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SCIENCE MEDICINES HEALTH

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Human Medicines Division

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

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/033

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	29/04/2024	29/04/2024
☐	CHMP Rapporteur Assessment Report	03/06/2024	03/06/2024
☐	CHMP members comments	17/06/2024	17/06/2024
☐	Updated CHMP Rapporteur Assessment Report	20/06/2024	20/06/2024
☒	CHMP adoption of conclusions:	27/06/2024	27/06/2024

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1. Introduction

On 27 March 2024, the MAH submitted a completed paediatric study for study 213171, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the present study aims to fulfil the paediatric obligation related to Article 46 of the Regulation (EC) No 1901/2006, which is applicable to the European marketed vaccines.

The present submission includes the final Clinical Study Report for study 213171 - MENABCWY-019 where Bexsero was administered only to ensure standard of care, having no related study objectives. Study MENABCWY-019 was not conducted in accordance with an agreed paediatric investigation plan for Bexsero.

2.2. Information on the pharmaceutical formulation used in the study

Table 1. Study interventions administered

Study Intervention Name	**MenABCWY**[1,2]		***Menveo***[3,2,4]		***Bexsero***[5]	**Placebo**[5,6]
Vaccine(s)/ Product	MenACWY lyo	rMenB+OMV NZ	MenA	MenCWY	rMenB+OMV NZ	NaCl
Presentation	Vial	Syringe	Vial	Vial	Syringe	Syringe
Dose form	Powder for suspension for injection	Suspension for injection	Powder for solution for injection	Solution for solution for injection	Suspension for injection	Solution for injection
Vaccines(s)/ Product Formulation[7]	MenA(10 µg)-CRM_{197}; MenC(5 µg)-CRM_{197}; MenW135(5 µg)-CRM_{197}; MenY(5 µg)-CRM_{197}	Recombinant *N. meningitidis* serogroup B NHBA fusion protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B NadA protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B fHbp fusion protein (50 µg) adsorbed on aluminum hydroxide; Outer membrane vesicles from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminum hydroxide; Aluminum hydroxide (0.5 mg Al^{3+}); Sucrose; Histidine; NaCl; Water for injections q.s. 0.5 mL[1]	Meningococcal group A oligosaccharides (10 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (16.7-33.3 µg); Potassium dihydrogen phosphate; Sucrose	Meningococcal group C oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (7.1-12.5 µg); Meningococcal group W-135 oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (3.3-8.3 µg); Meningococcal group W-135 oligosaccharides (5 µg) conjugated to Corynebacterium diphtheriae C7 (β197) M8 (CRM197) protein (5.6-10 µg); NaCl; Sodium dihydrogen phosphate monohydrate; Disodium phosphate dihydrate; Water for injections q.s. 0.5 mL	Recombinant *N. meningitidis* serogroup B NHBA fusion protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B NadA protein (50 µg) adsorbed on aluminum hydroxide; Recombinant *N. meningitidis* serogroup B fHbp fusion protein (50 µg) adsorbed on aluminum hydroxide; Outer membrane vesicles from *N. meningitidis*, serogroup B Strain NZ98/254 (25 µg PorA P1.4) adsorbed on aluminum hydroxide; Aluminum hydroxide (0.5 mg Al^{3+}); Sucrose; Histidine; NaCl; Water for injections q.s. 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections
Product type	Combination		Biological		Combination	Combination
Type	Study		Control		Additional	Additional
Route of Administration	Intramuscular use		Intramuscular use		Intramuscular use	Intramuscular use
Administration site:						

Location[8]	Deltoid	Deltoid	Deltoid	Deltoid
Laterality[8]	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered	2	1	2	1
Volume to be administered[9]	0.5 mL	0.5 mL	0.5 mL	0.65 mL[11]
Packaging, labeling	Refer to study reference manual for details	Refer to study reference manual for details	Refer to study reference manual for details	Refer to study reference manual for details
Manufacturer	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA	GSK Biologicals SA

Abbreviations: CRM = cross reacting material; fHbp = factor H binding protein; GSK= GlaxoSmithKline; NaCl = sodium chloride; NadA = Neisserial adhesin A; NHBA = Neisseria heparin binding antigen; NZ = New Zealand; OMV = outer membrane vesicles.

1 MenABCWY formulation consisting of a MenACWY lyo (lyophilized component) and of a rMenB+OMV liquid component, to be reconstituted together before administration (0.5 mL) by qualified health care practitioner.

2 Investigational vaccine.

3 *Menveo* commercial formulation consisting of a MenA lyophilized component and of a MenCWY liquid component, to be reconstituted together before administration (0.5 mL) by qualified health care practitioner.

4 In the US, the approved specifications for *Menveo* are described as 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=5 µg, 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.

5 Non-investigational vaccine or placebo.

6 Administered in the ABCWY group at Visit 4 to maintain the study observer-blind.

7 The composition per dose is presented here.

8 The non-dominant arm was the preferred arm of injection. In case it was not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm was performed.

9 Refer to the study reference manual for details.

2.3. Clinical aspects

2.3.1. Introduction

The main purpose of this phase IIIB clinical study was to assess the immunogenicity and safety of the Menace vaccine when administered as a booster in healthy adolescents and young adults, previously primed with a MenACWY vaccine.

Study Identifier: MENABCWY-019

EudraCT number: 2019-004982-42

Study number: 213171

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

Brief licensing history: Bexsero contains 3 recombinant proteins [factor H binding protein (fHbp), *Neisseria* adhesin A (NadA), and Neisserial Heparin Binding Antigen (NHBA)], combined with Outer Membrane Vesicles (OMV) components from the New Zealand outbreak strain NZ98/254.

In January 2013, a centralized marketing authorization in European Union (EU) was granted for Bexsero for use in individuals from 2 months of age and older. The vaccine is currently approved in 52 countries worldwide and is indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B with some differences in the age indication depending on the country where the vaccine is registered.

The 213171 (MENABCWY-019) study report is being submitted to comply with the requirements of Article 46 of the pediatric regulation 1901/2006.

The study has not been conducted according to an agreed pediatric investigation plan (PIP) for Bexsero.

Context of the study: Study 213171 (MENABCWY-019) evaluated the immunogenicity and safety of the MenABCWY vaccine when administered as a booster in healthy adolescents and young adults, 15 through 25 years of age, previously primed with a MenACWY vaccine.

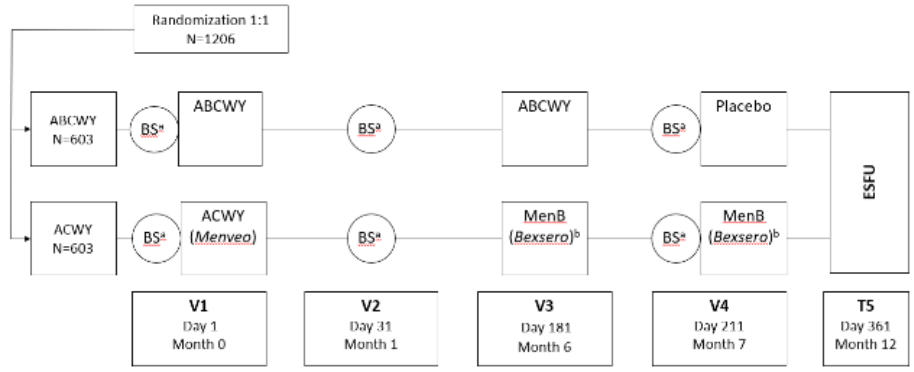
In this study, currently licensed Menveo (MenACWY) vaccine was used as comparator. To let the participants in the ACWY group receive 2 doses of Bexsero vaccine in line with Advisory Committee on Immunization Practices (ACIP) recommendations, the participants in this group received Bexsero vaccine on Visit 3 (Day 181) and Visit 4 (Day 211). There were no study objectives related to the Bexsero vaccine, as it was administered only to ensure standard of care.

2.3.2. Clinical study

Study Design

This multi-center, observer-blind study was conducted at 65 centers in 4 countries (Argentina, Australia, Canada, United States [US]). A total of 1250 healthy, 15 to 25-year-old, adolescents and adults who are previously primed with meningococcal ACWY vaccine were enrolled in the study. A total of 1083 participants completed the study. The study participants were randomized into 2 study groups (1:1 ratio) to receive injections as described below:

- ABCWY: 2 doses of the MenABCWY vaccine at Day 1 and Day 181 (0, 6-months schedule) and 1 dose of placebo at Day 211.
- ACWY: 1 dose of MenACWY vaccine at Day 1 (single dose) and 2 doses of MenB vaccine at Day 181 and Day 211.



ACWY = *Menveo*; BS = blood sample; ESFU = extended safety follow-up; MenB = *Bexsero*; N = number of participants; T = telephone contact; V = visit
[a] Insufficient blood volume may lead to test cancellation and jeopardize the statistical power. Hence, every effort must be made to collect blood volume as per protocol requirements.
[b] *Bexsero* is given for compliance with standard of care.
Note: The subjects number displayed in the figure are planned numbers.

Figure 1: Schematic of Study Design

Treatments

Participants were randomized to receive intramuscular injections of MenABCWY vaccine and placebo, or MenACWY (Menveo) vaccine and MenB (Bexsero) vaccine, as applicable.

Table 1 above.

