Amsterdam, 22 June 2023
EMA/CHMP/202524/2023
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

International non-proprietary name: fHbp fusion protein, Neisseria meningitidis, serogroup B, recombinant, NadA protein, Neisseria meningitidis, serogroup B, recombinant, outer membrane vesicles (OMV), Neisseria meningitidis, serogroup B, strain NZ98/254, NHBA fusion protein, Neisseria meningitidis, serogroup B, recombinant

Procedure no.EMEA/H/C/002333/P46/032

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 7 March 2023, the MAH submitted a completed paediatric study for Bexsero, 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 MENB REC 2ND GEN-038 (V72_72), number 205416 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Meningococcal Group B vaccine (rMenB+OMV NZ; *Bexsero*): The formulation used in the study is the same as the commercially available formulation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

205416: A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.

The rMenB+OMV NZ vaccine was approved in the US under the accelerated approval regulation in 2015. As part of the post-approval requirements set forth by the guideline, the Company was required to conduct post-marketing confirmatory study V72_72 to verify and describe the clinical benefit of the vaccine by demonstrating vaccine effectiveness using serum bactericidal assay with endogenous human complement (enc-hSBA). Study V72_72 for the rMenB+OMV NZ vaccine was later merged with the Phase 3 study, planned at that time for GSK pentavalent investigational meningococcal vaccine, MenABCWY, that combines the same drug substances in the same amounts as included in the licensed MenACWY vaccine and the licensed rMenB+OMV NZ vaccine. During the protocol negotiations with US, GSK was required to include 3 rMenB+OMV NZ vaccine schedules, 0,2-months, 0,6-months and 0,2,6-months, along with the MenACWY vaccine as a control for vaccine effectiveness in the study.

Of note, Bexsero was the control vaccine for evaluation of objectives pertaining to the MenB component of the MenABCWY vaccine. Only results relevant to Bexsero will be described in this report.

2.3.2. Clinical study

205416: A phase III, randomized, controlled, observer-blind study to demonstrate effectiveness, immunogenicity and safety of GSK's meningococcal Group B and combined ABCWY vaccines when administered to healthy adolescents and young adults.

Description

Methods

Study participants

The study was conducted in healthy male and female adolescents and young adults 10 to 25 years of age at the time of the first vaccination.

Treatments

Participants were randomized to one of the 6 parallel study groups

- MenB_0_2_6 group: subjects received 3 doses of rMenB+OMV NZ vaccine (Bexsero) at Day 1, Day 61 and Day 181 (0,2,6-months schedule). These subjects received 1 dose of the MenACWY vaccine (Menveo) at Day 211. Data from this group was used to assess both the 0,2-months and 0,2,6-months schedules; the 0,2-months schedule was assessed 1 month after the second rMenB+OMV NZ vaccination administered at Day 61 (Visit 3), and the 0,2,6-months schedule was assessed 1 month after the third rMenB+OMV NZ vaccination at Day 181 (Visit 5), in the same group.

- MenB_0_6 group: subjects received 2 doses of rMenB+OMV NZ vaccine at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (rMenB+OMV NZvaccine, 0,6-months schedule). These subjects received 1 dose of placebo at Day 211.

- ABCWY-1: subjects received 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 1 of the MenACWY lyophilized vial component of the vaccine. They received 1 dose of placebo at Day 61 and at Day 211.

- ABCWY-2: subjects received 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilized vial component of the vaccine. They received 1 dose of placebo at Day 61 and at Day 211.

- ABCWY-3: subjects received 2 doses of MenABCWY vaccine 6 months apart (0,6-months schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilized vial component of the vaccine. They received 1 dose of placebo at Day 61 and at Day 211.

- ACWY group: subjects received 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of rMenB+OMV NZ at Day 181 and Day 211

The currently approved posology for Bexsero from 11 years of age is 2 doses at least one month apart. Thus, the most relevant group is the second from above in the list (MnB_0_6 group).

