EMA/205221/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bexsero

International non-proprietary name: meningococcal group B vaccine (recombinant, component, adsorbed)

Procedure No. EMEA/H/C/002333/II/0074

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GSK Vaccines S.r.l submitted to the European Medicines Agency on 17 December 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIB and Annex A

Update of section 4.5 of the SmPC in order to include the possibility of concomitant administration with the MenACWY vaccine based on final results from study V72_56. This was a phase 3b study assessing the safety and immunogenicity of Bexsero administered concomitantly with MenACWY vaccine as compared to their individual administration in healthy infants at approximately 3, 5, 7 and 13 months of age. This submission constitutes follow-on to procedure EMEA/H/C/002333/P46/027.

The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes throughout the Product Information and Annex A.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Annex A.

2. Overall conclusion and impact on the benefit–risk balance

Bexsero (rMenB+OMV NZ) is a multicomponent meningococcal group B recombinant adsorbed vaccine, presented as a single-dose suspension for injection in a pre-filled syringe. The vaccine contains 3 purified recombinant proteins, Neisserial heparin binding antigen (NHBA) as fusion protein (also referred to as rp287-953), *Neisseria* adhesin A (NadA) as single protein (rp961c), factor H binding protein (fHbp) as fusion protein (rp936-741), and the outer membrane vesicles (OMV) from the New Zealand *Neisseria meningitidis* serogroup B strain NZ98/254 containing PorA P1.4 (the immunodominant antigen present in the OMV component), along with aluminium hydroxide as adjuvant adsorbent.

On 26 April 2018, in the framework of Article P46 procedure EMEA/H/C/002333/P46/027, the CHMP considered that information regarding concomitant administration of rMenB+OMV NZ and MenACWY vaccines should be added to the Product Information.

To this end, the MAH submitted variation II-74 and proposed to update section 4.5 of the SmPC to indicate that rMenB+OMV NZ vaccine can be given concomitantly, at a separate injection site, with meningococcal group A, C, W, Y conjugate antigens, either as monovalent or as combination vaccine, as well as with any other vaccine antigens already approved for concomitant use during the same visit.

The CHMP considered the results of clinical study V72_56, which evaluated the immunogenicity and safety of concomitant administration of rMenB+OMV NZ vaccine and GSK Biological's meningococcal group A, C, W and Y conjugate vaccine, Menveo (MenACWY) in healthy infants at 3, 5, 7 and 13 months of age. MenACWY vaccine contains meningococcal serogroups A, C, W and Y oligosaccharides, each conjugated to Corynebacterium diphtheriae CRM197 protein carrier. Of note, concomitant administration of the rMenB+OMV NZ and MenACWY vaccines was followed by an immune response non-inferior to that of either vaccine administered alone. The study raised no new safety concerns.

Based on the available evidence, the CHMP was of the view that the proposed updates in section 4.5 of the SmPC and the respective section of the Package Leaflet are acceptable.

The editorial updates of Annex A were considered acceptable.

The benefit–risk profile of Bexsero remains unchanged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIB and Annex A

Update of section 4.5 of the SmPC in order to include the possibility of concomitant administration with the MenACWY vaccine based on final results from study V72_56. This was a phase 3b study assessing the safety and immunogenicity of Bexsero administered concomitantly with MenACWY vaccine as compared to their individual administration in healthy infants at approximately 3, 5, 7 and 13 months of age. This submission constitutes follow-on to procedure EMEA/H/C/002333/P46/027.

The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes throughout the Product Information and Annex A.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Annex A.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and Annex A are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion ‘Bexsero-H-C-002333-II-74’ and to ‘Bexsero-H-C-002333-P46-27’.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Bexsero (rMenB+OMV NZ) is a multicomponent meningococcal group B recombinant adsorbed vaccine, presented as a single-dose suspension for injection in a pre-filled syringe. The vaccine contains 3 purified recombinant proteins, Neisserial heparin binding antigen (NHBA) as fusion protein (also referred to as rp287-953), *Neisseria* adhesin A (NadA) as single protein (rp961c), factor H binding protein (fHbp) as fusion protein (rp936-741), and the outer membrane vesicles (OMV) from the New Zealand *Neisseria meningitidis* serogroup B strain NZ98/254 containing PorA P1.4 (the immunodominant antigen present in the OMV component), along with aluminium hydroxide as adjuvant adsorbent.

The rMenB+OMV NZ vaccine was first registered in the European Union (EU) through the centralised procedure on January 14, 2013 and has received marketing authorization in 10 additional (non-EU) countries: Argentina, Australia, Brazil, Canada, Chile, Israel, New Zealand, Switzerland, the United States (US) and Uruguay. The vaccine is currently approved in 41 countries worldwide.