Objectives and Endpoints

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 1) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY[1] vaccine, as measured by the percentages of participants achieving a 4-fold rise[2] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[2] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the second vaccination for the ABCWY group (Day 211, Month 7), and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
Immunological non-inferiority: MenABCWY vs. MenACWY (Family 2) To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine given to healthy participants, previously primed with a MenACWY[1] vaccine, as measured by the percentages of participants achieving a 4-fold rise[2] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the first MenABCWY vaccination (0,6-months) and 1 month after the MenACWY vaccination (single dose).	• The percentages of participants with a 4-fold rise[2] in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of MenACWY vaccination for the ACWY group (Day 31, Month 1), relative to baseline (Day 1, Month 0).
Safety To evaluate the safety and reactogenicity of the MenABCWY and MenACWY vaccines.	• The frequencies and percentages of participants with solicited administration site events (i.e., injection site pain, erythema, swelling, induration) and solicited systemic events (i.e., fever [body temperature ≥38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) during the 7 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following vaccination at Day 1,

Objectives	Endpoints
	Month 0 (for the ABCWY and ACWY groups) and Day 181, Month 6 (for the ABCWY group). • The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).
Secondary	
To assess the immune response to MenABCWY (0,6-month schedule) and MenACWY (single dose) vaccines against *N. meningitidis* serogroups A, C, W, and Y, at pre-vaccination and 1 month after the first and last MenABCWY vaccinations and 1 month after the MenACWY vaccination.	• The percentages of participants with hSBA titers ≥ LLOQ against serogroups A, C, W, and Y: - at baseline (Day 1, Month 0) and at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group, and - at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The GMTs against serogroups A, C, W, and Y: - at baseline (Day 1, Month 0) and at 1 month after the first (Day 31, Month 1) and the last (Day 211, Month 7) vaccinations for the ABCWY group, and - at baseline (Day 1, Month 0) and 1 month after the single MenACWY vaccination for the ACWY group (Day 31, Month 1). • The GMRs against serogroups A, C, W, and Y: - at 1 month after the first (Day 31, Month 1) and the last vaccination (Day 211, Month 7) for the ABCWY group as compared to baseline (Day 1, Month 0) and - at 1 month after the MenACWY vaccination (Day 31, Month 1) for the ACWY group as compared to baseline (Day 1, Month 0).
To assess the immune response to the MenABCWY vaccine (0,6-month schedule) against *N. meningitidis* serogroup B indicator strains, at pre-vaccination and at 1 month after the last MenABCWY vaccination.	• The percentages of participants with hSBA titers ≥LLOQ for each and all serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the last vaccination (Day 211, Month 7) for the ABCWY group. • The percentages of participants with 4-fold rise[3] in hSBA titers against each *N. meningitidis* serogroup B indicator strains at 1 month after the last vaccination (Day 211,

Statistical Methods

A sensitivity analysis for each co-primary immunogenicity objective was conducted. A logistic regression with vaccine group as a factor and country as a stratum to account for randomization was fitted using PROC PLM. The predicted proportion of responders with 4-fold rise for each vaccine group were obtained from the SAS procedure PROC PLM. The percentage differences for the predicted proportions between the vaccine groups were obtained using the SAS procedure PROC SURVEYLOGISTIC. The associated 95% CI for the difference in predicted proportions were obtained using Newcombe's method within the SAS procedure PROC FREQ.

Results

Disposition

Table 3 below summarizes participant disposition for the Enrolled Set and the reasons for study discontinuation. A total of 1250 participants were enrolled in the study. Overall, 1247 (99.8%) participants received at least one dose of study vaccine. Of these, a total of 1208 (96.6%) participants were included in the full analysis set (FAS), from which a total of 274 (43.8%) participants were included in the per protocol set (PPS) for Family 1 and 1130 (90.4%) participants were included in the PPS for Family 2. Family 1 subset is comprised of ABCWY participants, only. The most common reason for elimination from PPS for Family 1 subset was lack of immunogenicity results (24.7%) and for Family 2 subset the most common reason for elimination from subset was protocol deviations (2.6%). A total of 1247 (99.8%) participants were included in the Overall Safety Set. A total of 3 participants in the ACWY group did not receive at least 1 dose of study intervention and were eliminated from the Exposed Set.

Table 3: Summary of participants disposition (enrolled set)

	ABCWY (N=626) n (%)	ACWY (N=624) n (%)	Total (N=1250) n (%)
Participants enrolled	626	624	1250
Participants randomized	626 (100.0)	624 (100.0)	1250 (100.0)
Participants not randomized			0
Participants who received at least 1 vaccination	626 (100.0)	621 (99.5)	1247 (99.8)
Participants who received full vaccination course	556 (88.8)	545 (87.3)	1101 (88.1)
Participants who did not receive any vaccination	0	3 (0.5)	3 (0.2)
Participants who completed the study	541 (86.4)	542 (86.9)	1083 (86.6)
Participants who discontinued the study	85 (13.6)	82 (13.1)	167 (13.4)
Reasons for discontinuing the study	85 (13.6)	82 (13.1)	167 (13.4)
Due to COVID-19 infection or overall pandemic	0	0	0
Adverse event requiring expedited reporting	3 (0.5)	3 (0.5)	6 (0.5)
Unsolicited non-serious adverse event	1 (0.2)	4 (0.6)	5 (0.4)
Protocol deviation	1 (0.2)	6 (1.0)	7 (0.6)
Withdrawal by participant	27 (4.3)	26 (4.2)	53 (4.2)
Sponsor study termination	0	0	0
Lost to follow-up	44 (7.0)	31 (5.0)	75 (6.0)
Migrated or moved from the study area	8 (1.3)	8 (1.3)	16 (1.3)
Solicited adverse event	1 (0.2)	2 (0.3)	3 (0.2)
Other	0	2 (0.3)	2 (0.2)
Participants who completed the vaccine	556 (88.8)	545 (87.3)	1101 (88.1)
Participants who discontinued the vaccine	70 (11.2)	76 (12.2)	146 (11.7)

Abbreviations: COVID-19 = coronavirus disease 2019; N = number of participants enrolled; n = number of participants included in analysis.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.
Participants enrolled = informed consent received.
Percentages are based on the number of participants enrolled.
Source: Table 14.1.2.1 (28DEC2023)

Protocol Deviations

Of the 1250 enrolled participants, protocol deviations leading to elimination from any analyses were reported for 195 participants (15.6%). The most common deviations leading to eliminations were visit schedule criteria (10.6% of participants overall), and laboratory assessment criteria (3.0% of participants overall).

Table 4: Summary of important protocol deviations leading to elimination from any Per Protocol Analysis-As randomized (enrolled set)

	ABCWY (N=626) n (%)	ACWY (N=624) n (%)	Total (N=1250) n (%)
Number of participants with at least 1 important deviation	101 (16.1)	94 (15.1)	195 (15.6)
Informed Consent Criteria	3 (0.5)	6 (1.0)	9 (0.7)
Eligibility And Entry Criteria	6 (1.0)	9 (1.4)	15 (1.2)
Concomitant Medication Criteria	2 (0.3)	3 (0.5)	5 (0.4)
Laboratory Assessment Criteria	19 (3.0)	19 (3.0)	38 (3.0)
Study Procedures Criteria	6 (1.0)	5 (0.8)	11 (0.9)
Serious Adverse Event Criteria	1 (0.2)	0	1 (0.1)
Visit Schedule Criteria	71 (11.3)	62 (9.9)	133 (10.6)
Investigational Product (IP) Compliance	1 (0.2)	2 (0.3)	3 (0.2)
Other Criteria	1 (0.2)	0	1 (0.1)

Abbreviations: N = number of participants in each vaccine group.
ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Note: The same participant may have more than 1 protocol deviation.
Source: Table 14.1.6.1 (28DEC2023)

Demographics

Table 5: Demographic and baseline characteristics

		ABCWY (N=626)	ACWY (N=624)	Total (N=1250)
Age (years) at time of first vaccination	n	626	621	1247
	Mean (SD)	17.2 (2.53)	17.2 (2.63)	17.2 (2.58)
	Median	16.0	16.0	16.0
	Min - Max	15 - 25	15 - 25	15 - 25
Age category				
Adolescents (15-17 years)	n (%)	450 (71.9)	441 (70.7)	891 (71.3)
Adults (18-25 years)	n (%)	176 (28.1)	180 (28.8)	356 (28.5)
Age [EudraCT] category				
Adolescents (12-17 years)	n (%)	450 (71.9)	441 (70.7)	891 (71.3)
Adults (18-64 years)	n (%)	176 (28.1)	180 (28.8)	356 (28.5)
Sex				
Male	n (%)	283 (45.2)	299 (47.9)	582 (46.6)
Female	n (%)	343 (54.8)	325 (52.1)	668 (53.4)
Race				
Black or African American	n (%)	94 (15.0)	86 (13.8)	180 (14.4)
American Indian or Alaska Native	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Asian	n (%)	22 (3.5)	33 (5.3)	55 (4.4)
Native Hawaiian or Other Pacific Islander	n (%)	2 (0.3)	6 (1.0)	8 (0.6)
White	n (%)	474 (75.7)	467 (74.8)	941 (75.3)
Other	n (%)	33 (5.3)	31 (5.0)	64 (5.1)
Country				
Argentina	n (%)	116 (18.5)	116 (18.6)	232 (18.6)
Australia	n (%)	119 (19.0)	119 (19.1)	238 (19.0)
Canada	n (%)	25 (4.0)	24 (3.8)	49 (3.9)
United States of America	n (%)	366 (58.5)	365 (58.5)	731 (58.5)

Region				
USA	n (%)	366 (58.5)	365 (58.5)	731 (58.5)
Non USA	n (%)	260 (41.5)	259 (41.5)	519 (41.5)
Ethnicity				
Hispanic or Latino	n (%)	179 (28.6)	192 (30.8)	371 (29.7)
Not Hispanic or Latino	n (%)	447 (71.4)	432 (69.2)	879 (70.3)
Weight (kg)	n	626	624	1250
	Mean (SD)	71.6 (20.2)	71.8 (20.2)	71.7 (20.2)
	Median	67.1	67.0	67.0
	Min - Max	40 - 159	41 - 201	40 - 201
Height (cm)	n	626	624	1250
	Mean (SD)	168.6 (9.8)	169.3 (9.4)	169.0 (9.6)
	Median	167.9	169.0	168.3
	Min - Max	145 - 204	143 - 196	143 - 204
Body Mass Index (BMI) (kg/m^2)	n	626	624	1250
	Mean (SD)	25.1 (6.3)	25.0 (6.5)	25.1 (6.4)
	Median	23.4	23.5	23.5
	Min - Max	15.1 - 52.6	14.9 - 63.5	14.9 - 63.5

Abbreviations: BMI = body mass index; cm = centimeters; kg = kilograms; m = meters; Max = maximum; mg = milligrams; Min = minimum; SD = standard deviation; N = number of participants enrolled; n = number of participants included in analysis.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.
Age (years) - calculated relative to time of first vaccination.
Percentages were calculated from the number of enrolled participants (N).
Source: Table 14.1.3.1 (28DEC2023)