Objectives and Endpoints

Objectives and endpoints pertaining to rMenB+OMVNZ from the study V72_72 are presented below:

Primary	
Objectives	Endpoints
Vaccine effectiveness (Test-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc- hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6-months; 0,2-months) vaccination series when compared to 1 month after the MenACWY vaccination. *Criterion* *Lower limit (LL) of the two-sided 97.5% confidence interval (CI) for vaccine effectiveness is above 65% against a randomly selected strain panel between the:* • *MenB_0_2_6 and ACWY groups (for 0,2,6-months schedule)* • *MenB_0_6 and ACWY groups (for 0,6- months schedule),* • *MenB_0_2_6 and ACWY groups (for 0,2-months schedule)*	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains, at 1 month after the: • 3-dose vaccination series in MenB_0_2_6 group (Day 211, Month 7) • 2-dose vaccination series in MenB_0_6 group (Day 211, Month 7), and • 2-dose vaccination series in MenB_0_2_6 group (Day 91, Month 3) • 1 month after the MenACWY vaccination in ACWY group (Day 31, Month 1)
Effectiveness (Responder-based): rMenB+OMV NZ To demonstrate the effectiveness of the rMenB+OMV NZ vaccine by assessing the percentages of subjects whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0,2,6-months) and 2-dose (0,6- months; 0,2-months) vaccination series of the rMenB+OMV NZ. *Criterion:* *LL of the two-sided 97.5% CI for the percentages of subjects whose sera kill ≥70% of strains is above 65%, tested for:* • *MenB_0_2_6 group (for 0,2,6-months schedule)* • *MenB_0_6 group (for 0,6-months schedule),* • *MenB_0_2_6 group (for 0,2-months schedule)*	The percentages of subjects whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group), • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group)
The 3 vaccine schedules will be tested for both, test-based and responder-based, in a hierarchical way (starting from 0-2-6, to 0-6 and 0-2). Refer to Statistical methods for details on continuing the evaluation.	

Safety To evaluate the safety and reactogenicity of the MenB, MenABCWY, and the MenACWY Vaccines	• The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥ 38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The frequencies and percentages of subjects with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181. • The percentages of subjects with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period [Month 0 to Month 12].
	Secondary
To assess the effectiveness of the rMenB+OMV NZ and MenABCWY vaccines against each of the randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series when compared to 1 month after the MenACWY vaccination.	The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic US *N. meningitidis* serogroup B strains at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group) • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7), and • MenACWY vaccination (Day 31, Month 1 in ACWY group).
To describe the distribution of subjects by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the 3-dose (0,2,6-months in MenB_0_2_6 group) and 2-dose (0,6-months in MenB_0_6 group, 0,2-months in MenB_0_2_6 group and 0,6-months in the ABCWY (pooled) group) vaccination series of rMenB+OMV NZ and MenABCWY vaccines.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7)
To assess the immune response to the rMenB+OMV NZ (0,2,6-months, 0,6-months and 0,2-months) and MenABCWY (0,6-months) vaccines against *N. meningitidis* serogroup B, indicator strains at pre-vaccination (Day 1, Month 0) and at 1 month after the last MenABCWY vaccination and at 1 month after the second and third vaccination of rMenB+OMV NZ.	The immune response to the rMenB+OMV NZ and ABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following: 1. The percentages of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group)

	• 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) 2. The percentages of subjects with 4-fold rise** in hSBA titers at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 90, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7 relative to baseline (Day 1, Month 0). 3. hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) 4. hSBA GMRs at 1 month after the: • 3-dose vaccination series (Day 211, Month 7 in MenB_0_2_6 group) • 2-dose vaccination series (Day 211, Month 7 in MenB_0_6 group) • 2-dose vaccination series (Day 91, Month 3 in MenB_0_2_6 group), and • last vaccination for the ABCWY group (pooled lots) (Day 211, Month 7) relative to the baseline (Day 1, Month 0).