The vaccine is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *N. meningitidis* serogroup B. The indicated age range varies depending on the country, according to national recommendations.

Purpose of the variation

Immunogenicity and safety data from clinical study V72_56 evaluating concomitant administration of rMenB+OMV NZ vaccine and GSK Biological's meningococcal group A, C, W and Y conjugate vaccine, Menveo (MenACWY) in healthy infants at 3, 5, 7 and 13 months of age are available. MenACWY vaccine contains meningococcal serogroups A, C, W and Y oligosaccharides, each conjugated to *Corynebacterium diphtheriae* CRM197 protein carrier.

The study results have been submitted to the European Medicines Agency as required by Article 46 for pediatric studies (EMA/H/C/2333 P46 027). Following assessment, the Rapporteur requested that information regarding concomitant administration of rMenB+OMV NZ and MenACWY vaccines be added to section 4.5 of the Summary of Product Characteristics.

The MAH agrees with the request and proposes to update the prescribing information (PI) 'Interactions' section of rMenB+OMV NZ vaccine to indicate that it can be given simultaneously but at a separate injection site, with meningococcal group A, C, W, Y conjugate antigens, either as monovalent or as combination vaccine, as well as with any other vaccine antigens already approved for concomitant use during the same visit.

Concomitant administration of rMenB+OMV NZ vaccine with meningococcal group C CRM conjugate vaccine is already approved. To align to country-specific recommendations, which are based on vaccine registration status and antigens content and do not specify the protein carrier used for the conjugation [Green Book, UK], the MAH proposes to remove the specification of the protein carrier CRM for serogroup C and include A, W, and Y antigens to allow concomitant administration with all 4 serogroup antigens. Of note, administration of the monovalent meningococcal C vaccine remains a possibility.

Note that the most current nomenclature, i.e. serogroup W has been used throughout the submission to indicate the same as serogroup W-135 of the V72_56 clinical study report (CSR). The nomenclature W-135 has been used historically and the number has since been removed as it did not provide any additional useful information [Harrison OB 2013].

In addition, the MAH proposes minor corrections and/or non-substantive changes made for clarification purposes.

6. Clinical efficacy aspects

6.1. Methods – analysis of data submitted

Clinical study supporting the proposed changes of the Prescribing Information

Clinical study V72_56, was a phase 3b study assessing the safety and immunogenicity of rMenB+OMV NZ vaccine when administered concomitantly with MenACWY vaccine as compared to their individual administration in healthy infants at approximately 3, 5, 7 and 13 months of age. The study was conducted at 7 sites; 3 in Argentina and 4 in Mexico (Table 1).

This study was designed as an open-label study; therefore, no blinding procedures were used. Subjects were to be randomized to 1 of 3 treatment arms in a 1:1:1 ratio as follows:

- rMenB+ACWY group: rMenB+OMV NZ vaccine given concomitantly with MenACWY vaccine;
- rMenB group: rMenB+OMV NZ vaccine alone;
- MenACWY group: MenACWY vaccine alone.

Table 1. Overview of clinical study V72_56.

Study ID (number)	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects		
					PPS for immuno-genicity[a]	FAS for immuno-genicityb	Overall Safety set
V72_56 (205240)	Argentina Mexico	Phase 3b, open-label, randomised 1:1:1, multicenter noninferiority study Primary immunogenicity objective: Immunological noninferiority of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered compared to either alone as measured by the ratio of human serum bactericidal assay (hSBA) geometric mean titers (GMTs) against each of the serogroup B indicator strains (for rMenB+OMV NZ) and serogroups A, C, Wand Y (for MenACWY) at 1 month after the 4th vaccination. Secondary immunogenicity objectives: Immune response of rMenB+OMV NZ and MenACWY vaccines (1 month after the 4th vaccination, 1 month after the 3rd vaccination and 6 months after the 3rd vaccination) when concomitantly administered compared to either alone. Secondary safety objectives: Safety and tolerability of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered, compared to either alone.	Healthy infants (3 months of age at enrolment) 4 doses at 3, 5, 7 and 13 months of age	rMenB+ACWY: rMenB+OMV NZ and MenACWY vaccines given concomitantly rMenB: rMenB+OMV NZ vaccine given alone MenACWY: MenACWY vaccine given alone	161 163 156 (Total: 480)	199 201 204 (Total: 604)	249 249 246 (Total: 744)

Source: CSR V72_56 Table 11.1-1 and Table 12.1-1 PPS = Per-protocol set, FAS = Full analysis set.
Note: immunogenicity sets shown in the table are 1 month post 4th vaccination.
a PPS primary and secondary immunogenicity objectives; b FAS secondary immunogenicity objectives.

The study was performed according to the ethical principles of the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements for the countries in which it was conducted, with the exception of the GCP compliance issue described below.

