participants in the MenB+MenACWY group, 89.9% in the MenB group, and 84.1% in the MenACWY group). A total of 8.4% of participants in the MenB+MenACWY group, 10.1% in the MenB group, and 9.3% in the MenACWY group reported severe pain.
- At Vaccination at Visit 1, 80.1% of participants in the MenB+MenACWY group and 80.7% in the MenB group reported pain (Severe pain: 3.9% of participants in both groups).
- At Vaccination at Visit 3, 84.8% of participants each in MenB+MenACWY group and MenB group and 82.9% in the MenACWY group reported pain (Severe pain: 6.0%, 8.2% and 7.0%, respectively).
- At Vaccination at Visit 4, 76.2% of participants in the MenACWY group reported pain (Severe pain: 3.3%).

Solicited administration-site events after administration of the MenACWY vaccine were reported in 31.0% of participants in the MenB+MenACWY group, 14.0% in the MenB group, and 33.1% in the MenACWY group (Table).

- The most frequently reported solicited administration-site event after administration of the MenACWY vaccine was pain (30.3% of participants in the MenB+MenACWY group, 14.7% in the MenB group, and 32.6% in the MenACWY group). A total of 0.7% of participants in the MenB+MenACWY group and 0.3% in the MenACWY group reported severe pain.
- At Vaccination at Visit 1, 30.3% of participants in the MenB+MenACWY group and 32.6% in the MenACWY group had pain (Severe pain: 0.7% and 0.3%, respectively).
- At Vaccination at Visit 4, 14.4% of participants in the MenB group had pain (no severe pain reported).

Most of the solicited administration-site events were mild to moderate in intensity and severe solicited administration-site events were reported in ≤10.1% of participants across groups.

The first onset of the administration-site solicited events in majority of participants was reported from Day 1 through Day 3 following any injection across groups and the mean duration was less than ≤4.5 days for any solicited administration-site event across groups.

Solicited systemic events were reported in 72.6% of participants in the MenB+MenACWY group, 72.7% in the MenB group, and 71.3% in the MenACWY group (Table).

- The most frequently reported solicited systemic event was headache (57% participants in the MenB+MenACWY group, 59.4% in the MenB group, and 57.5% in the MenACWY group. A total of 2.3% of participants in the MenB+MenACWY group, 3.6% in the MenB group, and 4.4% in the MenACWY group had severe headache.
- Fever (≥38°C) was reported in 1.9% of participants in the MenB+MenACWY group, 4.2% in the MenB group, and 2.5% in the MenACWY group). Fever (≥40°C) was reported in 0.3% of participants each in MenB+MenACWY group and MenB group and none in the MenACWY group.

- Any analgesic/antipyretic use for prophylaxis of pain and/or fever was reported in 31.4% of participants in the MenB+MenACWY group, 29.2% in the MenB group, and 30.9% in the MenACWY group.
- Any analgesic/antipyretic use for the treatment of pain and/or fever was reported in 43.7% of participants in the MenB+MenACWY group, 43.5% in the MenB group, and 41.6% in the MenACWY group.

Most of the solicited systemic events were mild to moderate in intensity and severe systemic solicited events were reported in ≤4.4% of participants.

The first onset of the solicited systemic events in majority of participants was reported from Day 1 through Day 3 following any injection across groups and the mean duration was ≤3.4 days for any solicited systemic event across groups.

Assessor's comments

As expected, the vast majority of participants experience a solicited AE in all treatment groups. There was no notable difference in solicited local or systemic events when Bexsero or Menveo was given alone or concomitantly.

Unsolicited AEs

During the 30-day post-vaccination period after Visit 1:

- The most frequently reported unsolicited AE by SOC was infections and infestations (5.5% of participants in the MenB+MenACWY group, 5.8% in the MenB group, and 4.1% in the MenACWY group).
- The most frequently reported unsolicited AE by PT was oropharyngeal pain (2.3% of participants in the MenB+MenACWY group and 1.6% each in the MenB group and the MenACWY group).
- Related unsolicited AEs were infrequently reported, see Table .

During the 30-day post-vaccination period after Visit 3:

- The most frequently reported unsolicited AE by SOC was infections and infestations (6.3% of participants in the MenB+MenACWY group, 6% in the MenB group, and 6.8% in the MenACWY group).
- The most frequently reported unsolicited AE by PT was nasopharyngitis (1.7% of participants in the MenB+MenACWY group, 0.3% in the MenB group, and 2.3% in the MenACWY group).
- Related unsolicited AEs were infrequently reported, see Table .

During the 30-day post-vaccination period after Visit 4:

- The most frequently reported unsolicited AE by SOC was infections and infestations (5% of participants in the MenB+MenACWY group, 6.3% in the MenB group, and 7.3% in the MenACWY group).
- The most frequently reported unsolicited AE by PT was nasopharyngitis (1% of participants in the MenB+MenACWY group, 0.7% in the MenB group, and 1.7% in the MenACWY group).
- Related unsolicited AEs were infrequently reported, see Table .