Exposure and Compliance

Table 6: Exposure and Compliance (exposed set)

		ABCWY (N=626)	ACWY (N=621)	Total (N=1247)
Exposure to study vaccine (days)	n	626	621	1247
	Mean (SD)	350.2 (58.51)	345.0 (68.41)	347.6 (63.66)
	Median	364.0	363.0	363.0
	Min - Max	16 - 492	7 - 505	7 - 505
Received Vaccine - within specified window				
One Dose	n (%)	92 (14.7)	89 (14.3)	181 (14.5)
Two Doses	n (%)	152 (24.3)	161 (25.9)	313 (25.1)
Three Doses (all)	n (%)	382 (61.0)	371 (59.7)	753 (60.4)
Received Vaccine - outside of specified window				
One Dose	n (%)	147 (23.5)	154 (24.8)	301 (24.1)
Two Doses	n (%)	32 (5.1)	25 (4.0)	57 (4.6)
Three Doses (all)	n (%)	0	0	0
Received Vaccine - outside of specified window due to COVID-19				
One Dose	n (%)	9 (1.4)	10 (1.6)	19 (1.5)
Two Doses	n (%)	1 (0.2)	0	1 (0.1)
Three Doses (all)	n (%)	0	0	0
Missed Vaccine due to COVID-19				
One Dose	n (%)	0	0	0
Two Doses	n (%)	0	0	0
Three Doses (all)	n (%)	0	0	0

Abbreviations: Max = maximum; Min = minimum; N = number of participants in each vaccine group; n = number of participants included in analysis; SD = standard deviation.
ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Exposure to study drug is defined as number of days from first vaccination to the last contact date on End of Study Visit form (date of last telephone contact scheduled on Day 361).
Received vaccine = Number of doses received can include any order of vaccine doses received/missed (i.e., not the study defined order of vaccines).
Specified window is as defined in the SAP Section 14 (Appendix 16.1.9).
Source: Table 14.1.5.2 (28DEC2023)

Efficacy results

The primary immunogenicity analyses were carried out using the PPS. The secondary and available tertiary analyses were based on FAS.

Primary: Immunological Non-inferiority: 2-doses MenABCWY vs. 1-dose MenACWY (Family 1)

The first co-primary immunological endpoint, non-inferiority of MenABCWY vaccine compared with MenACWY vaccine against N. meningitidis serogroups A, C, W, and Y was demonstrated as the lower limit (LL) of the 2-sided 95% CI for the group differences in overall percentages for participants achieving a 4-fold rise in hSBA titers were above the pre-defined criterion of -10% (Table 7).

Table 7: Immunological non-inferiority: percentages of participants with 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W and Y, and Vaccine group difference, 1 month after second vaccination for ABCWY group (Day 211) and 1 month after single MenACWY vaccination dose for the ACWY group (Day 31) (Per protocol Set)

		ABCWY			ACWY			ABCWY - ACWY	
Serogroup	Four-fold increase	N	n (%)	95% CI	N	n (%)	95% CI	% difference	95% CI
A	Four-fold increase, overall	168	160 (95.2)	(90.83, 97.92)	505	480 (95.0)	(92.78, 96.77)	0.2	(**-4.43***, 3.48)
	Four-fold increase, pre < LOD	119	119 (100.0)	(96.95, 100.00)	356	349 (98.0)	(95.99, 99.21)		
	Four-fold increase, LOD ≤ pre < LLOQ	0	0	(NE, NE)	3	3 (100.0)	(29.24, 100.00)		
	Four-fold increase, pre ≥ LLOQ	49	41 (83.7)	(70.34, 92.68)	146	128 (87.7)	(81.22, 92.53)		
C	Four-fold increase, overall	180	170 (94.4)	(90.02, 97.30)	546	513 (94.0)	(91.62, 95.80)	0.5	(**-4.19***, 3.96)
	Four-fold increase, pre < LOD	62	62 (100.0)	(94.22, 100.00)	198	194 (98.0)	(94.91, 99.45)		
	Four-fold increase, LOD ≤ pre < LLOQ	11	11 (100.0)	(71.51, 100.00)	39	39 (100.0)	(90.97, 100.00)		
	Four-fold increase, pre ≥ LLOQ	107	97 (90.7)	(83.48, 95.43)	309	280 (90.6)	(86.80, 93.62)		
W	Four-fold increase, overall	180	172 (95.6)	(91.43, 98.06)	544	511 (93.9)	(91.59, 95.79)	1.6	(**-2.77***, 4.88)
	Four-fold increase, pre < LOD	103	103 (100.0)	(96.48, 100.00)	354	341 (96.3)	(93.80, 98.03)		
	Four-fold increase, LOD < pre < LLOQ	3	3 (100.0)	(29.24, 100.00)	11	10 (90.9)	(58.72, 99.77)		
	Four-fold increase, pre ≥ LLOQ	74	66 (89.2)	(79.80, 95.22)	179	160 (89.4)	(83.92, 93.49)		
Y	Four-fold increase, overall	179	170 (95.0)	(90.67, 97.68)	537	507 (94.4)	(92.12, 96.20)	0.6	(**-3.98***, 3.89)
	Four-fold increase, pre < LOD	98	98 (100.0)	(96.31, 100.00)	330	318 (96.4)	(93.73, 98.11)		
	Four-fold increase, LOD ≤ pre < LLOQ	4	4 (100.0)	(39.76, 100.00)	21	19 (90.5)	(69.62, 98.83)		
	Four-fold increase, pre ≥ LLOQ	77	68 (88.3)	(78.97, 94.51)	186	170 (91.4)	(86.41, 95.00)		

Abbreviations: hSBA = human serum bactericidal assay; N = number of participants in each vaccine group with available results (which additionally satisfy the baseline (pre) criteria, where applicable); n = number of participants with 4-fold rise in hSBA titer at respective timepoints per vaccine group; NE = not estimable; LOD = limit of detection; LLOQ = lower limit of quantitation.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.
Exact confidence intervals are based on Clopper-Pearson method.
Standardized asymptotic 95% confidence intervals between group differences are derived using Miettinen and Nurminen method.
* Non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine, is met when lower limit of the 2-sided 95% CI is above -10%.
For participants with a baseline titer less than LOD, a four-fold increase is relative to LOD. For participants with a baseline titer greater than or equal to LOD but less than LLOQ, a four-fold increase is relative to LLOQ.
Source: Table 14.2.2.1 (28DEC2023)

Primary: Immunological Non-inferiority: MenABCWY vs. MenACWY (Family 2)

The second-co-primary immunological endpoint, non-inferiority of the MenABCWY vaccine compared with MenACWY vaccine against N. meningitidis serogroups A, C, W, and Y was demonstrated as the LL of the 2-sided 95% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titers were above the pre-defined criterion of -10% (Table 8).

Table 8: Immunological non-inferiority: percentages of participants with 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W and Y, and Vaccine group difference, 1 month after second vaccination for ABCWY group (Day 31) and 1 month after single MenACWY vaccination dose for the ACWY group (Day 31) (Per protocol Set)

		ABCWY			ACWY			ABCWY – ACWY	
Serogroup	Four-fold increase	N	n (%)	95% CI	N	n (%)	95% CI	% difference	95% CI
A	Four-fold increase, overall	509	471 (92.5)	(89.90, 94.66)	505	480 (95.0)	(92.78, 96.77)	-2.5	(**-5.59***, 0.47)
	Four-fold increase, pre < LOD	370	364 (98.4)	(96.50, 99.40)	356	349 (98.0)	(95.99, 99.21)		
	Four-fold increase, LOD ≤ pre < LLOQ	0	0	(NE, NE)	3	3 (100.0)	(29.24, 100.00)		
	Four-fold increase, pre ≥ LLOQ	139	107 (77.0)	(69.08, 83.69)	146	128 (87.7)	(81.22, 92.53)		
C	Four-fold increase, overall	570	536 (94.0)	(91.76, 95.83)	546	513 (94.0)	(91.62, 95.80)	0.1	(**-2.76***, 2.94)
	Four-fold increase, pre < LOD	197	194 (98.5)	(95.61, 99.68)	198	194 (98.0)	(94.91, 99.45)		
	Four-fold increase, LOD ≤ pre < LLOQ	42	41 (97.6)	(87.43, 99.94)	39	39 (100.0)	(90.97, 100.00)		
	Four-fold increase, pre ≥ LLOQ	331	301 (90.9)	(87.31, 93.80)	309	280 (90.6)	(86.80, 93.62)		
W	Four-fold increase, overall	565	533 (94.3)	(92.10, 96.09)	544	511 (93.9)	(91.59, 95.79)	0.4	(**-2.41***, 3.25)
	Four-fold increase, pre < LOD	351	345 (98.3)	(96.32, 99.37)	354	341 (96.3)	(93.80, 98.03)		
	Four-fold increase, LOD < pre < LLOO	8	7 (87.5)	(47.35, 99.68)	11	10 (90.9)	(58.72, 99.77)		
	Four-fold increase, pre ≥ LLOQ	206	181 (87.9)	(82.61, 91.99)	179	160 (89.4)	(83.92, 93.49)		
Y	Four-fold increase, overall	567	531 (93.7)	(91.32, 95.51)	537	507 (94.4)	(92.12, 96.20)	-0.8	(**-3.62***, 2.09)
	Four-fold increase, pre < LOD	333	326 (97.9)	(95.72, 99.15)	330	318 (96.4)	(93.73, 98.11)		
	Four-fold increase, LOD ≤ pre < LLOQ	21	20 (95.2)	(76.18, 99.88)	21	19 (90.5)	(69.62, 98.83)		
	Four-fold increase, pre ≥ LLOQ	213	185 (86.9)	(81.56, 91.08)	186	170 (91.4)	(86.41, 95.00)		

Abbreviations: hSBA = human serum bactericidal assay; N = number of participants in each vaccine group with available results (which additionally satisfy the baseline (pre) criteria, where applicable); n = number of participants with 4-fold rise in hSBA titer at respective timepoints per vaccine group; NE = not estimable; LOD = limit of detection; LLOQ = lower limit of quantitation.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.
Exact confidence intervals are based on Clopper-Pearson method.
Standardized asymptotic 95% confidence intervals between group differences are derived using Miettinen and Nurminen method.
* Non-inferiority of the MenABCWY vaccine, compared to MenACWY vaccine, is met when lower limit of the 2-sided 95% CI is above -10%.
For participants with a baseline titer less than LOD, a four-fold increase is relative to LOD. For participants with a baseline titer greater than or equal to LOD but less than LLOQ, a four-fold increase is relative to LLOQ.
Source: Table 14.2.2.2 (28DEC2023)

Secondary: Immune Response Against N. Meningitidis Serogroups A, C, W, and Y

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

Secondary: Immune Response Against N. Meningitidis Serogroup B Indicator Strains

Percentages of participants with hSBA titers ≥LLOQ

Table 9 summarizes the percentages of participants with hSBA titers ≥LLOQ against each N. meningitidis serogroup B indicator strain (fHbp, NadA, NHBA, PorA) at pre-vaccination and 1 month after second vaccination for the ABCWY group.