A serious GCP compliance issue occurred during the study that led to exclusion of 1 study center in Mexico, which enrolled 38 subjects, from the analysis set and resulted in the decision to terminate the

participation of the investigator to this study. Data collected from this center were not used for any analysis of study data with the exception of the safety data which were included in the V72_56 CSR.

Overview of study design

The study included 4 study vaccinations (days 1, 61, 121 and 301) and comprised 6 clinical visits (days 1, 61, 121, 151, 301, and 331), 8 reminder calls (2 and 4 days after each vaccination visit) and 2 safety calls (days 201 and 251, Table 2).

Table 2. Overview of study design of clinical study V72_56.

Study groups	Visit 1/ Study Day 1	Visit 2/ Study Day 61	Visit 3/ Study Day 121	Visit 4[a]/ Study Day 151	Visit 7/ Study Day 301	Visit 8/ Study Day 331
rMenB+ACWY	Blood draw; Vaccination: rMenB+OMV NZ and MenACWY vaccines	Vaccination: rMenB+OMV NZ and MenACWY vaccines	Vaccination: rMenB+OMV NZ and MenACWY vaccines	Blood draw	Blood draw; Vaccination: rMenB+OMV NZ and MenACWY vaccines	Blood draw
rMenB	Blood draw; Vaccination: rMenB+OMV NZ vaccine	Vaccination: rMenB+OMV NZ vaccine	Vaccination: rMenB+OMV NZ vaccine	Blood draw	Blood draw; Vaccination: rMenB+OMV NZ vaccine	Blood draw
MenACWY	Blood draw; Vaccination: MenACWY vaccine	Vaccination: MenACWY vaccine	Vaccination: MenACWY vaccine	Blood draw	Blood draw; Vaccination: MenACWY vaccine	Blood draw

Source: CSR V72_56 Table 2-1

[a] Visit 5 and Visit 6 were safety phone calls

Routine vaccines, including diphtheria, tetanus and whole-cell (or acellular) pertussis (DTwP/DTaP), were to be administered at 2, 4, 6 and 12 months of age, intercalated to the study vaccinations and according to local infant vaccination schedules. The routine infant's vaccinations schedule was to be implemented as per local recommendation during the trial. However, a 14-day window period before and after experimental treatment had to be elapsed between the administration of routine vaccine(s) and the administration of clinical study vaccines in order to minimize any concomitant reactogenicity from administration of routine vaccines.

Methods used to evaluate immunogenicity

A total of 4 blood samples were to be drawn: before 1st vaccination, 1 month after the 3rd vaccination (day 151), before (day 301) and 1 month after (day 331) the 4th vaccination from all enrolled subjects for immunogenicity evaluation (Table 2).

This study used the serum bactericidal activity (SBA) as a serological surrogate marker for protection to measure the immunogenicity of the study vaccines. SBA is a functional measure of the ability of antibodies, in conjunction with complement, to kill meningococci, and is widely used and generally recognized as the serological correlate of protection in clinical studies of meningococcal vaccines [Green Book (UK), Holst J 2009]. The SBA using human plasma as the source of exogenous complement (hSBA) was to be used to measure the induction of antibodies directed against N. meningitidis serogroups A, B, C, Wand Y following vaccination with rMenB+OMV NZ and MenACWY vaccines. For secondary endpoints, assay cut-offs of hSBA titers ≥5 and ≥8 against each of the serogroup B indicator strains, and hSBA titers ≥4 and ≥8 against each of the serogroups A, C, W and Y were used.

Statistical criteria for evaluating immunogenicity

Immunogenicity endpoints evaluated

Primary immunogenicity endpoints

The hSBA geometric mean titers (GMTs) against each of the serogroup B indicator strains (for rMenB+OMV NZ vaccine) and serogroups A, C, W and Y (for MenACWY vaccine) at 1 month after the 4th vaccination, and corresponding between-group ratios of GMTs for rMenB+ACWY versus rMenB (serogroup B indicator strains), and rMenB+ACWY versus MenACWY (serogroups A, C, W and Y).

Noninferiority was to be concluded if, at 1 month following the 4th vaccination (day 331), the lower limits (LL) of the 2-sided 95% confidence intervals (CIs) for the between- group ratios of GMTs (rMenB+ACWY versus rMenB and rMenB+ACWY versus MenACWY) were >0.5 for all serogroup B indicator strains and all serogroups A, C, W and Y. Noninferiority was only to be concluded if all 8 predefined noninferiority criteria were met, i.e., all 8 noninferiority hypotheses were considered co-primary.

