EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

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

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/014.1

Note

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

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Administrative information

Invented name of the medicinal product:	Bexsero
INN (or common name) of the active substance(s):	NHBA fusion protein, *Neisseria meningitidis*, serogroup B, recombinant , NadA protein, *Neisseria meningitidis*, serogroup B, recombinant, fHbp fusion protein, *Neisseria meningitidis*, serogroup B, recombinant , outer membrane vesicles (OMV), *Neisseria meningitidis*, serogroup B, strain NZ98/254
MAH:	Novartis Vaccines and Diagnostics S.r.l.
Currently approved Indication(s):	Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B
Pharmaco-therapeutic group (ATC Code):	J07AH09
Pharmaceutical form(s) and strength(s):	Suspension for injection
Rapporteur:	Kristina Dunder

1. Introduction

On October 20, 2014, 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.

The current procedure relates to a question raised in procedure EMA/H/C/2333/P46 014. Thus, the AR for EMA/H/C/2333/P46 014 is reproduced below, and the response to the question is assessed at the end of the report for clarity.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study V72P12E2 "A Phase 3, Open Label, Multicenter, Extension Study to Assess Antibody Persistence and Response to a Third or Fifth Dose of Novartis Meningococcal B Recombinant Vaccine in 4-Year-Old Children Who Previously Participated in Study V72P12E1" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- V72P12E2 "A Phase 3, Open Label, Multicenter, Extension Study to Assess Antibody Persistence and Response to a Third or Fifth Dose of Novartis Meningococcal B Recombinant Vaccine in 4-Year-Old Children Who Previously Participated in Study V72P12E1"

2.3.2. Clinical study

V72P12E2 "A Phase 3, Open Label, Multicenter, Extension Study to Assess Antibody Persistence and Response to a Third or Fifth Dose of Novartis Meningococcal B Recombinant Vaccine in 4-Year-Old Children Who Previously Participated in Study V72P12E1"

Description

Methods

Objectives

Primary

To explore antibody persistence in 4-year-old children after a fourth dose boost of rMenB+OMV NZ administered at either 12, 18, or 24 months of age in study V72P12E1, in toddlers who previously

received a three-dose primary series of rMenB+OMV NZ (at 2, 3, 4 or 2, 4, 6 months of age) as infants in the original parent study V72P12.

Secondary

a. To explore antibody persistence in 4-year-old children after two catch-up doses of rMenB+OMV NZ administered to toddlers at 12 and 14, 18 and 20, or 24 and 26 months of age in study V72P12E1.

b. To characterize the antibody response to a fifth dose boost of rMenB+OMV NZ administered to 4-year-old children after a fourth dose boost of rMenB+OMV NZ, previously administered to toddlers at 12, 18, or 24 months of age in study V72P12E1.

c. To characterize the antibody response to a third dose boost of rMenB+OMV NZ administered to 4-year-old children after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14, 18 and 20, or 24 and 26 months of age in study V72P12E1.

d. To demonstrate a sufficient immune response to two catch-up doses of rMenB+OMV NZ administered 2 months apart to naïve 4-year-old children.

Safety Objectives:

a. To assess the safety and tolerability of a fifth dose boost of rMenB+OMV NZ administered to 4-year-old children after fourth dose boost of rMenB+OMV NZ previously administered to toddlers at 12, 18, or 24 months of age in V72P12E1 study.

b. To assess the safety and tolerability of a third dose boost of rMenB+OMV NZ administered to 4-year-old children after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14, 18 and 20, or 24 and 26 months of age in V72P12E1 study.

c. To assess the safety and tolerability of two catch-up doses of rMenB+OMV NZ administered 2 months apart to naïve 4-year-old children.

Study design

This trial (V72P12E2) is an extension of study V72P12E1. It was conducted as a multicenter study and enrolled approximately 4-year-old subjects, who completed the vaccination course of study V72P12E1 (called follow-on subjects in this report), and who met all other enrollment criteria for this extension study, were eligible to participate. The description of the vaccine groups in this study and their vaccination schedule in the previous extension trial is detailed in Table 2-1.