The percentages of participants in the ABCWY group with hSBA titers ≥LLOQ ranged from 2.7% to 20.2% at baseline, and 75.6% to 96.3% one month after the last vaccination in the ABCWY group.

The percentages of participants in the ABCWY group with hSBA titers ≥LLOQ for all serogroup B indicator strains (composite response) were 1.1%, and 72.0% at baseline, and Month 7, respectively.

Table 9: Percentages of participants with hSBA titers ≥LLOQ for each and all N. meningitidis serogroup B indicator strains at pre-vaccination (Day 1), (Day 31) and 1 month after last vaccination for ABCWY group (Day 211) (full analysis set)

			ABCWY		
MenB antigen	Timepoint		N	n (%)	95% CI
fHbp	Baseline	% of participants with titers ≥ LLOQ	184	16 (8.7)	(5.05, 13.74)
[redacted]					
	Month 7	% of participants with titers ≥ LLOQ	165	146 (88.5)	(82.60, 92.92)
NadA	Baseline	% of participants with titers ≥ LLOQ	183	14 (7.7)	(4.25, 12.50)
[redacted]					
	Month 7	% of participants with titers ≥ LLOQ	165	158 (95.8)	(91.45, 98.28)
NHBA	Baseline	% of participants with titers ≥ LLOQ	183	37 (20.2)	(14.65, 26.77)
[redacted]					
	Month 7	% of participants with titers ≥ LLOQ	164	158 (96.3)	(92.21, 98.65)
PorA P1.4	Baseline	% of participants with titers ≥ LLOQ	184	5 (2.7)	(0.89, 6.23)
[redacted]					
	Month 7	% of participants with titers ≥ LLOQ	164	124 (75.6)	(68.30, 81.97)
All Serogroup B indicator strains	Baseline	% of participants with titers ≥ LLOQ	181	2 (1.1)	(0.13, 3.93)
[redacted]					
	Month 7	% of participants with titers ≥ LLOQ	164	118 (72.0)	(64.41, 78.68)

Abbreviations: hSBA = human serum bactericidal assay; N = number of participants in each vaccine group with available results (for All Serogroup B indicator strains N = number of participants in each vaccine group with available results for all antigens); n = number of participants with hSBA titer ≥ LLOQ at respective timepoints per vaccine group (for All Serogroup B indicator strains n = number of participants with hSBA titer ≥ LLOQ at respective timepoints per vaccine group for all antigens); LLOQ = lower limit of quantitation.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.
Exact confidence intervals are based on Clopper-Pearson method.
Source: Table 14.2.2.7 (28DEC2023) Table 14.2.2.8 (17JAN2024)

Percentages of participants with 4-fold rise in hSBA titers

Table 10 summarizes the percentages of participants with 4-fold rise against each N. meningitidis serogroup B indicator strain after second vaccination for the ABCWY group.

The overall percentages of participants with 4-fold rise against each serogroup B indicator strain ranged from 45.7% to 90.1% in the ABCWY group at Month 7.

Table 10: Percentages of participants with 4-fold rise in hSBA titers against each N. meningitidis serogroup B indicator 1 month after last vaccination for ABCWY group (Day 211) (full analysis set)

			ABCWY		
MenB antigen	**Timepoint**	**Four-fold increase**	**N**	**n (%)**	**95% CI**
fHbp	[redacted]				
	Month 7	Four-fold increase, overall	163	111 (68.1)	(60.35, 75.17)
		Four-fold increase, pre < LOD	152	108 (71.1)	(63.15, 78.11)
		Four-fold increase, LOD ≤ pre < LLOQ	0	0	(NE, NE)
		Four-fold increase, pre ≥ LLOQ	11	3 (27.3)	(6.02, 60.97)
NadA	[redacted]				
	Month 7	Four-fold increase, overall	162	146 (90.1)	(84.46, 94.25)
		Four-fold increase, pre < LOD	133	121 (91.0)	(84.77, 95.25)
		Four-fold increase, LOD ≤ pre < LLOQ	17	17 (100.0)	(80.49, 100.00)
		Four-fold increase, pre ≥ LLOQ	12	8 (66.7)	(34.89, 90.08)
NHBA	[redacted]				
	Month 7	Four-fold increase, overall	161	104 (64.6)	(56.68, 71.96)
		Four-fold increase, pre < LOD	129	85 (65.9)	(57.03, 74.01)
		Four-fold increase, LOD ≤ pre < LLOQ	0	0	(NE, NE)
		Four-fold increase, pre ≥ LLOQ	32	19 (59.4)	(40.64, 76.30)
PorA P1.4	[redacted]				
	Month 7	Four-fold increase, overall	162	74 (45.7)	(37.84, 53.68)
		Four-fold increase, pre < LOD	159	73 (45.9)	(37.99, 53.99)
		Four-fold increase, LOD ≤ pre < LLOQ	0	0	(NE, NE)
		Four-fold increase, pre ≥ LLOQ	3	1 (33.3)	(0.84, 90.57)

Abbreviations: hSBA = human serum bactericidal assay; N = number of participants in each vaccine group with available results (which additionally satisfy the baseline (pre) criteria, where applicable); n = number of participants with 4-fold rise in hSBA titer at respective timepoints; NE = not estimable; LOD = limit of detection; LLOQ = lower limit of quantitation.

ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.

ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and 2 doses of MenB at Months 6 and 7.

Exact confidence intervals are based on Clopper-Pearson method.

For participants with a baseline titer less than LOD, a four-fold increase is relative to LOD. For participants with a baseline titer greater than or equal to LOD but less than LLOQ, a four-fold increase is relative to LLOQ.

Source: Table 14.2.2.6 (28DEC2023)

Table 11 summarizes geometric mean hSBA titers and geometric mean hSBA ratios at baseline, and 1 month after last vaccination for ABCWY. The hSBA GMTs against each serogroup B indicator strain were

low and increased following each vaccination. The GMT ranges were 2.84 to 8.62 at baseline, , and 11.44 to 143.61 for 1 month after last vaccination., a fold increase in hSBA GMTs at 1 month after MenABCWY last vaccination compared to baseline ranging from 161 to 163 was observed.

Table 11: Geometric Mean hSBA titers for each N.meningitidis serogroup B indicator strains and Geometric Mean Ratio at pre-vaccination (Day 1), and 1 month after last vaccination for ABCWY group (Day 211) (Full analysis set)

			ABCWY		
MenB antigen	Timepoint		n	Value	95% CI
fHbp	Baseline	N	184		
		GMT		2.84	(2.53, 3.19)
[redacted]					
	Month 7	N	165		
		GMT		17.56	(13.52, 22.80)
[redacted]					
	Month 7 / Baseline	N	163		
		GMR		6.29	(4.84, 8.18)
NadA	Baseline	N	183		
		GMT		8.62	(7.39, 10.06)
[redacted]					
	Month 7	N	165		
		GMT		143.61	(106.71, 193.26)
[redacted]					
	Month 7 / Baseline	N	162		
		GMR		16.67	(12.25, 22.70)
NHBA	Baseline	N	183		
		GMT		3.28	(2.59, 4.15)
[redacted]					
	Month 7	N	164		
		GMT		24.82	(19.19, 32.11)
[redacted]					
	Month 7 / Baseline	N	161		
		GMR		7.69	(6.08, 9.72)
PorA P1.4	Baseline	N	184		
		GMT		3.13	(2.86, 3.43)
[redacted]					
	Month 7	N	164		
		GMT		11.44	(8.61, 15.19)
[redacted]					
	Month 7 / Baseline	N	162		
		GMR		3.65	(2.76, 4.83)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; N = number of participants with hSBA titers at the timepoint.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
GMT and 95% CI of the log-transformed titers obtained from an ANOVA with a factor of country.
Source: Table 14.2.2.4 (28DEC2023)

Examination of Subgroups

Subgroup Analysis: MenABCWY vs. MenACWY (Family 1)
Percentages of participants with 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W, and Y were comparable within each subgroup analysis.
Subgroup Analysis: MenABCWY vs. MenACWY (Family 2)
Percentages of participants with 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W, and Y were comparable within each subgroup analysis.

MAH Immunogenicity Conclusions

- Primary objectives were met as non-inferiority was demonstrated following both first and second dose of MenABCWY administered in a 0,6-month schedule, compared to a single dose of MenACWY in participants previously primed with MenACWY.
- The MenABCWY vaccine induced a robust immune response as shown by GMTs percentages with participants with hSBA titers ≥LLOQ, and the percentages with participants achieving 4-fold rise of hSBA titers against serogroups A, C, W, and Y after first and second dose, and each serogroup B indicator strains after the second dose.