Secondary immunogenicity endpoints

The immune response to rMenB+OMV NZ vaccine at all sampling timepoints when administered alone and concomitantly with MenACWY vaccine (rMenB+ACWY versus rMenB) was assessed by:

- hSBA GMTs against each of the serogroup B indicator strains;
- the percentage of subjects with hSBA titers ≥5 and ≥8 against each of the serogroup B indicator strains.

The immune response to MenACWY vaccine at all sampling timepoints when administered alone and concomitantly with rMenB+OMV NZ vaccine (rMenB+ACWY versus MenACWY) was assessed by:

- hSBA GMTs against each of the serogroups A, C, Wand Y;
- the percentage of subjects with hSBA titers ≥4 and ≥8 against each of the serogroups A, C, W and Y.

Additionally, the following were assessed for each of the serogroup B strains and each of the serogroups A, C, W and Y:

- within-subject geometric mean ratios were calculated for GMTs at 1 month after 4th vaccination (day 331) versus pre 4th vaccination (day 301),
- the percentage of subjects with 4-fold increases in hSBA titers at 1 month after 4th vaccination (day 331) versus pre 4th vaccination (day 301).

Please note, for serogroup B indicator strains, 4-fold increase in titer was defined as post 4th vaccination titer ≥8 (if pre 4th vaccination titer was <2) or post 4th vaccination titer ≥ 4 times pre 4th vaccination titer (if pre 4th vaccination titer was ≥2). For serogroups A, C, W-135, and Y, 4-fold increase in titers was defined as post 4th vaccination titer ≥16 (if pre 4th vaccination titer was <4) or post 4th vaccination titer ≥ 4 times pre 4th vaccination titer (if pre 4th vaccination titer was ≥4).

Data sets analysed

The primary immunogenicity analyses were based on the per-protocol set (PPS) and the secondary immunogenicity analyses on the full analysis set (FAS).

FAS immunogenicity set: This analysis set involved all enrolled subjects who were randomized, received at least 1 study vaccination and provided evaluable immunogenicity data at the respective vaccination visit.

PPS immunogenicity set: This was the primary analysis set for the primary immunogenicity objective of this study (i.e., noninferiority). It was a subset of the FAS 1 month post 4th vaccination which included all subjects who:

- correctly received the vaccine (i.e., received the vaccine to which the subjects was randomised and at the scheduled time points);
- had no reportable protocol deviations leading to exclusion, as defined prior to analysis;
- were not excluded due to other reasons defined prior to analysis.

Population evaluated

Healthy infants aged 3 months whose parents/legal guardians had given written informed consent and were available for all the visits scheduled in the study were enrolled.

Subjects with previous meningococcal vaccination, suspected disease or contact with *N. meningitidis* were not enrolled. Informed consent was to be obtained prior to any study- related procedures and subjects were enrolled after their eligibility for participation was confirmed by the investigator.

6.2. Results

Efficacy Results

The demographic and baseline characteristics were balanced across all study groups. The mean age of the subjects enrolled into the study was 102.7±10.77 days overall. Most of the subjects (93%) were categorized under the race category of 'Other' (i.e., subjects who were not white, American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other pacific islander). Only a few subjects (7–8%) were categorised as 'White'.

Among 750 enrolled subjects in the study, 744 subjects received a study vaccination. Across groups, 63%-65% of enrolled subjects were included in the PPS analysis for primary objectives. Overall, 79%-86% of enrolled subjects were included in the different FAS populations for secondary objectives, which were defined based on the different study visits (Table 3).

Table 3. Number of subjects planned and analysed for immunogenicity in clinical study V72_56.

Group	Planned	Enrolled	Analyzed for immunogenicity			
			FAS post 3rd vacc.	FAS pre 4th vacc.	FAS post 4th vacc.	PPS post 4th vacc.
rMenB+ACWY	250	252	215 (85%)	205 (81%)	199 (79%)	161 (64%)
rMenB	250	250	209 (84%)	204 (82%)	201 (80%)	163 (65%)
MenACWY	250	248	214 (86%)	204 (82%)	204 (82%)	156 (63%)

Source: CSR V72_56 Table 2-2 (Table 14.1.1.1)
FAS = full analysis set; PPS = per-protocol set; vacc = vaccination.

Primary objective: immunological noninferiority

The primary objective of the study was met as the immune responses to rMenB+OMV NZ and MenACWY vaccines when concomitantly administered (rMenB+ACWY) were noninferior to those elicited by either vaccine administered alone. At 1 month post 4th vaccination (day 331), the LLs of the 2-sided 95% CIs for the between-group ratios of GMTs (rMenB+ACWY versus rMenB, and rMenB+ACWY versus MenACWY) were >0.5, the predefined noninferiority margin, for all serogroup B indicator strains and all serogroups A, C, W and Y (Table 4).