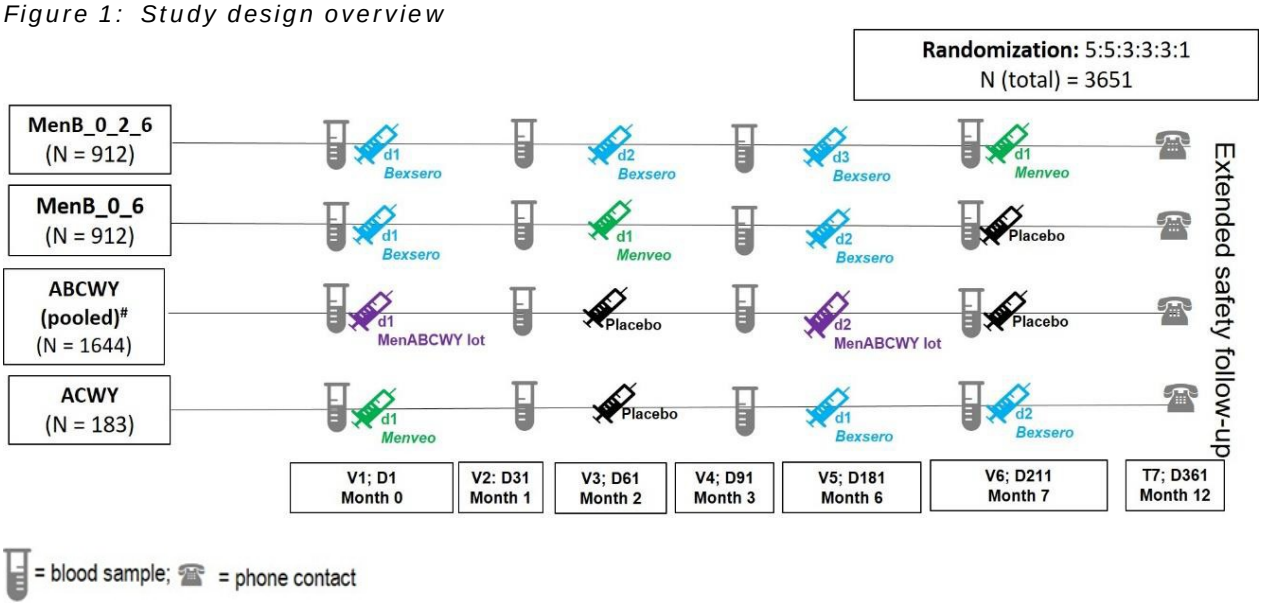
Sample size

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

Randomisation and blinding (masking)

This was a phase III, randomized, controlled, observer-blind, multicenter, self-contained study. Participants were randomized (5:5:3:3:3:1 ratio, Fig.1). Data were collected in an observer-blind manner. To do so, vaccine preparation and administration were done by qualified healthcare professional who did not participate in any of the study clinical evaluation. The serological data, which could have led lead to the unblinding of the study groups, were not available during the course of the study to any investigator or any person involved in the clinical conduct of the study or analysis.

Figure 1: Study design overview



N = number of subjects; d = dose; V = visit; D = day; T = telephone call;

Statistical Methods

Three thousand six hundred fifty-one (3,651) subjects were to be enrolled in the study with the breakdown of sample size per study arm according to the following:

- MenB_0_2_6: 912 subjects
- MenB_0_6: 912 subjects
- ABCWY-1: 548 subjects
- ABCWY-2: 548 subjects
- ABCWY-3: 548 subjects
- ACWY: 183 subjects.

It was assumed that 25% of the subjects would drop-out. The remaining subjects who would give an evaluable result would provide 90% power to reject all hypothesis for the primary objectives of rMenB+OMV NZ and 92% power to reject all hypotheses for the primary objectives of MenABCWY vaccine. Additionally, the study was powered to reject key secondary objective for three N. meningitidis serogroup B indicator strains (96217 (NadA), M14459 (fHbp), and M13520 (NHBA)) with 81% power.

Immunogenicity and effectiveness methods

Serum bactericidal activity is a functional measure of the ability of antibodies, in conjunction with human complement, to kill meningococci, and it is widely accepted as the serological surrogate marker for protection.

Effectiveness of the MenB component was evaluated with serum bactericidal assays using endogenous source of human complement (enc-hSBA), on a panel of 110 US representative N. meningitidis serogroup B invasive disease strains.

Immunogenicity of the vaccine against serogroups A, B, C, W and Y was evaluated by serum bactericidal assays using exogenous source of human complement (hSBAs), using indicator strains representing serogroups A, B, C, W and Y.