Table 11: Summary of participants with at least one related unsolicited adverse event by SOC and PT during the 30-day (Day 1-30) period after each vaccination As Treated - Exposed Set (Modified by the Assessor)

	MenB+MenACWY				MenB				MenACWY			
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Vaccination at visit 1												
Any related unsolicited AE	8	2.6	1.1	5.0	7	2.3	0.9	4.6	7	2.2	0.9	4.5
General disorders and administration-site conditions	4	1.3	0.4	3.3	2	0.6	0.1	2.3	4	1.3	0.3	3.2
Gastrointestinal disorders	1	0.3	0.0	1.8	2	0.6	0.1	2.3	0	0.0		
Nervous system disorders	2	0.6	0.1	2.3	0	0.0			1	0.3	0.0	1.7
Skin and subcutaneous tissue disorders	0	0.0			2	0.6	0.1	2.3	0	0.0		
Rash	0	0.0			2	0.6	0.1	2.3	0	0.0		
Blood and lymphatic system disorders	0	0.0			0	0.0			1	0.3	0.0	1.8
Injury poisoning and procedural complications	0	0.0			1	0.3	0.0	1.8	0	0.0		
Musculoskeletal and connective tissue disorders	1	0.3	0.0	1.8	0	0.0			0	0.0		
Respiratory, thoracic and mediastinal disorders	0	0.0			0	0.0			1	0.3	0.0	1.8
Vaccination at visit 3												
Any related unsolicited AE	5	1.7	0.5	3.8	5	1.7	0.5	3.9	6	1.9	0.7	4.2
General disorders and administration-site conditions	3	1.0	0.2	2.9	2	0.7	0.1	2.4	3	1.0	0.2	2.8
Chills	1	0.3	0.0	1.8	1	0.3	0.0	1.8	2	0.6	0.1	2.3
Gastrointestinal disorders	1	0.3	0.0	1.8	2	0.7	0.1	2.4	1	0.3	0.0	1.8
Blood and lymphatic system disorders	1	0.3	0.0	1.8	0	0.0			1	0.3	0.0	1.8
Nervous system disorders	0	0.0			1	0.3	0.0	1.8	1	0.3	0.0	1.8
Infections and infestations	0	0.0			0	0.0			1	0.3	0.0	1.8
Injury poisoning and procedural complications	1	0.3	0.0	1.8	0	0.0			0	0.0		
Respiratory, thoracic and mediastinal disorders	0	0.0			0	0.0			1	0.3	0.0	1.8
Vaccination at visit 4												
Any related unsolicited AE	5	1.7	0.5	3.9	3	1.0	0.2	3.0	1	0.3	0.0	1.8
General disorders and administration-site conditions	3	1.0	0.2	2.9	2	0.7	0.1	2.5	1	0.3	0.0	1.8
Injection-site bruising	2	0.7	0.1	2.4	0	0.0			0	0.0		
Eye disorders	1	0.3	0.0	1.8	0	0.0			0	0.0		
Reproductive system and breast disorders	1	0.3	0.0	1.8	0	0.0			0	0.0		
Skin and subcutaneous tissue disorders	0	0.0			1	0.3	0.0	1.9	0	0.0		

Assessor's comments

There was no notable difference in unsolicited events when Bexsero or Menveo was given alone or concomitantly. Unsolicited AEs considered related to study vaccines were reported by <3% of participants in all treatment groups after any vaccination. All unsolicited AEs considered related to the vaccines are already included in the respective SmPC's and/or reported by only 1 participant.

Serious adverse events, deaths and other significant events

No deaths or AESIs (arthritis or potential immune mediated diseases) were reported in the study.

During 0-12 months follow-up, SAEs were reported in 2 participants in the MenB+MenACWY group, 4 in the MenB group, and 7 in the MenACWY group (Table).

None of the SAEs reported during the study were related to the study interventions, as assessed by the investigator.

Table 12: Summary of participants with at least one SAE reported during the overall study period As Treated - Exposed Set

	MenB+MenACWY				MenB				MenACWY			
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Follow-up period: 0-12 months												
Any SAE	2	0.6	0.1	2.3	4	1.3	0.4	3.3	7	2.2	0.9	4.5
Psychiatric disorders	1	0.3	0.0	1.8	2	0.6	0.1	2.3	3	0.9	0.2	2.7
Suicidal ideation	0	0.0			2	0.6	0.1	2.3	0	0.0		
Adjustment disorder with depressed mood	0	0.0			0	0.0			1	0.3	0.0	1.7
Depression	1	0.3	0.0	1.8	0	0.0	0	0.0				
Drug abuse	0	0.0			0	0.0			1	0.3	0.0	1.7
Major depression	0	0.0			0	0.0			1	0.3	0.0	1.7
Injury poisoning and procedural complications	1	0.3	0.0	1.8	0	0.0			1	0.3	0.0	1.7
Fibula fracture	0	0.0			0	0.0			1	0.3	0.0	1.7
Lumbar vertebral fracture	1	0.3	0.0	1.8					0	0.0		
Musculoskeletal and connective tissue disorders	0	0.0			0	0.0			2	0.6	0.1	2.2
Pain in extremity	0	0.0			0	0.0			1	0.3	0.0	1.7
Rhabdomylosis	0	0.0			0	0.0			1	0.3	0.0	1.7
Infections and infestations	0	0.0			1	0.3	0.0	1.8	0	0.0		
Appendicitis	0	0.0			1	0.3	0.0	1.8	0	0.0		
Metabolism and nutrition disorder	0	0.0			1	0.3	0.0	1.8	0	0.0		
Hypoglycaemia	0	0.0			1	0.3	0.0	1.8	0	0.0		
Pregnancy, puerperium and perinatal conditions	0	0.0			0	0.0			1	0.3	0.0	1.7
Abortion spontaneous	0	0.0			0	0.0			1	0.3	0.0	1.7