Table 4. Clinical study V72_56: hSBA geometric mean titers and vaccine group ratios against N. meningitidis serogroup B strains (for rMenB+OMV NZ vaccine) and serogroups A, C, W and Y (for MenACWY vaccine) at 1 month post 4th vaccination – Per-Protocol Set.

	GMTs and GMTs group ratios (95% CI)		
rMenB strains	rMenB+ACWY	rMenB	rMenB+ACWY:rMenB
H44/76 (fHbp)	**N = 115**	**N = 153**	
1 month post 4th vaccination	92 (67-128)	104 (77-141)	0.89 (**0.71**-1.10)
5/99 (NadA)	**N = 113**	**N = 148**	
1 month post 4th vaccination	1850 (1122-3050)	1790 (1128-2842)	1.03 (**0.74**-1.45)
NZ98/254 (PorA P1.4)	**N = 148**	**N = 158**	
1 month post 4th vaccination	39 (29-53)	38 (28-52)	1.01 (**0.82**-1.25)
M10713 (NHBA)	**N = 131**	**N = 157**	
1 month post 4th vaccination	13 (7.82-21)	12 (7.72-20)	1.03 (**0.77**-1.40)
MenACWY serogroups	rMenB+ACWY	MenACWY	rMenB+ACWY:MenACWY
Serogroup A	**N = 159**	**N = 156**	
1 month post 4th vaccination	409 (300-556)	165 (122-224)	2.48 (**1.97**-3.11)
Serogroup C	**N = 157**	**N = 149**	
1 month post 4th vaccination	452 (312-655)	421 (294-602)	1.07 (**0.83**-1.38)
Serogroup W	**N = 144**	**N = 143**	
1 month post 4th vaccination	721 (493-1053)	536 (370-776)	1.34 (**1.04**-1.74)
Serogroup Y	**N = 161**	**N = 156**	
1 month post 4th vaccination	410 (293-575)	391 (280-546)	1.05 (**0.82**-1.35)

Source: CSR V72_56 Table 2-3 (Table 14.2.1.5; Table 14.2.1.5.1)
CI = confidence interval; GMT = geometric mean titer; hSBA = human serum bactericidal assay; NA = not applicable.
Note: Noninferiority was to be concluded if at 1 month following the 4th vaccination, if the lower limits (LL) of the 2-sided 95% CI for the between-group ratios of GMTs (rMenB+ACWY versus rMenB alone, and rMenB+ACWY versus MenACWY alone) was >0.5 for all serogroup B indicator strains and all serogroups A, C, W and Y. **Bold LL of 95% CI** indicates noninferiority criterion met.

Secondary objectives: rMenB+OMV NZ vaccine immune response

The immune response following administration of rMenB+OMV NZ vaccine were similar between the rMenB+ACWY and rMenB groups post 3rd and 4th vaccination:

- At 1 month post 3rd vaccination (day 151), 96%-100% of subjects achieved hSBA titers ≥5 against serogroup B strains H44/76, 5/99 and NZ98/254, and 68%-70% of subjects for strain M10713 across groups;
- At 1 month post 4th vaccination (day 331), 97%-100% of subjects achieved hSBA titers ≥5 against serogroup strains H44/76, 5/99 and NZ98/254, and 87% of subjects for strain M10713 across groups.

The hSBA GMTs increased across all strains in both groups post 3rd and 4th rMenB+OMV NZ vaccination compared to pre 3rd and 4th vaccination, respectively, with similar titers in the rMenB+ACWY group compared with those in rMenB group.

At 1 month post 4th vaccination, the percentages of subjects with 4-fold increase in titers over pre 4th vaccination ranged from 92%-95% for strains H44/76 and 5/99; from 79–81 % for strain NZ98/254 and from 58–60 % for strain M10713, in rMenB+ACWY and rMenB groups.

Secondary objectives: MenACWY vaccine immune response

The immune responses following administration of MenACWY vaccine were slightly numerically higher or similar in the rMenB+ACWY group compared with those in the MenACWY group post 3rd and 4th vaccination.

At 1 month post 3rd vaccination (day 151) as well as at 1 month post 4th vaccination (day 331), 96%-100% of subjects in groups rMenB+ACWY and MenACWY achieved hSBA titers ≥8 across serogroups A, C, W and Y.

The hSBA GMTs increased across all serogroups in both groups post 3rd and 4th MenACWY vaccination compared to pre 3rd and 4th vaccination, respectively, with slightly numerically higher (for serogroup A) or similar (for serogroups C, W and Y) titers in the rMenB+ACWY group compared with those in MenACWY group.

At 1 month post 4th MenACWY vaccination, the percentages of subjects with at least 4- fold increase in titers ranged from 71–90 % in both groups against all serogroups, A, C, W and Y.

6.3. Discussion

Of note, the submitted study has been assessed in a previous submission (see Chapter 2.).