An Enzyme-Linked Immunosorbent Assay (ELISA), or equivalent, was used to evaluate the serotype-specific IgG responses to A, C, W, and Y. The intent was to characterize whether the immunogenicity measured by hSBA using the MenA, C, W and Y indicator strains may be confounded by the contribution of the responses against the MenB antigens of the combination vaccine. The ELISA procedure was used to detect the amount of serum immunoglobulin G (IgG) antibodies in response to specific N. meningitidis polysaccharide antigens.

Effectiveness testing by enc-hSBA and MenACWY immunogenicity testing by hSBA was prioritised over any other assays using exogenous source of human complement, or ELISA (or equivalent), based on the volume of serum available for a visit from one subject.

The methods for immunogenicity testing and estimation of effectiveness were similar to what was done in the studies assessed in the initial MAA, although a different strain panel and hSBA were used. The study report does not provide details regarding the strains used in the assays, and mostly the methods section of the study report refers to the study protocol.

Results

Participant flow and numbers analysed

A total of 3657 subjects were enrolled in the study. Overall, 3638 (99.5%) subjects received at least one dose of study vaccine. Of these, a total of 3333 (91.6%) subjects were included in the full analysis set (FAS), from which a total of 2994 (89.8%) subjects were included in the per protocol set (PPS). The most common reasons for elimination from PPS were out of window treatment administration (3.5%, overall) and out of window assessment for immunogenicity (3.0%, overall). A total of 370 subjects (10.2%) withdrew prematurely from the study. The most common reasons for premature withdrawal throughout the study were withdrawal of consent, not due to an (S)AE (4%, overall) and lost to follow-up (3.9%, overall). A total of 3619 (99.5%) and 3618 (99.5%) subjects were included in the Exposed Set for the Unsolicited Safety Set and Solicited Safety Set, respectively. No safety follow-up was the reason for the elimination of a few subjects from both these sets.

The participant flow is adequately described, and generally as expected in terms of drop-outs.

Baseline data

Demography and baseline characteristics were comparable across study groups.

- The mean age of subjects who participated in this study was 16.5 (SD, 4.7) years across groups. There was a slightly higher percentage of 10–17-year-olds (59.3%) than 18–25-year-olds (40.6%).
- Overall, 53.5% of enrolled subjects in the study were women.
- A total of 89% of subjects were of White heritage and the majority (93.7%) identified as Not Hispanic or Latino ethnicity.
- Thirty percent of the enrolled subjects were from US and the rest of the subjects were from Australia, Canada, Czechia, Estonia, Finland and Turkey.

Efficacy results

Primary confirmatory objectives:
Test-based and responder-based vaccine effectiveness (VE) of rMenB+OMV NZ vaccine were demonstrated against a randomly selected panel of endemic US *N. meningitidis* serogroup B invasive disease strains, as assessed by the endogenous hSBA (enc-hSBA), as the LL of the 2-sided 97.5% CI for VE was above the pre-defined criterion of 65%, whether administered as a 2-dose (2 or 6 months apart), or a 3-dose schedule (at 0, 2, and 6 months)
The estimated efficacy (97.5% CI) for each schedule were:
Test based (Per protocol set):
0, 2, 6 month schedule: 83.2 % (81,9%; 84.4%)
0,6 month schedule:81.8 % (80.4%;83.1%)
0,2 month schedule: 78.7 % (77.2%; 80.1%)

Responder based: (Full analysis set)
0, 2, 6 month schedule: 93.4 % (91.2%; 95.2%)
0,6 month schedule:89.8 % (87.2%;92.0%)
0,2 month schedule: 84.8 % (81.8%; 87.5%)

Secondary objectives:

- At baseline, the hSBA GMTs were low in MenB and ACWY groups and increased following the vaccinations in all groups.
- The overall percentages of subjects with 4-fold rise for serogroup B indicator strains fHbp, NadA, NHBA and PorA ranged from 56.5% to 98.7% for MenB_0_2_6 group (0,2,6-months schedule), 53.5% to 96.3% for MenB_0_2_6 group (0,2-months schedule) and 57.2% to 95.3% for MenB_0_6 group.
- The percentages of subjects with hSBA titers ≥LLOQ for serogroup B indicator strains ranged from 85.8% to 100% for MenB_0_2_6 group (0,2,6-months schedule), 80% to 99.5% for MenB_0_2_6 group (0,2-months schedule) and 82.6% to 98% for MenB_0_6 group.
- The percentages of subjects with hSBA titers ≥LLOQ for all serogroup B indicator strains (composite response) ranged from 75.5% to 83.3% for the rMenB+OMV NZ 3-dose and 2-dose schedules.