Safety results

Solicited Events

Systemic Events

- After each vaccination with MenABCWY in the ABCWY group, fatigue and headache were the most commonly reported solicited systemic events. Fatigue was reported by 40.1% and 33.1% after vaccination 1 and vaccination 2, respectively, and headache was reported in 41.0% and 33.1% of participants after vaccination 1 and vaccination 2, respectively. Severe fatigue was reported in 1.2% and 2.4% of participants after MenABCWY vaccination 1 and vaccination 2, respectively. Severe headache was reported in 1.2% and 1.4% of participants after MenABCWY vaccination 1 and vaccination 2, respectively.
- Fatigue and headache were also the most common solicited systemic events reported after vaccination 1 in the ACWY group. Fatigue was reported by 37.0% of participants, and headache was reported by 34.6% of participants. Severe fatigue was reported by 0.5% of participants, and severe headache was reported by 0.7% of participants, after vaccination 1.
- Most of the other solicited systemic events were mild to moderate in intensity. Severe solicited systemic events were reported in ≤2.9% of participants across study groups.
- Fever (defined as body temperature ≥38.0°C) was reported by 2.0% and 1.8% of participants in the ABCWY group after vaccination 1 and vaccination 2, respectively, and by 1.2% of participants in ACWY group after vaccination 1. Severe fever (defined as body temperature ≥40.0°C) was reported by 0.2% and 0.4% of participants after vaccination 1 and vaccination 2, respectively, in the ABCWY group and by 0.2% of participants in the ACWY group after both vaccination 1 and vaccination 2.

Other Indicators of Reactogenicity

- The first onset of solicited events in majority of participants was reported from Day 1 through Day 3 following any vaccination, across study groups and the mean duration was less than 4 days for any solicited administration site or systemic event.

- Within 7 days following any vaccination, prophylactic analgesic/antipyretic medications were taken by 24.3% of participants in ABCWY group, and 13.5% of participants in ACWY group. Analgesic/antipyretics were taken for treatment of pain or fever after any vaccination by 35.8% of participants in ABCWY group and 24.2% of participants in ACWY group. Most of the medication for these indications were taken from Day 1 through Day 3 following each vaccination, within the 7-day follow-up period. Table 12 below illustrates the local and systemic events Day 1-7 after each vaccination.

Table 12: Participants with Solicited Administration Site Events or Solicited Systemic Events Reported from Day y to Day 7 following each vaccination and overall (solicited safety set)

		ABCWY		ACWY	
		n (%)	95% CI	n (%)	95% CI
Vaccination 1	N	626		621	
	Any solicited event	529 (84.5)	(81.43, 87.25)	372 (59.9)	(55.93, 63.78)
	Any solicited administration site event	488 (78.0)	(74.50, 81.14)	197 (31.7)	(28.08, 35.54)
	Injection site pain				
	n	608		601	
	Any	486 (79.9)	(76.53, 83.05)	191 (31.8)	(28.07, 35.67)
	Mild	233 (38.3)	(34.44, 42.32)	155 (25.8)	(22.34, 29.48)
	Moderate	234 (38.5)	(34.60, 42.48)	34 (5.7)	(3.95, 7.82)
	Severe	19 (3.1)	(1.89, 4.84)	2 (0.3)	(0.04, 1.20)
	None	122 (20.1)	(16.95, 23.47)	410 (68.2)	(64.33, 71.93)
	Missing	18 (3.0)	(1.76, 4.64)	20 (3.3)	(2.04, 5.09)
	Erythema (mm)				
	n	608		600	
	Any (≥25mm)	29 (4.8)	(3.22, 6.78)	9 (1.5)	(0.69, 2.83)
	25-50mm	13 (2.1)	(1.14, 3.63)	6 (1.0)	(0.37, 2.16)
	51-100mm	13 (2.1)	(1.14, 3.63)	3 (0.5)	(0.10, 1.45)
	>100mm	3 (0.5)	(0.10, 1.44)	0	(0.00, 0.61)
	None	579 (95.2)	(93.22, 96.78)	591 (98.5)	(97.17, 99.31)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Swelling (mm)				
	n	608		600	
	Any (≥25mm)	26 (4.3)	(2.81, 6.20)	13 (2.2)	(1.16, 3.68)
	25-50mm	16 (2.6)	(1.51, 4.24)	8 (1.3)	(0.58, 2.61)
	51-100mm	8 (1.3)	(0.57, 2.58)	3 (0.5)	(0.10, 1.45)
	>100mm	2 (0.3)	(0.04, 1.18)	2 (0.3)	(0.04, 1.20)
	None	582 (95.7)	(93.80, 97.19)	587 (97.8)	(96.32, 98.84)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Induration (mm)				
	n	608		600	
	Any (≥25mm)	24 (3.9)	(2.55, 5.82)	14 (2.3)	(1.28, 3.88)
	25-50mm	11 (1.8)	(0.91, 3.21)	12 (2.0)	(1.04, 3.47)
	51-100mm	4 (0.7)	(0.18, 1.68)	1 (0.2)	(0.00, 0.93)
	>100mm	9 (1.5)	(0.68, 2.79)	1 (0.2)	(0.00, 0.93)
	None	584 (96.1)	(94.18, 97.45)	586 (97.7)	(96.12, 98.72)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Any solicited systemic event	369 (58.9)	(54.98, 62.83)	320 (51.5)	(47.52, 55.53)
	Fever (≥38°C/100.4°F)				
	n	608		600	
	Any	12 (2.0)	(1.02, 3.42)	7 (1.2)	(0.47, 2.39)
	38.0 - 38.9 °C	8 (1.3)	(0.57, 2.58)	6 (1.0)	(0.37, 2.16)
	39.0 - 39.9 °C	3 (0.5)	(0.10, 1.44)	0	(0.00, 0.61)
	≥40 C	1 (0.2)	(0.00, 0.91)	1 (0.2)	(0.00, 0.93)
	None	596 (98.0)	(96.58, 98.98)	593 (98.8)	(97.61, 99.53)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Nausea				
	n	608		600	
	Any	88 (14.5)	(11.77, 17.52)	75 (12.5)	(9.96, 15.42)
	Mild	60 (9.9)	(7.62, 12.52)	50 (8.3)	(6.25, 10.84)
	Moderate	25 (4.1)	(2.68, 6.01)	21 (3.5)	(2.18, 5.30)
	Severe	3 (0.5)	(0.10, 1.44)	4 (0.7)	(0.18, 1.70)
	None	520 (85.5)	(82.48, 88.23)	525 (87.5)	(84.58, 90.04)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)

	Fatigue				
	n	608		600	
	Any	244 (40.1)	(36.21, 44.15)	222 (37.0)	(33.13, 41.00)
	Mild	157 (25.8)	(22.39, 29.50)	144 (24.0)	(20.63, 27.62)
	Moderate	80 (13.2)	(10.57, 16.11)	75 (12.5)	(9.96, 15.42)
	Severe	7 (1.2)	(0.46, 2.36)	3 (0.5)	(0.10, 1.45)
	None	364 (59.9)	(55.85, 63.79)	378 (63.0)	(59.00, 66.87)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Myalgia				
	n	608		600	
	Any	90 (14.8)	(12.07, 17.88)	66 (11.0)	(8.61, 13.78)
	Mild	62 (10.2)	(7.91, 12.88)	48 (8.0)	(5.96, 10.47)
	Moderate	27 (4.4)	(2.95, 6.40)	16 (2.7)	(1.53, 4.29)
	Severe	1 (0.2)	(0.00, 0.91)	2 (0.3)	(0.04, 1.20)
	None	518 (85.2)	(82.12, 87.93)	534 (89.0)	(86.22, 91.39)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Arthralgia				
	n	608		600	
	Any	45 (7.4)	(5.45, 9.78)	49 (8.2)	(6.10, 10.65)
	Mild	36 (5.9)	(4.18, 8.10)	32 (5.3)	(3.68, 7.45)
	Moderate	9 (1.5)	(0.68, 2.79)	17 (2.8)	(1.66, 4.50)
	Severe	0	(0.00, 0.60)	0	(0.00, 0.61)
	None	563 (92.6)	(90.22, 94.55)	551 (91.8)	(89.35, 93.90)
	Missing	18 (3.0)	(1.76, 4.64)	21 (3.5)	(2.18, 5.30)
	Headache				
	n	608		601	
	Any	249 (41.0)	(37.02, 44.98)	208 (34.6)	(30.81, 38.56)
Vaccination 2	N	571		562	
	Any solicited event	405 (70.9)	(67.01, 74.62)	431 (76.7)	(72.97, 80.13)
	Any solicited administration site event	378 (66.2)	(62.16, 70.07)	402 (71.5)	(67.60, 75.23)
	Injection site pain				
	n	507		510	
	Any	377 (74.4)	(70.32, 78.11)	401 (78.6)	(74.81, 82.11)
	Mild	195 (38.5)	(34.21, 42.85)	192 (37.6)	(33.43, 42.01)
	Moderate	167 (32.9)	(28.86, 37.22)	198 (38.8)	(34.57, 43.21)
	Severe	15 (3.0)	(1.67, 4.83)	11 (2.2)	(1.08, 3.83)
	None	130 (25.6)	(21.89, 29.68)	109 (21.4)	(17.89, 25.19)
	Missing	64 (12.6)	(9.86, 15.83)	52 (10.2)	(7.71, 13.16)
	Erythema (mm)				
	n	505		506	
	Any (≥25mm)	31 (6.1)	(4.21, 8.60)	22 (4.3)	(2.74, 6.51)
	25-50mm	22 (4.4)	(2.75, 6.52)	16 (3.2)	(1.82, 5.08)
	51-100mm	6 (1.2)	(0.44, 2.57)	5 (1.0)	(0.32, 2.29)
	>100mm	3 (0.6)	(0.12, 1.73)	1 (0.2)	(0.01, 1.10)
	None	474 (93.9)	(91.40, 95.79)	484 (95.7)	(93.49, 97.26)
	Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
	Swelling (mm)				
	n	505		507	
	Any (≥25mm)	30 (5.9)	(4.04, 8.37)	26 (5.1)	(3.38, 7.42)