The primary objective of the study was met as at 1 month post 4th vaccination, the LLs of the 2-sided 95 % CI for the between-group ratios of GMTs (rMenB+ACWY versus rMenB, and rMenB+ACWY versus MenACWY) were >0.5 for all serogroup B indicator strains and all serogroups A, C, W and Y.

An immune response was observed, in terms of percentages of subjects achieving titers ≥5 and ≥8 (rMenB+OMV NZ vaccine) / ≥8 and ≥4 (MenACWY vaccine), 4-fold increase in titers (post 4th over pre 4th vaccination), and increased hSBA GMTs after the 3rd and 4th vaccination of either rMenB+OMV NZ or MenACWY vaccines administered alone or either concomitantly. The immune response following administration of rMenB+OMV NZ vaccine was similar between the rMenB+ACWY and rMenB groups. The immune response following administration of MenACWY vaccine was slightly numerically higher (for serogroup A) or similar (for serogroups C, Wand Y) in the rMenB+ACWY group compared with the MenACWY group.

Taken together, the results of clinical study V72_56 support the concomitant administration of the rMenB+OMV NZ and MenACWY vaccines, as a robust immune response is seen following concomitant administration which is noninferior to that of either vaccine administered alone.

7. Clinical safety aspects

7.1. Methods – analysis of data submitted

Subjects were observed at the clinical site for at least 30 minutes after each vaccination for any immediate reactions. Each subject's parent/legal guardian were instructed to complete a diary card to describe (i) solicited local and systemic AEs occurring during the day of each vaccination and for the following 6 days (from day 1 to day 7); (ii) all medications (excluding food supplements) taken during the day of each vaccination and for the following 6 days (from day 1 to day 7); (iii) any unsolicited AEs and related medications occurring during the day of each vaccination and for the following 6 days, including any Serious Adverse Events (SAEs), AEs leading to withdrawal and medically attended AEs. Only selected

safety measures (SAEs, AEs leading to withdrawal and medically attended AEs) and related medications were to be collected throughout the study period i.e. from first vaccination to study termination.

Routine vaccinations received during the study were also to be captured in the diary card.

Methods used to evaluate safety

Safety endpoints evaluated

The safety objective of the study was to assess the safety and tolerability of rMenB+OMV NZ and MenACWY vaccines when concomitantly administered, compared to either vaccine alone, in healthy infants at 3, 5, 7 and 13 months of age.

The term "reactogenicity" refers to selected signs and symptoms ('adverse events') occurring in the hours and days following a vaccination.

The following safety endpoints were assessed:

- The frequencies and percentages of subjects with solicited local (injection site tenderness, injection site erythema, swelling, and induration) and systemic (change in eating habits, sleepiness, persistent crying, vomiting, diarrhea, irritability, rash) AEs, as well as fever (defined as body temperature ≥38° C) and use of medication to treat and or prevent fever and/or pain during the 7 days (including the day of vaccination) following vaccination visits at days 1, 61, 121, and 301 for all vaccine groups;
- The frequencies and percentages of subjects with any other (unsolicited) AEs, AEs leading to withdrawal and medically attended AEs during the 7 days (including the day of vaccination) following vaccination visits at days 1, 61, 121, and 301 for all vaccine groups;
- The frequencies and percentages of subjects with SAEs, AEs leading to withdrawal and medically attended AEs throughout the whole study period.

Data sets analysed

Safety analyses were performed on the safety set:

Solicited safety set: All subjects in the Exposed Set (all subjects who receive a study vaccination) with solicited AE data for each of the 4 vaccinations.

Unsolicited safety set: All exposed subjects with unsolicited AE data.

Overall safety set: All subjects who were in the solicited safety set and/or in the unsolicited safety set.

7.2. Results

A total of 750 subjects were enrolled into clinical study V72_56, of which 744 subjects (99%) were exposed to at least 1 dose of study vaccine. Of the 744 exposed subjects included in the overall safety set and unsolicited safety set, 709 were included in the solicited AE set (6 hour - Day 7 after vaccination) after any vaccination (Table 5).

Overall 498 subjects received at least 1 dose of rMenB+OMV NZ vaccine and 495 subjects received at least 1 dose of MenACWY vaccine.

Solicited AEs

Any solicited AEs (6 hours through Day 7) was reported in 54%-87% of subjects over the 4 vaccinations across vaccine groups. The percentages of subjects with solicited local and systemic AEs were higher in the rMenB+ACWY and rMenB groups than those in MenACWY group (Table 6). No increase in solicited local and systemic AEs was observed after the concomitant administration of rMenB+OMV NZ and MenACWY vaccines compared with administration of rMenB+OMV NZ vaccine alone, which tends to be

more reactogenic than MenACWY vaccine alone, and there was no increase in reactogenicity with the subsequent doses (Table 6).