Efficacy conclusions

It is agreed that the pre-defined vaccine effectiveness endpoints were met. The results are generally in agreement with those in the initial MAA (Marketing Authorisation application), as well as observational effectiveness results.

Safety results

Solicited AEs (7-day post-vaccination period): Pain, fatigue and headache were the most reported solicited AEs in the MenB_0_2_6, MenB_0_6 and ACWY groups.

- Severe (grade 3) pain was reported by 5.5% and 10.6% of subjects in the MenB_0_2_6 and MenB_0_6 groups, respectively and was not reported in the ACWY group.

- Severe fatigue was reported by 1.2% and 2.9% of subjects in the MenB_0_2_6 and MenB_0_6 groups, respectively and by 2.2% of subjects in ACWY group.
- Severe headache was reported by 1.1% and 2.4% of subjects in the MenB_0_2_6 and MenB_0_6 groups, respectively and by 2.2% of subjects in ACWY group

Most of the other solicited local and systemic AEs were mild to moderate in intensity and severe solicited local and systemic AEs were reported in less than 3% of subjects in MenB and ACWY groups. The mean duration was less than 4 days for any solicited local or systemic AE. Overall, no increase in the frequency of reporting of solicited AEs was observed with subsequent doses of the vaccine.

Unsolicited AEs (30-day post-vaccination period): During the 30-day follow-up period after any vaccination, at least one unsolicited AE was reported by 29.6% to 31.7% of subjects in MenB and ACWY groups.

- The most commonly reported unsolicited AE after any vaccination, by preferred term (PT), was COVID-19 followed by upper respiratory tract infection in the MenB_0_2_6 and MenB_0_6 groups. In ACWY group, nasopharyngitis was the most commonly reported unsolicited AE followed by headache and COVID-19.
- Unsolicited AEs assessed as causally related to vaccination were reported by 7.4%, 6.2% and 5.6% of subjects in the MenB_0_2_6, MenB_0_6 and ACWY groups, respectively. The most commonly reported causally related unsolicited AEs, by PT, was injection site induration in the MenB_0_2_6 group (8 subjects) and ACWY group (2 subjects). In the MenB_0_6 group, the most commonly reported causally related unsolicited AE, by PT, was injection site pain (8 subjects).
- Overall, no increase in the frequency of reporting of unsolicited AEs was observed after subsequent doses of the vaccine.
- SAEs (throughout the study period): A total of 20, 22 and 5 subjects reported at least 1 SAE in the MenB_0_2_6, MenB_0_6 and ACWY groups, respectively. There were 2 fatal events (poisoning [subject in MenB_0_2_6 group] and overdose in MenB_0_6 group]) in the study. Both these events were assessed as not causally related to vaccination by the investigator. For 2 subjects in MenB_0_6 group, the following SAEs were assessed as causally related to vaccination by the investigator: nausea, vomiting, pyrexia and headache, all in 1 subject, and colitis ulcerative in 1 subject.

Withdrawals due to AEs/SAEs (throughout the study period): A total of 11 subjects withdrew/were withdrawn from the study due to an AE (6 from MenB_0_2_6 group, 4 from MenB_0_6 group and 1 from ACWY group). Seven subjects experienced at least one SAE that led to withdrawal from the study, none of these SAEs were assessed as causally related to vaccination by the investigator. Three of the non-serious AEs (arthritis reported in 1 subject in MenB_0_2_6 group, pyrexia and injection site hematoma reported in 1 subject each in MenB_0_6 group) leading to premature withdrawal were assessed as causally related to vaccination by the investigator.

Other significant AEs: Two subjects reported an AESI (non-serious arthritis in 1 subject in the MenB_0_2_6 group which led to premature withdrawal from study and colitis ulcerative (SAE) in 1 subject in the MenB_0_6 group). Both the AESI were classified as NOCDs and were considered as causally related to vaccination by the investigator.