Assessor's comments

The frequency of occurrence of SAEs is low, <2.5%, in all treatment groups. The Applicant states that none of the SAEs are related, which could not be assessed as narratives were not provided. The Applicant is encouraged to always include the narratives of the SAEs in future CSR submissions, to enable assessment of relatedness.

Discontinuations

During the study period, 1 participant in the MenACWY group reported AE leading to withdrawal (pain in extremity; not related to the study intervention) during the 30-day period after the vaccination at Visit 1. The AE of pain in extremity was also reported as SAE due to hospitalization that was resolved after 7 days of onset.

Assessor's comments

One participant discontinued the study due to an (S)AE. This SAE (pain in extremity) was stated not to be related to study intervention.

2.3.3. Discussion on clinical aspects

Study V72_79 was conducted to assess concomitant administration of Bexsero (MenB vaccine) and Menveo (MenACWY vaccine) in an adolescent population. Concomitant administration of Menveo with Bexsero is approved in the EU [Menveo SmPC, 2024; Bexsero SmPC, 2017], based on information obtained in infants aged 3 to 13 months. However, no data was available on the concomitant use of Bexsero and Menveo in adolescents. GSK was requested by US CBER to assess the concomitant use of Bexsero with a second dose of Menveo in individuals 16 years through 18 years of age, as a post marketing commitment safety and immunogenicity study.

Immunogenicity of the concomitant administration of MenB and MenACWY vaccines compared to sequential administration of these vaccines was evaluated by serum bactericidal assays using human complement (hSBAs), using indicator strains representing 4 MenB strains and serogroups A, C, W and Y. The primary immunogenicity objectives of GMT ratios (concomitant/sequential) are appropriate for the purpose of this study since it is a continuous outcome and likely more sensitive to small differences than the dichotomized responder analysis (% with hSBA >LLOQ).

The study met the pre-specified non-inferiority margins of 0.5 for the lower limit of the two-sided 95% CI for the between group ratio of GMTs for all 4 MenB strains and all serogroups. This non-inferiority margin is considered very broad, however, as the results show that the LL of the 2-sided 95% CI were all ≥0.73 (ranging from 0.73 to 0.86) for all MenB strains and all serogroups, which is reassuring.

A substantial increase in hSBA titres were observed after the complete 2-dose MenB primary series. In the concomitant group GMRs were comparable to those in the MenB alone group. After completion of the 2-dose primary series, the point estimate of the percentage of participants achieving hSBA titres ≥LLOQ for all 4 MenB strains was 72.2% (95% CI 66.4, 77.4) in the concomitant group versus 74.8% (95% CI: 69.1, 79.9) in the MenB only group. Although it is acknowledged that the LL of the 95% CI of the difference in percentage is slighty >10% (-10.09), it should be noted that the study was not powered on this dichotomized responder analysis. In addition, an hSBA titre >1:4 is considered protective and for all 4 strains LLOQ was at least 1:6, and therefore considered conservative.

As expected after a booster dose of MenACWY, the GMTs increased substantially and GMRs were high, ranging from 130 to 324 in the concomitant group vs 132 to 300 in the MenACWY group. This was also reflected in the percentage of participants achieving hSBA titre ≥LLOQ, which ranged from 99.0% to 100% in the concomitant group and 99.3% to 100% in the MenACWY group for all 4 strains. No difference between the concomitant group and the MenACWY alone group were observed.

During the current study no new safety signals were observed. No notable differences were observed when Bexsero or Menveo were given alone or concomitantly. The most frequently reported solicited AEs were pain, headache and fatigue in all treatment groups. The profile of solicited AEs is in line with the SmPCs for MenB and MenACWY vaccine. Unsolicited AEs considered related to study vaccination were reported by <3% of participants in all treatment groups after any vaccination. All unsolicited AEs considered related to the vaccines were reported by only 1 participant and/or already included in the SmPCs of the commercial products. No deaths or AESI were reported during the study. Approximately 2.5% of subjects reported at least one SAE. Narratives of the SAEs were not provided, which hampers assessment of relatedness.

Overall, the results indicate that concomitant administration did not substantially impact the immune response or the safety profile in the adolescent population.

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

3. CHMP overall conclusion and recommendation

In conclusion, in the current study concomitant administration of MenB and MenACWY vaccines generated an immune response in adolescents which was generally comparable to the immune response generated when the vaccines were administered alone. No new safety signals were reported.

☒ **Fulfilled:**

No regulatory action required.