Solicited local AEs were reported in 37%-79% of subjects over the 4 vaccinations across vaccination groups (Table 6). Tenderness was the most common solicited local AE reported after each vaccination with the incidence being higher in rMenB+ACWY and rMenB groups (60–70 % of subjects) compared with the MenACWY group (27–31 % of subjects, Module 2.7.4, Table 3). Most of the reported solicited local AEs after either dose of vaccine were mild to moderate in intensity with onset from 6 hours to Day 3 after vaccination. Induration and swelling were the most frequently reported reactions ongoing after 7 days of the 4 vaccinations and were more frequently reported in rMenB+ACWY and rMenB groups than in the MenACWY group. Severe tenderness was the most commonly reported severe solicited local AE reported after each vaccination with the incidence being higher in rMenB+ACWY and rMenB groups (6–15% of subjects) compared with the MenACWY group (<1–1 % of subjects).

Solicited systemic AEs were reported in 47%-76% of subjects over the 4 vaccinations across vaccine groups (Table 6). The most common solicited systemic AEs reported after each vaccination across the groups were persistent crying and irritability. Incidence of fever (body temperature ≥38 °C) was higher in rMenB+ACWY and rMenB groups (17–26 % of subjects) compared with the MenACWY group (4–11 % of subjects) and mostly reported on Day 1, while incidence of severe fever (body temperature ≥40 °C) was low; reported by 0–1 % of subjects overall.

Table 5. Number of subjects planned and analysed for safety in clinical study V72_56.

Group	Planned	Enrolled	Exposed	Analyzed for Safety	
				Solicited	Unsolicited
rMenB+ACWY	250	252	249 (99%)	240 (95%)	249 (99%)
rMenB	250	250	249 (>99%)	232 (93%)	249 (>99%)
MenACWY	250	248	246 (99%)	237 (96%)	246 (99%)

Source: CSR V72_56 Table 2-2 (Table 14.1.1.1)

Table 6. Clinical study V72_56: Numbers (%) of subjects with at least 1 solicited local and systemic adverse event reported from 6 hours through Day 7 after each vaccination – Solicited Safety Set.

	Number (%) of subjects		
Vaccine group	**rMenB+ACWY**	**rMenB**	**MenACWY**
1st Vaccination	**N = 239**	**N = 230**	**N = 235**
Any	203 (85%)	200 (87%)	146 (62%)
Local	179 (75%)	181 (79%)	96 (41%)
Systemic	171 (72%)	174 (76%)	129 (55%)
2nd Vaccination	**N = 227**	**N = 221**	**N = 230**
Any	183 (81%)	177 (80%)	132 (57%)
Local	162 (71%)	157 (71%)	94 (41%)
Systemic	153 (67%)	150 (68%)	109 (47%)
3rd Vaccination	**N = 218**	**N = 215**	**N = 223**
Any	172 (79%)	167 (78%)	124 (56%)
Local	154 (71%)	154 (72%)	82 (37%)
Systemic	138 (63%)	133 (62%)	106 (48%)
4th Vaccination	**N = 203**	**N = 200**	**N = 204**
Any	165 (81%)	167 (84%)	111 (54%)
Local	140 (69%)	149 (75%)	79 (39%)
Systemic	137 (67%)	134 (67%)	96 (47%)

Unsolicited AEs

Unsolicited AEs were reported by a total of 74%-79% of subjects across groups throughout the study, with 11%-41% of subjects experiencing unsolicited AEs considered at least possibly related to study vaccination (Table 7). The most commonly affected system organ class (SOC) was 'infections and infestations' (64%-71%, across groups) while the most common unsolicited AEs by preferred term (PT) were nasopharyngitis (32–35%) and viral upper respiratory tract infection (29–35 %). Most of the unsolicited AEs were mild to moderate in intensity and most of them resolved before study termination.

Table 7. Clinical study V72_56: Numbers (%) of subjects reporting unsolicited adverse events during the whole study period after any vaccination – Unsolicited Safety Set.

	Number (%) of subjects		
Vaccine group	**rMenB+ACWY**	**rMenB**	**MenACWY**
	N = 249	**N = 249**	**N = 246**
Any AEs*	185 (74%)	197 (79%)	189 (77%)
At least possibly related AEs*	93 (37%)	102 (41%)	27 (11%)
Any SAEs	6 (2%)	13 (5%)	11 (4%)
At least possibly related SAEs	0	1 (<1%)	0
AEs leading to premature withdrawal	0	2 (1%)	1 (<1%)
AEs leading to dose reduction, interruption or delay in vaccination	11 (4%)	15 (6%)	17 (7%)
AEs requiring medical attention	177 (71%)	188 (76%)	183 (74%)
AEs leading to death	0	0	0

Source: CSR V72_56 Table 2-5 (Table 14.3.1.12; Table 14.3.1.17; Table 14.3.1.18; Table 14.3.1.19; Table 14.3.1.20; Table 14.3.1.22; Table 14.3.1.24; Table 14.3.2.1.)