One case of arthritis leading to premature withdrawal from the study and one case of ulcerative colitis were reported. Both cases were considered causally related to vaccination by the investigators. Narratives for the cases of arthritis and ulcerative colitis were requested to be submitted within this procedure to evaluate whether there was a clustering in time to onset after vaccination and if the cases resolved spontaneously. These cases have been submitted. No safety signal was detected.

2.3.3. Discussion on clinical aspects

Bexsero is a vaccine used to protect individuals from the age of two months against invasive meningococcal disease caused by group *Neisseria meningitidis.* In the study MENB REC 2ND GEN-038 (V72_72), Bexsero was the study vaccine and was also used as one of the active comparator vaccines to the investigational MenABCWY vaccine.

In the current study, vaccine effectiveness (test-based and responder-based) of rMenB+OMV NZ was evaluated against a randomly selected panel of *N. meningitidis* serogroup B invasive disease strains (110-MenB strain panel), administered as a 2-dose (2- or 6-months apart), or as a 3-dose (at 0, 2, and 6 months) schedule. All 3 schedules met the pre-defined criterion for success (LL of the 2-sided 97.5% CI for VE >65%) for both effectiveness endpoints, showing that rMenB+OMV NZ vaccine, whether administered as a 2-dose, or a 3-dose schedule is effective against disease causing MenB strains. The rMenB+OMV NZ vaccine was generally well tolerated in the study. The safety results were generally found to be in line with the established safety profile of the rMenB+OMV NZ vaccine, irrespective of the dosing schedule. However, narratives for one case of arthritis and one case of ulcerative colitis should be submitted, along with a discussion on the relevance of these cases.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

Narratives for the cases of arthritis and ulcerative colitis to further assess causality to Bexsero along with a discussion on the relevance of these cases were requested.

MAH responses to Request for supplementary information

Arthritis

Summary of the case

A case of arthritis was reported by a 24-year-old male subject who was enrolled in study MENB REC 2ND GEN-038 (V72_72). The subject received the first dose of the study vaccine

(rMenB + OMV NZ) on 2021 and the second dose of the study vaccine (rMenB+OMV NZ) two months after. 10 days after receiving the first dose of the study vaccine, the subject had pain in the left metatarsophalangeal (MTP) joint of the fourth toe, fluctuating swelling and redness of the joint; there were no symptoms in the other joints. According to the subject, there was no trauma. Two months after laboratory tests were performed due to these symptoms, showing leukocytopenia and lymphocytopenia. The left foot x-ray was normal while the magnetic resonance imaging (MRI) showed signs of arthritis, mild subluxation of the joint, hydrops and synovitis in the joint and reactive edema in the surroundings. A month after, human leukocyte antigen B27 (HLA- B*27) assay result was positive and Monoarthritis (Grade 2, moderate) was diagnosed. The event was considered non serious. Onset or relation to previous exercise could not be verified from site
source documents; anamnesis states that there was no atypical physical exertion before. The etiology of the subluxation and inflammation captured by the MRI at the involved joint is unknown and could be either secondary to arthritis or previous trauma and instability. The subject was treated with cortisone and etoricoxib. The outcome of the event was reported as resolved 4 months after the first dose. The administration of study vaccine was discontinued due to the event.

Investigator's assessment
The event of arthritis was assessed by the investigator as non-serious adverse event of special interest (AESI). In the opinion of the investigator, the arthritis was considered related to the study vaccine.

Company medical assessment
The company considers that there is insufficient evidence to conclude on the causal association between the event "arthritis" and rMenB+OMV NZ. The aetiology of the subluxation and inflammation captured by the MRI is unknown and according to radiologist's evaluation it could be due to arthritis or previous unperceived trauma and instability. Moreover, the time-to-onset (TTO) seems to be biologically implausible (i.e., too short) for a possible vaccine-induced possible immune-mediated disorder (pIMD). It is worth mentioning that arthritis constitutes an important potential risk for Bexsero in the European Union Risk Management Plan (EU-RMP) and Periodic Benefit-Risk Evaluation Report (PBRER). Events of arthritis are monitored through the AESI collection in the Bexsero clinical trials. As part of the risk mitigation strategies, GSK has developed an ad hoc eCRF page to further characterize this risk. The investigators are asked to compile the ad hoc eCRF page and to report the events of arthritis to GSK within 24 hours (regardless of the seriousness of the event). Cases of arthritis are also monitored as part of routine pharmacovigilance (PV) activities which include the use of a targeted follow up questionnaire for the collection of information from spontaneous sources and the periodic monitoring through PBRER. Based on the available data, no safety issue relating to this important potential risk is identified. The Company will continue to closely monitor arthritis through routine PV.