25-50mm	22 (4.4)	(2.75, 6.52)	18 (3.6)	(2.12, 5.55)
51-100mm	5 (1.0)	(0.32, 2.30)	7 (1.4)	(0.56, 2.82)
>100mm	3 (0.6)	(0.12, 1.73)	1 (0.2)	(0.00, 1.09)
None	475 (94.1)	(91.63, 95.96)	481 (94.9)	(92.58, 96.62)
Missing	66 (13.1)	(10.25, 16.33)	55 (10.8)	(8.28, 13.89)
Induration (mm)				
n	505		506	
Any (≥25mm)	22 (4.4)	(2.75, 6.52)	27 (5.3)	(3.55, 7.67)
25-50mm	17 (3.4)	(1.97, 5.34)	21 (4.2)	(2.59, 6.27)
51-100mm	2 (0.4)	(0.05, 1.42)	4 (0.8)	(0.22, 2.01)
>100mm	3 (0.6)	(0.12, 1.73)	2 (0.4)	(0.05, 1.42)
None	483 (95.6)	(93.48, 97.25)	479 (94.7)	(92.33, 96.45)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Any solicited systemic event	253 (44.3)	(40.18, 48.49)	266 (47.3)	(43.14, 51.55)
Fever (≥38°C/100.4°F)				
n	505		506	
Any	9 (1.8)	(0.82, 3.36)	9 (1.8)	(0.82, 3.35)
38.0 - 38.9 °C	6 (1.2)	(0.44, 2.57)	5 (1.0)	(0.32, 2.29)
39.0 - 39.9 °C	1 (0.2)	(0.01, 1.10)	3 (0.6)	(0.12, 1.72)
≥40 C	2 (0.4)	(0.05, 1.42)	1 (0.2)	(0.01, 1.10)
None	496 (98.2)	(96.64, 99.18)	497 (98.2)	(96.65, 99.18)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Nausea				
n	505		506	
Any	58 (11.5)	(8.84, 14.59)	65 (12.8)	(10.06, 16.08)
Mild	42 (8.3)	(6.06, 11.08)	47 (9.3)	(6.90, 12.16)
Moderate	11 (2.2)	(1.09, 3.86)	11 (2.2)	(1.09, 3.86)
Severe	5 (1.0)	(0.32, 2.30)	7 (1.4)	(0.56, 2.83)
None	447 (88.5)	(85.41, 91.16)	441 (87.2)	(83.92, 89.94)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Fatigue				
n	505		506	
Any	167 (33.1)	(28.98, 37.36)	180 (35.6)	(31.40, 39.92)
Mild	93 (18.4)	(15.13, 22.08)	114 (22.5)	(18.96, 26.42)
Moderate	62 (12.3)	(9.54, 15.46)	54 (10.7)	(8.12, 13.69)
Severe	12 (2.4)	(1.23, 4.11)	12 (2.4)	(1.23, 4.11)
None	338 (66.9)	(62.64, 71.02)	326 (64.4)	(60.08, 68.60)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Myalgia				
n	505		506	
Any	67 (13.3)	(10.43, 16.54)	62 (12.3)	(9.52, 15.43)
Mild	44 (8.7)	(6.40, 11.52)	46 (9.1)	(6.73, 11.94)
Moderate	21 (4.2)	(2.59, 6.29)	12 (2.4)	(1.23, 4.11)
Severe	2 (0.4)	(0.05, 1.42)	4 (0.8)	(0.22, 2.01)
None	438 (86.7)	(83.46, 89.57)	444 (87.7)	(84.57, 90.48)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Arthralgia				
n	505		506	
Any	30 (5.9)	(4.04, 8.37)	32 (6.3)	(4.37, 8.81)
Mild	21 (4.2)	(2.59, 6.29)	18 (3.6)	(2.12, 5.56)
Moderate	8 (1.6)	(0.69, 3.10)	11 (2.2)	(1.09, 3.86)
Severe	1 (0.2)	(0.01, 1.10)	3 (0.6)	(0.12, 1.72)
None	475 (94.1)	(91.63, 95.96)	474 (93.7)	(91.19, 95.63)
Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)

	Headache				
	n	505		506	
	Any	167 (33.1)	(28.98, 37.36)	169 (33.4)	(29.30, 37.70)
	Mild	112 (22.2)	(18.63, 26.06)	119 (23.5)	(19.89, 27.46)
	Moderate	48 (9.5)	(7.09, 12.40)	42 (8.3)	(6.05, 11.05)
	Severe	7 (1.4)	(0.56, 2.84)	8 (1.6)	(0.68, 3.09)
	None	338 (66.9)	(62.64, 71.02)	337 (66.6)	(62.30, 70.70)
	Missing	66 (13.1)	(10.25, 16.33)	56 (11.1)	(8.47, 14.13)
Any Vaccination	N	626		621	
	Any solicited event	556 (88.8)	(86.08, 91.18)	522 (84.1)	(80.94, 86.85)
	Any solicited administration site event	521 (83.2)	(80.07, 86.07)	447 (72.0)	(68.27, 75.48)
	Injection site pain				
	n	615		611	
	Any	519 (84.4)	(81.28, 87.17)	446 (73.0)	(69.29, 76.48)
	Mild	195 (31.7)	(28.04, 35.55)	219 (35.8)	(32.04, 39.79)
	Moderate	291 (47.3)	(43.31, 51.35)	214 (35.0)	(31.24, 38.95)
	Severe	33 (5.4)	(3.72, 7.45)	13 (2.1)	(1.14, 3.61)
	None	96 (15.6)	(12.83, 18.72)	165 (27.0)	(23.52, 30.71)
	Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
	Erythema (mm)				
	n	615		611	
	Any (≥25mm)	52 (8.5)	(6.38, 10.94)	27 (4.4)	(2.93, 6.36)
	25-50mm	29 (4.7)	(3.18, 6.70)	18 (2.9)	(1.76, 4.62)
	51-100mm	17 (2.8)	(1.62, 4.39)	8 (1.3)	(0.57, 2.56)
	>100mm	6 (1.0)	(0.36, 2.11)	1 (0.2)	(0.00, 0.91)
	None	563 (91.5)	(89.06, 93.62)	584 (95.6)	(93.64, 97.07)
	Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
	Swelling (mm)				
	n	615		611	
	Any (≥25mm)	46 (7.5)	(5.53, 9.85)	34 (5.6)	(3.88, 7.69)
	25-50mm	30 (4.9)	(3.32, 6.89)	22 (3.6)	(2.27, 5.40)
	51-100mm	12 (2.0)	(1.01, 3.38)	9 (1.5)	(0.68, 2.78)
	>100mm	4 (0.7)	(0.18, 1.66)	3 (0.5)	(0.10, 1.43)
	None	569 (92.5)	(90.15, 94.47)	577 (94.4)	(92.31, 96.12)
	Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
	Induration (mm)				
	n	615		611	
	Any (≥25mm)	42 (6.8)	(4.97, 9.12)	36 (5.9)	(4.16, 8.06)
	25-50mm	27 (4.4)	(2.91, 6.32)	28 (4.6)	(3.07, 6.56)
	51-100mm	5 (0.8)	(0.26, 1.89)	5 (0.8)	(0.27, 1.90)
	>100mm	10 (1.6)	(0.78, 2.97)	3 (0.5)	(0.10, 1.43)
	None	573 (93.2)	(90.88, 95.03)	575 (94.1)	(91.94, 95.84)
	Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
	Any solicited systemic event	427 (68.2)	(64.40, 71.85)	404 (65.1)	(61.16, 68.81)
	Fever (≥38°C/100.4°F)				
	n	615		611	
	Any	19 (3.1)	(1.87, 4.78)	15 (2.5)	(1.38, 4.02)
	38.0 - 38.9 °C	12 (2.0)	(1.01, 3.38)	10 (1.6)	(0.79, 2.99)
	39.0 - 39.9 °C	4 (0.7)	(0.18, 1.66)	3 (0.5)	(0.10, 1.43)
	≥40 C	3 (0.5)	(0.10, 1.42)	2 (0.3)	(0.04, 1.18)
	None	596 (96.9)	(95.22, 98.13)	596 (97.5)	(95.98, 98.62)
	Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
	Nausea				
	n	615		611	

Any	130 (21.1)	(17.98, 24.58)	123 (20.1)	(17.02, 23.53)
Mild	89 (14.5)	(11.79, 17.50)	84 (13.7)	(11.12, 16.74)
Moderate	33 (5.4)	(3.72, 7.45)	29 (4.7)	(3.20, 6.75)
Severe	8 (1.3)	(0.56, 2.55)	10 (1.6)	(0.79, 2.99)
None	485 (78.9)	(75.42, 82.02)	488 (79.9)	(76.47, 82.98)
Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
Fatigue				
n	615		611	
Any	310 (50.4)	(46.38, 54.43)	289 (47.3)	(43.28, 51.35)
Mild	173 (28.1)	(24.61, 31.86)	165 (27.0)	(23.52, 30.71)
Moderate	119 (19.3)	(16.30, 22.70)	109 (17.8)	(14.88, 21.11)
Severe	18 (2.9)	(1.74, 4.59)	15 (2.5)	(1.38, 4.02)
None	305 (49.6)	(45.57, 53.62)	322 (52.7)	(48.65, 56.72)
Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
Myalgia				
n	615		611	
Any	134 (21.8)	(18.59, 25.26)	109 (17.8)	(14.88, 21.11)
Mild	86 (14.0)	(11.34, 16.98)	77 (12.6)	(10.07, 15.50)
Moderate	45 (7.3)	(5.39, 9.67)	26 (4.3)	(2.80, 6.17)
Severe	3 (0.5)	(0.10, 1.42)	6 (1.0)	(0.36, 2.13)
None	481 (78.2)	(74.74, 81.41)	502 (82.2)	(78.89, 85.12)
Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
Arthralgia				
n	615		611	
Any	66 (10.7)	(8.40, 13.45)	74 (12.1)	(9.63, 14.96)
Mild	48 (7.8)	(5.81, 10.22)	44 (7.2)	(5.28, 9.55)
Moderate	17 (2.8)	(1.62, 4.39)	27 (4.4)	(2.93, 6.36)
Severe	1 (0.2)	(0.00, 0.90)	3 (0.5)	(0.10, 1.43)
None	549 (89.3)	(86.55, 91.60)	537 (87.9)	(85.04, 90.37)
Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)
Headache				
n	615		611	
Any	316 (51.4)	(47.35, 55.40)	288 (47.1)	(43.12, 51.18)
Mild	201 (32.7)	(28.99, 36.55)	194 (31.8)	(28.07, 35.61)
Moderate	101 (16.4)	(13.58, 19.59)	82 (13.4)	(10.82, 16.38)
Severe	14 (2.3)	(1.25, 3.79)	12 (2.0)	(1.02, 3.41)
None	299 (48.6)	(44.60, 52.65)	323 (52.9)	(48.82, 56.88)
Missing	11 (1.8)	(0.90, 3.18)	10 (1.6)	(0.79, 2.99)

Abbreviations: mm = millimeters; N = number of participants in each vaccine group at the timepoint; n = number of participants documenting presence or absence of the event at the timepoint.
ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Participants can have multiple administration site events and multiple events within an event type but will only be counted once at the worst severity.
Participants can have multiple systemic events and multiple events within an event type but will only be counted once at the worst severity.
Percentages are based on n, the number of participants documenting absence or presence of each event.
The CRF data, collected at 30 minutes post vaccination, are not included in this summary.
Exact confidence intervals are based on Clopper-Pearson method.
Source: Table 14.3.1.2 (28DEC2023)

Frequency of reported solicited events within 30 min are described in Table 13 below.