AEs = Adverse events; SAEs = Serious adverse events.

* Unsolicited AEs were collected within 7 days of vaccination, however here any AEs also includes unsolicited AEs ongoing after day 7 and AEs leading to premature withdrawal and AEs requiring medical attention which were collected throughout the study period.

Serious adverse events

SAEs were reported by a total of 2–5 % of subjects across groups throughout the study (Table 7). One subject in the rMenB group had an SAE (anemia at Day 35 after 1st vaccination, leading to hospitalisation which recovered after 175 days) that was considered to be at least possibly related to study vaccination by the investigator.

Fatal events

No deaths were reported in the study (Table 7).

Other significant adverse events

AEs requiring medical attention were reported by 71%-76% of subjects and AEs leading to dose reduction, interruption or delay in vaccination were reported by 4%-7% of subjects during the study (Table 7). A total of 2 subjects in the rMenB group (anemia which was an SAE, described above, and pyrexia) and 1 subject in the MenACWY group (dermatitis atopic) had AEs leading to premature withdrawal from the study.

7.3. Discussion

Of note, the submitted study has been assessed in a previous submission (see Chapter 2.).

The vaccines were generally well tolerated although, as expected, the reactogenicity was very common and higher in the rMenB+ACWY and rMenB groups than in MenACWY group, as the rMenB+OMV NZ vaccine is known to be more reactogenic than the MenACWY vaccine.

Tenderness was the most common solicited local AE reported after each vaccination across study groups, with the incidence being higher after rMenB+OMV NZ vaccination compared to MenACWY vaccination both when given alone and concomitantly. Most of the reported solicited local AEs after any dose of vaccine were mild to moderate in intensity with onset 6 hours to day 3 after vaccination.

The most common solicited systemic AEs reported were persistent crying and irritability. Overall, no increase in solicited local and systemic AEs was observed after the concomitant administration of MenACWY and rMenB+OMV NZ vaccines compared with administration of rMenB+OMV NZ vaccine alone, which has a higher reactogenicity than MenACWY vaccine alone. Additionally, there was no increase in reactogenicity with the subsequent doses.

The overall incidence of unsolicited AEs reported was similar across the groups. The most commonly affected SOCs were 'infections and infestations' while the most common unsolicited AEs by PT were nasopharyngitis and viral upper respiratory tract infection. SAEs were reported by 2–5 % of subjects. No death was reported in the study. Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

No new clinical concerns were raised with respect to the safety data available in this study and the safety data included in the PI of each individual vaccine.

7.1. Conclusion

In conclusion, the study demonstrated the non-inferiority of combined rMenB+MenACWY vaccine to either rMenB or MenACWY administered alone. This is shown by lower limits of the 2-sided 95 % CIs of > 0.5 for the between ratios of GMTs (rMenB+ACWY vs. rMenB, and rMenB+ACWY vs. MenACWY) after the 4th vaccination for all serogroup B indicator strains and all serogroups A, C, W-135 and Y.

When comparing the vaccine groups rMenB+ACWY and rMenB, equally strong and potent immunogenicity against all MenB strains could be demonstrated as shown by the high proportion of subjects reaching hSBA GMTs ≥ 5 in both vaccine groups after the 4th vaccination.

Acceptable immune responses against the Men-groups A, C, W and Y were reached with the combined vaccine, demonstrated by strong increases of hSBA GMTs ≥8 across all strains already after the 3rd vaccination (96–100 % for rMenB+ACWY) and by a comparable proportion of individuals showing an at least 4-fold increase of titers compared to pre-4th vaccination (71–90 % range for both vaccine groups;

equal or higher proportions in the combined vaccine setup compared to MenACWY given alone), besides the fulfilment of the primary endpoint.

The safety profile is aligned with what has been reported previously. The vaccines were generally well tolerated but the reactogenicity was higher in the rMenB+ACWY and rMenB groups than in MenACWY group, as the rMenB+OMV NZ vaccine is known to be more reactogenic than the MenACWY vaccine. Overall, no new safety concerns were raised.

It can be concluded that the data adequately supports the proposed change, which is acceptable. The benefit–risk profile for rMenB+OMV NZ remains favorable following the review of the available data.

8. Changes to the Product Information

As a result of this variation, section 4.5 of the SmPC is updated to include information on concomitant administration of rMenB+OMV NZ and MenACWY vaccines. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

N/A