Assessor's comment:

The patient was positive for HLA-B27, which is known to be associated with reactive arthritis. A causal relationship between vaccination and arthritis therefore not be established. The arthritis was assessed as a non-serious and resolved during the reporting period.

Ulcerative colitis

Summary of the case
A case of ulcerative colitis was reported by a 25-year-old male subject who was enrolled in study MENB REC 2ND GEN-038 (V72_72). The subject received the first vaccination (rMenB+OMV NZ) on 2020, the

second vaccination (MenACWY) two months after, the third vaccination (rMenB+OMV NZ) six months after and the fourth injection (Placebo) seven months after. The subjects concurrent medical condition included dislocation and subluxury of shoulder joint. Family medical history included Crohn's disease. The subject's concomitant medication included tozinameran ([Covid-19 Vaccine]), esomeprazole magnesium, proctosedyl nos (l) and citric acid, magnesium oxide, picosulfuric acid sodium. Five months after the first dose, the subject experienced bloody diarrhea, loss of weight, fatigue and anorexia. Stool analysis result was positive. 44 days after receiving the third vaccination, the subject was diagnosed with colitis ulcerative (Grade 3, severe), as diagnosed through rectoscopy, colonoscopy and abdominal biopsy. The event was considered serious as it required hospitalization and clinically significant/intervention. Blood iron result was 3.7 mmol/L (normal range: 11.6 to 31) and hemoglobin (Hb) result was 117 g (normal range 134 to 170). The subject was hospitalized: CRP 25.7, leucocytes 10.7*10/9/l, Hgb 109g/l. Colonoscopy showed left side colitis, high activity, pseudo polyposis, ulcers, crypt abscesses.
The subject received intravenous infusion of Prednisolon 75mg. Four days after hospitalization, the subject was discharged from the hospital. The subject was treated with azathioprine, pantoprazole, metronidazole, prednisolone, sodium chloride, iron polymaltose, esomeprazole magnesium , metronidazole, ciprofloxacin , budenoside, and mesalazine .
106 days after receiving the third vaccination), colonoscopy morphology showed active chronic inflammation coli, foci destructions and granulations, crypt abscesses. Given the chronic nature of the ulcerative colitis, the outcome of the event was reported as not resolved at the time of this report.

Investigator's assessment
The event of colitis ulcerative was assessed by the investigator as serious pIMD. In the opinion of the investigator, the colitis ulcerative was considered related to the study vaccine.

Company medical assessment
The company considers that there is insufficient evidence to conclude on the causal association between the event "colitis ulcerative" and rMenB+OMV NZ vaccine as the concomitant administration of the Covid -19 vaccine and the positive family history of Crohn's disease (patient's sister) represent confounding risk factors. Events of ulcerative colitis are monitored through pIMDs collection, as part of AESI collection in the Bexsero clinical trials. A non-exhaustive list of pIMDs is included in the protocols of Bexsero trials; the investigator may exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin. For these events the investigator is asked to compile an ad hoc eCRF page and to report the events to GSK within 24 hours (regardless of the seriousness of the event). A continuous update on pIMD cases following Bexsero vaccination is provided by the company to Health Authorities through periodic pharmacovigilance reports (i.e., DSUR). From the review of the most up-to-date available information, as reported in the latest DSUR (reporting period 14 Jan 2022-13 Jan 2023), no safety issue was identified and the previously established favourable benefit-risk profile for Bexsero remains unchanged. Cases of pIMDs will continue to be monitored as part of routine PV.

Assessor's comment:

One patient was reported with ulcerative colitis. The condition was assessed as serious by the investigator. The patient also received Comirnaty in conjunction with Bexero vaccination. An association between Comirnaty and inflammatory bowel disease has not been established. The patient did report a family history of IBD. A causal relationship between Bexero vaccination and ulcerative colitis cannot therefore be established.