Table 13: Participants with solicited Events for each solicited event type, within 30 minutes following each vaccination and overall solicited safety set

		ABCWY		ACWY	
		n (%)	95% CI	n (%)	95% CI
Vaccination 1	N	626		621	
	Any solicited event	65 (10.4)	(8.11,13.04)	52 (8.4)	(6.32,10.84)
	Any solicited administration site event	50 (8.0)	(5.99,10.39)	44 (7.1)	(5.20, 9.40)
	Any solicited systemic event	21 (3.4)	(2.09, 5.08)	12 (1.9)	(1.00, 3.35)
Vaccination 2	N	571		562	
	Any solicited event	56 (9.8)	(7.49,12.55)	50 (8.9)	(6.68,11.56)
	Any solicited administration site event	51 (8.9)	(6.72,11.58)	41 (7.3)	(5.29, 9.77)
	Any solicited systemic event	13 (2.3)	(1.22, 3.86)	12 (2.1)	(1.11, 3.70)
Any Vaccination	N	626		621	
	Any solicited event	106 (16.9)	(14.08,20.10)	93 (15.0)	(12.26,18.03)
	Any solicited administration site event	88 (14.1)	(11.49,17.03)	79 (12.7)	(10.20,15.60)
	Any solicited systemic event	32 (5.1)	(3.52, 7.14)	22 (3.5)	(2.23, 5.31)

ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7. ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
N = Number of participants in the study at the timepoint.
Percentages are based on N.
Exact confidence intervals are based on Clopper-Pearson method.

Unsolicited Adverse Events

During the 30-day post-vaccination period following any vaccination (Table 14):

- At least one unsolicited AE was reported by 24.0% and 24.2% of participants in the ABCWY and ACWY groups, respectively, after any vaccination. Unsolicited AEs assessed as causally related to vaccination by the investigator were reported by 2.9% and 5.0% of participants in the ABCWY and ACWY groups, respectively. At least one unsolicited SAE was reported by 0.6% of participants in the ABCWY group and 0.2% of participants in the ACWY group. At least one unsolicited adverse event leading to premature withdrawal from the study was reported by 0.3% and 0.5% of participants in the ABCWY and ACWY groups, respectively.
- The most commonly reported unsolicited AEs were classified under the SOC Infections and Infestations (9.9% and 9.3% of participants across the study groups, respectively). The most commonly reported unsolicited AEs in the ABCWY group, by PT, were COVID-19 (reported by 3.5% of participants) and headache (reported by 1.8% of participants). The most commonly reported unsolicited AEs in the ACWY group, by PT, were COVID-19 (reported by 3.1% of participants) and oropharyngeal pain (1.6% of participants).
- Most of the unsolicited AEs were mild to moderate in intensity and resolved before the end of the study.
- Unsolicited AEs assessed as related to vaccination by investigator within first 30 days following each vaccination were reported by 2.2% and 2.1% of participants in ABCWY and ACWY groups, respectively. The most commonly reported causally related unsolicited AEs, by PT, were lymphadenopathy, dizziness, abdominal pain, diarrhea, and myalgia. The majority of the AEs that were considered related to vaccination by the investigator happened within the first 7 days.

Table 14: Summary of participants wint unsolicited adverse events wit onset within 30 days after any vaccination

Unsolicited AE category	ABCWY (N=626) n (%)	ACWY (N=621) n (%)	Total (N=1247) n (%)
At least one unsolicited adverse event	150 (24.0)	150 (24.2)	300 (24.1)
At least one related unsolicited adverse event	18 (2.9)	31 (5.0)	49 (3.9)
At least one fatal unsolicited adverse event	0	0	0
At least one related fatal unsolicited adverse event	0	0	0
At least one unsolicited SAE	4 (0.6)	1 (0.2)	5 (0.4)
At least one related unsolicited SAE	0	0	0
At least one unsolicited adverse event leading to premature withdrawal from the study	2 (0.3)	3 (0.5)	5 (0.4)
At least one related unsolicited adverse event leading to premature withdrawal from the study	1 (0.2)	1 (0.2)	2 (0.2)
At least one unsolicited AESI	0	1 (0.2)	1 (0.1)
At least one related unsolicited AESI	0	0	0
At least one medically attended unsolicited adverse event	82 (13.1)	77 (12.4)	159 (12.8)
At least one related medically attended unsolicited adverse event	7 (1.1)	11 (1.8)	18 (1.4)

Abbreviations: AE = adverse event; AESI = AE of special interest; eCRF = electronic case report form; N = number of participants in each vaccine group.
ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.
Related is as assessed by the Investigator.
Leading to premature withdrawal from the study = AEs on the AE eCRF with Did the participant withdraw from study due to this event? = Yes or records on the Study Conclusion eCRF as participant discontinuing the study due to an Adverse Event
AESIs are recorded on the Expedited AE report.
Medically attended event = AEs on the AE eCRF with Medically attended visit = "Hospitalization", "Emergency room" or "Medical personnel".
Includes AEs with an onset date on or after the date of first vaccine only (i.e., not including those AEs after informed consent but before first vaccination).
Percentages are calculated based on the number of participants in the unsolicited safety analysis set per study vaccine group.
Source Table 14.3.2.1.2 (28DEC2023)

Table 15: Summary of participants with unsolicited adverse events during the entire study.

Unsolicited AE category	ABCWY (N=626) n (%)	ACWY (N=621) n (%)	Total (N=1247) n (%)
At least one unsolicited adverse event	266 (42.5)	264 (42.5)	530 (42.5)
At least one related unsolicited adverse event	21 (3.4)	32 (5.2)	53 (4.3)
At least one fatal unsolicited adverse event	1 (0.2)	1 (0.2)	2 (0.2)
At least one related fatal unsolicited adverse event	0	0	0
At least one unsolicited SAE	18 (2.9)	7 (1.1)	25 (2.0)
At least one related unsolicited SAE	0	0	0
At least one unsolicited adverse event leading to premature withdrawal from the study	4 (0.6)	6 (1.0)	10 (0.8)
At least one related unsolicited adverse event leading to premature withdrawal from the study	1 (0.2)	1 (0.2)	2 (0.2)
At least one unsolicited AESI	0	4 (0.6)	4 (0.3)
At least one related unsolicited AESI	0	0	0
At least one medically attended unsolicited adverse event	223 (35.6)	206 (33.2)	429 (34.4)
At least one related medically attended unsolicited adverse event	10 (1.6)	11 (1.8)	21 (1.7)

Abbreviations: AE = adverse event; AESI = AE of special interest; eCRF = electronic case report form; N = number of participants in each vaccine group.
ABCWY = participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7.
ACWY = participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.
Related is as assessed by the Investigator.
Leading to premature withdrawal from the study = AEs on the AE eCRF with Did the participant withdraw from study due to this event? = Yes or records on the Study Conclusion eCRF as participant discontinuing the study due to an Adverse Event
AESIs are recorded on the Expedited AE report.
Medically attended event = AEs on the AE eCRF with Medically attended visit = "Hospitalization", "Emergency room" or "Medical personnel".
Includes AEs with an onset date on or after the date of first vaccine only (i.e., not including those AEs after informed consent but before first vaccination).
Percentages are calculated based on the number of participants in the unsolicited safety analysis set per study vaccine group.
Events that occur after 30 days post-vaccination that are not medically attended and are not serious adverse events are not included in this summary.
Source Table 14.3.2.1 (28DEC2023)

Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events, and Other Clinically Relevant Adverse Events

Deaths

An unsolicited AE leading to death (completed suicide) was reported for 1 participant in each vaccine group. Both deaths were assessed as not causally related to the study vaccinations by the investigator.

Other Serious Adverse Events

Overall, there were 25 (2.0%) SAEs reported during the entire study with Infections and Infestations (0.6%) and Psychiatric Disorders (0.6%) with the most reports.
There were 4 SAEs (pilonidal disease; suicidal ideation; vomiting; wolf-parkinson-white syndrome) reported in the ABCWY group with onset within 30 days of vaccination 1 (none in the ACWY group); for vaccination 2, there was 1 SAE in the ACWY group within 30 days of vaccination (none in ABCWY group). No SAEs were assessed as causally related to the study vaccinations by the investigator.

Discontinuations Due to Adverse Events

During the entire study period, 6 participants were reported to have unsolicited AE leading to discontinuation or delay in study vaccination (2 participants in ABCWY group and 4 participants in ACWY group) and 1 of the unsolicited AEs (diarrhea) in the ACWY group was assessed by the investigator as causally related to study vaccination.