Table 2-1: Vaccination Schedule

V72P12E1		V72P12E2		
			Procedure	
Groups	Vaccination Schedule	Groups	Antibody Persistence	Immunogenicity and safety
B+R246 12[a] B+R246 18[b] B+R246 24[c]	rMenB+OMV NZ +Routine vac at 2, 4, 6 months Booster at 12, 18, or 24 months (N=481)	B+R246 12_48, B+R246 18_48, B+R246 24_48	Subset #1 and #2[j]: Blood sample at ~4 years of age	Subset #2[j]: Fifth dose boost of rMenB+OMV NZ at ~4 years of age Blood sample at 1 month after 5th dose boost.
B246 12[d] B246 18[e] B246 24[f]	rMenB+OMV NZ at 2, 4, 6 months + Routine vac. at 3, 5, 7 months, Booster at 12, 18, or 24 months (N=449)	B246 12_48,B246 18_48 , B246 24_48		
B+R234 12[g] B+R234 18[h] B+R234 24[i]	rMenB+OMV NZ + Routine vac at 2, 3, 4 months Booster at 12, 18, or 24months (N=244)	B+R234 12_48	Blood sample at ~4 years of age. Fifth dose boost of rMenB+OMV NZ at ~4 years of age. Blood sample at 1 month after 5th dose boost.	
		B+R234 18_48		
		B+R234 24_48		
B12 14	rMenB+OMV NZ catch up doses at 12&14 months (N=237)	B12 14_48	Blood sample at ~4 years of age. Third dose boost of rMenB+OMV NZ at ~4 years of age. Blood sample at 1 month after 3rd dose boost.	
B18 20	rMenB+OMV NZ catch up doses at 18&20 months (N=51)	B18 20_48		
B24 26	rMenB+OMV NZ catch up doses at 24&26 months (N=52)	B24 26 _48		
		B48_50 (Naïve subjects at ~4 years of age; (N=190)	Blood sample at baseline. 2 catch up doses of rMenB+OMV NZ two months apart. 2 blood samples 1 month after each dose.	

Note: Groups names as used in original study V72P12E1 - aGroup 1a; bGroup 1b; cGroup 1c; dGroup 2a; eGroup 2b; fGroup 2c; gGroup 3a, hGroup 3b, iGroup 3c. Subjects of B+R246 (12/18/24) and B246 (12/18/24) groups from V72P12E1 were randomized in 2:1 ratio into: Nonvaccination subset #1 and vaccination subset #2.

Study population /Sample size

Number of Subjects:

Based on the number of subjects who completed their vaccination course in study V72P12E1, up to a maximum of ~1510 subjects (follow-on groups) were eligible to participate in this extension study. The

study centers in Germany and Belgium, which had enrolled 271 and 175 subjects respectively, in the V72P12E1 study, did not participate in this extension study.

A group of approximately 190 newly recruited vaccine naive subjects (B48_50 group), of similar age to the follow-on subjects were also planned to be enrolled into the study from the same study centers as the previous study V72P12E1. In total, up to approximately 1700 subjects could be enrolled in this study.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Healthy children, approximately 4 years of age, who participated and completed the vaccination course as toddlers in study V72P12E1 and who met all other enrollment criteria for this extension study, were eligible to participate.

An additional study group (vaccine naive subjects group B48_50), consisting of 190 newly recruited, vaccine naive, of similar age to the follow-on subjects (approximately 4 years) were enrolled into the study. These subjects served as a baseline comparator for comparison of antibody persistence with the vaccine-treated groups. The immune response following the first dose also served as a comparator for the booster responses in the vaccine groups.

Treatments

The investigational vaccine used in this study was the meningococcal B recombinant vaccine formulated with outer membrane vesicles derived from *N meningitidis* serogroup B strain NZ98/254 (OMV NZ) (rMenB+OMV NZ), (lot number: 112801). The meningococcal B recombinant (rMenB+OMV NZ) vaccine was provided as offwhite opalescent suspension for injection. This vaccine was supplied as a single-dose syringe. It was administered intramuscularly (IM) in the deltoid region.

Outcomes/endpoints

Immunogenicity Endpoints:

Following are the endpoints for evaluating immunogenicity against *N meningitidis* serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713.

Primary:

For groups with primary vaccination at 2, 4 6 months of age (with [B+R246] or without [B246] concomitant routine vaccinations) and at 2, 3, 4 months of age, [B+R234] (all groups with 4th dose at 12, 18 or 24 Months of age), the persistence of serum bactericidal activity at 4 years of age was assessed by calculating percentage of subjects with hSBA titers ≥ 5, hSBA titers ≥ 8, hSBA geometric mean titers (GMTs), and geometric mean ratio (GMRs) based on GMTs at 1 month after the last rMenB+OMV NZ booster vaccination (4th dose) in the V72P12E1 study, to each of the 4 indicator strains. All immunogenicity analyses were performed on the full analysis set (FAS)2.