Summary of Participants with Unsolicited Adverse Events Leading to Discontinuation, or Delay in Study Vaccination, by System Organ Class and Preferred Term
Unsolicited Safety Set

System organ class MedDRA preferred term	ABCWY (N=626) n (%)	ACWY (N=621) n (%)	Total (N=1247) n (%)
Participants with any AE leading to discontinuation or delay in study vaccination	2 (0.3)	4 (0.6)	6 (0.5)
Psychiatric disorders	1 (0.2)	1 (0.2)	2 (0.2)
Bipolar disorder	0	1 (0.2)	1 (0.1)
Suicidal ideation	1 (0.2)	0	1 (0.1)
Nervous system disorders	1 (0.2)	0	1 (0.1)
Seizure	1 (0.2)	0	1 (0.1)
Syncope	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders	0	2 (0.3)	2 (0.2)
Colitis ulcerative	0	1 (0.2)	1 (0.1)
Diarrhoea	0	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	0	1 (0.2)	1 (0.1)
Arthritis	0	1 (0.2)	1 (0.1)

AE = Adverse event. MedDRA = Medical dictionary for regulatory activities. N = Number of participants in each vaccine group.
ABCWY = Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7. ACWY = Participants received 1 dose of MenACWY vaccine at Month 0 and two doses of MenB at Months 6 and 7.
Number (%) of participants with unsolicited AEs, sorted by international order for system organ class and alphabetically for preferred term.
Participants with multiple events in the same preferred term are counted only once in that preferred term.
Participants with events in more than one preferred term are counted once in each of those preferred terms.
Includes AEs with an onset date on or after the date of first vaccine only (i.e. not including those AEs after informed consent but before first vaccination).
Percentages are calculated based on the number of participants in the unsolicited safety analysis set per study vaccine group.
Note: Solicited events starting more than 7 days after the vaccination will also be considered as unsolicited AEs.
MedDRA version 26.0
Events that occur after 30 days post vaccination that are not medically attended and are not serious adverse events are not included in this summary.

Adverse Events of Special Interest

During the entire study, there were 4 AESIs (celiac disease, colitis ulcerative, Crohn's disease, and arthritis) reported in the ACWY group. Of these 4 AESIs, three (celiac's disease, Crohn's disease, and arthritis) were pre-existing chronic conditions and 1 new onset AESI of colitis ulcerative, which was reported within 30 days following the second vaccination. All were assessed as non-serious and none were causally related to study intervention as assessed by the investigator. There were no AESIs reported within 7 days of any vaccination.

Other Adverse Events

There were 5 pregnancies reported during this study. Three pregnancies were reported in the ABCWY group (1 spontaneous abortion and 2 were lost to follow-up) and 2 in the ACWY group (2 live births, 1 with congenital anomaly).

During the entire study, at least one unsolicited AE leading to a medically attended visit was reported by 35.6% and 33.2% of participants in the ABCWY and ACWY groups, respectively. The most commonly reported medically attended AEs were Infections and Infestations (17.7% and 17.9% of participants in each vaccine group) with COVID-19, anxiety, influenza, upper respiratory tract infection, and urinary tract infection being the most common PTs reported.

MAH Discussion

The MenABCWY vaccine study was a phase IIIB, randomized controlled, observer-blind study designed to demonstrate immunogenicity and safety when administered in healthy adolescents and adults, previously primed with MenACWY vaccine.
Overall, 1250 participants were enrolled in the study. Demographics were comparable across groups. A total of 58.5% of the enrolled participants were from centers in the US.
Protocol deviations were similar across study groups. A total of 96.6% of the Exposed Set were included in the FAS and 90.4% of participants from FAS were included in PPS at Visit 2, and 21.9% of participants in the ABCWY group were included in the PPS at Visit 4.
After the first and second vaccination, the co-primary immunological endpoints of non-inferiority of MenABCWY vaccine compared with MenACWY vaccine against N. meningitidis serogroups A, C, W, and Y given to healthy participants previously primed with MenACWY were demonstrated as the LL of the 2-sided 95% CI for the group differences in overall percentages for participants achieving a 4-fold rise in hSBA titers were above the pre-defined criterion of -10%.
Overall, a robust immune response was induced against each and all serogroup B indicator strains and

against serogroups A, C, W, and Y after vaccination with MenABCWY vaccine.
The MenABCWY vaccine was well-tolerated when given as 2-dose schedule in previously MenACWY-primed individuals.
As previously observed in other studies, reactogenicity was higher after MenABCWY compared to MenACWY, and is consistent with the one generally observed with Bexsero.
Pain, fatigue, and headache most commonly reported solicited events, and in similar rates of unsolicited AEs across both groups.
Subsequent dose of MenABCWY did not result in increase in AE reporting. None of the reported SAEs were considered related.

MAH Overall Conclusions

- Primary objectives were met as non-inferiority was demonstrated following both second and first dose of ABCWY administered in a 0,6-month schedule, compared to a single dose of MenACWY in participants previously primed with MenACWY.
- The MenABCWY vaccine induced a robust immune response against serogroups A, C, W and Y after first and second dose, and against each serogroup B indicator strains following the second dose.
- The MenABCWY vaccine was well-tolerated in the study with a favorable safety profile when administered in a 0,6-month schedule to participants previously primed with MenACWY.

2.3.3. Discussion on clinical aspects

Bexsero was authorized by EMA in 2013 for use in individuals from 2 months of age and older against invasive meningococcal disease caused by Neisseria meningitidis group B.

Study MENABCWY-019, study number 213171 is a phase IIIB, randomized, controlled, observer-blind study to evaluate safety and immunogenicity of the meningococcal ABCWY vaccine (n=626) and ACWY group (n=624) when administered to healthy adolescents and young adults 15-25 years of age (median 16 years), previously primed with meningococcal ACWY vaccine "Menveo". The study was executed in Argentina, Australia, Canada and US.

The subjects were randomized to either ABCWY group (2 doses at D1 and D181, and placebo at D211) or ACWY group (1 dose MenACWY "Menveo" at D1 and 2 doses MenB "Bexsero" vaccine at D 181 and 211). The first dose was administered to >99% of the participants and 1101 (88%) received the full vaccination course, the study was completed by 1083 (87%) of the participants. The most common reason for discontinuing the study was withdrawal by participant (4%). The most common deviation leading to elimination were visit schedule criteria (11%).

Efficacy:

The non-inferiority criteria were met when for 2-dose MenABCWY vs 1-dose MenACWY (Menveo) in subjects previously primed with a single dose Menveo, against N.meningitidis serogropus A,C, W and Y, which was the primary endpoint.

One secondary endpoint evaluated the immune response against serogroups A, C, W and Y, for which the hSBA titers ≥LLOQ ranged from 97.9% to 98.9% and from 99.5% to 100% for MenABCWY group at 1 month after first vaccination and last vaccination, respectively. For the ACWY group, the percentages ranged from 96.8% to 99% 1 month after vaccination.

Another secondary endpoint evaluated the immune response against N. meningitidis serogroup B indicator strains, where the percentages of participants in the ABCWY group with hSBA titers ≥LLOQ ranged from 2.7% to 20.2% at baseline, and 75.6% to 96.3% one month after the last vaccination in

the ABCWY group. The percentages of participants in the ABCWY group with hSBA titers ≥LLOQ for all serogroup B indicator strains (composite response) were 1.1%, and 72.0% at baseline, and Month 7, respectively. A 4-fold rise in hSBA titers against each serogroup B indicator strain ranged from 45.7% to 90.1% in the ABCWY group at Month 7. The hSBA GMTs against each serogroup B indicator strain were low at baseline and increased following each vaccination.

Safety:

After the first vaccination any solicited event was reported in 85% of the participants receiving ABCWY and among 23% of the participants receiving ACWY "Menveo". After the 2nd vaccination the frequency was 71% in the ABCWY group and 77% in the ACWY "Bexsero" group. Pain at injection site was the most frequent reported local reaction, reported at a frequency of 74-80% among the subjects that received ABCWY. The frequency in the ACWY group was 32% (Menveo) and 79% (Bexsero). In the ABCWY group fatigue (40% dose 1; 33% dose 2), headache (41% dose 1; 33% dose 2) and myalgia (15% dose 1; 13% dose 2) was the most reported systemic events. Fever was reported by 2% of the subjects after each dose of ABCWY. In the ACWY group fatigue was reported at 37% (Menveo) and 36% (Bexsero); headache 35%(Menveo) and 33%(Bexsero); myalgia 11% (Menveo) and 12% (Bexsero). Fever was reported at 1% (Menveo) and 2% (Bexsero) in the ACWY group.

Unsolicited events were reported by 24% of the subjects in both study groups. Unsolicited AEs considered related to vaccination was reported by 2% in each vaccine group, of which lymphadenopathy, dizziness, abdominal pain, diarrhoea and myalgia were the most commonly reported in the ACWY group. Lymphadenopathy and myalgia are already included in the product information of Bexsero, whereas dizziness, abdominal pain and diarrhoea are not described in section 4.8 of the SmPC. It is noted that the comparator vaccine has implemented dizziness in the SmPC. Even though the numbers are low, the MAH is asked to evaluate a possible association with Bexsero and dizziness, abdominal pain and diarrhoea in the next PSUR or upcoming type II variation. In addition, since fatigue was the most commonly reported systemic event in the ACWY group and not included in the SmPC, fatigue should also be taken into account in next PSUR or upcoming type II variation.

One event of suicide was reported in each study group. In the ABCWY group there were 4 SAEs reported after the 1st dose and none after the 2nd dose. Whereas in the ACWY group there was no SAE reported after dose 1 and one SAE after dose 2. None of the SAEs were considered related to vaccination. Four participants in the ACWY group discontinued the study due to AEs of which one (diarrhoea) was considered related to vaccination. In the ACWY groups there were 4 AESIs (celiac disease, colitis ulcerative, Crohn's disease, and arthritis) reported during the study, none of them were considered related to vaccination and all of them were non-serious.

3. CHMP overall conclusion and recommendation

In this phase IIIB study, non-inferiority was demonstrated following both second and first dose of ABCWY administered 6 months in between, compared to a single dose of MenACWY in subjects previously primed with MenACWY. The safety profile was in line with previous data for ACWY vaccines, except for fatigue, dizziness, abdominal pain and diarrhoea that were three of the most commonly reported unsolicited related events which are not included in the SmPC for Bexsero. Even though there are low numbers of subjects that reported these events, the MAH is requested to evaluate and address this in the next PSUR or type II variation, and if relevant also update the SmPC accordingly.

☒ **Fulfilled:**

No further action required within this procedure; however, the MAH is requested to evaluate possible association with vaccination and dizziness, abdominal pain and diarrhoea in next PSUR or type II variation.