Secondary:

For groups that received two catch-up doses at either 12, 14 (group B12 14), or 18, 20 (group B18 20) or 24, 26 months of age (group B24 26) the persistence of serum bactericidal activity at 4 years of age was assessed by calculating percentage of subjects with hSBA titers ≥ 5, hSBA titers ≥ 8, hSBA GMTs, and GMRs based on GMTs at 1 month after the last rMenB+OMV NZ vaccination in the V72P12E1 study, to each of the 4 indicator strains. All immunogenicity analyses were performed on the FAS population.

For subset#2 of groups B+R246 (12/18/24) and B246 (12/18/24) and for all subjects in B+R234 (12/18/24): induction of bactericidal antibodies at 1 month following a 5th dose boost of rMenB+OMV NZ vaccination was characterized by calculating hSBA GMTs, percentage of subjects with hSBA titers ≥ 5 and ≥ 8, and 4-fold increase to each of the 4 indicator strains.

For groups that received a two-dose catch-up in V72P12E1, induction of bactericidal antibodies at 1 month following a 3rd dose boost of rMenB+OMV NZ vaccination was characterized by calculating SBA GMTs, percentage of subjects with hSBA titers ≥ 5 and ≥ 8, and 4-fold increase to each of the 4 indicator strains.

In healthy naïve children of ~4 years of age after a two-dose catch-up, a sufficient immune response of rMenB+OMV NZ was defined as the lower limit of the twosided 95% CI for the percentage of subjects achieving hSBA titers ≥ 5 at 1 month after the two-dose series to be ≥70% for all 3 indicator strains. Analysis on strain M10713 for naive group was descriptive.

Baseline antibody levels measured in vaccine naive subjects at approximately 4 years of age (B48_50) served as a descriptive comparator to evaluate antibody persistence at 4 years of age in follow-on subjects from parent study V72P12E1. The immune response following the first dose also served as a comparator for the booster responses in the follow-on groups. The antibody response to catch-up doses at 4 years of age in vaccine naïve subjects also served to gain experience with catch-up immunizations with rMenB+OMV NZ in older age group.

Safety Endpoints

All subjects who received at least one dose of rMenB+OMV NZ vaccine in this study and who provided any postvaccination safety data were included in the safety and tolerability analyses. All safety analyses were descriptive.

Solicited local and systemic adverse events:

Incidences of solicited local adverse events (AEs) (i.e., pain, erythema, induration, swelling) and systemic AEs (i.e., fever [defined as axillary temperature ≥ 38.0 °C], change in eating habits, sleepiness, vomiting, diarrhea, irritability, headache, arthralgia, and rash) occurring during the 7 days following each study vaccination were summarized by maximal severity and study group.

Erythema, induration and swelling were categorized as none, 0 to < 10 mm, 10 to < 25 mm, 25 to < 50 mm, 50 to < 100 mm and ≥ 100 mm. Temperature was taken by the axillary route and was analyzed in 0.5 °C increments as follows: < 38.0°C (no fever), 38.0 - 38.4°C, 38.5°C - 38.9°C, 39.0°C – 39.4°C, 39.5°C – 39.9°C, ≥ 40.0°C. All other systemic AEs were categorized as mild, moderate or severe.

Additionally, the numbers of subjects who used antipyretic medication (prophylactically or therapeutically) within 7 days of study vaccination were summarized.

Unsolicited Adverse Events

All AEs occurring during the 7 days following each study vaccination were collected. Medically attended fever was also specifically collected during this time period. Serious adverse events (SAEs) as well as AEs that require a medical visit and/or result in premature withdrawal from the study were collected throughout the study period.

Statistical Methods

Immunogenicity: The primary analysis population for immunogenicity analysis is the full analysis set (FAS). Immunogenicity was evaluated for persistence, booster response and for immunogenicity after two catch-up doses in 4-year-old vaccine naïve subjects.

The percentage of subjects with hSBA titers ≥ 5 and ≥ 8 and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) were computed for follow-on groups and vaccine naive group (B48_50). In addition, differences in percentages and 95% CIs between follow-on groups vaccine naive group were also calculated for persistence and booster analysis.

All GMTs and associated 95% CIs were computed per group and per strain. For each vaccine group, adjusted GMTs and their 95% CIs were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs of the log transformed or concentrations (base 10). These were obtained from a two-way analysis of variance (ANOVA) with factors for vaccine and study country. Additionally, GMT ratios of follow-on groups to vaccine naive subjects (group B48_50) were computed. Further, 95% CIs for the ratios of GMTs were constructed by exponentiating the difference of the least square means of the log transformed titers and the lower and upper limits of the 95% CIs.

The percentage of subjects achieving 4-fold rise over baseline were calculated after 3rd or 5th dose boost in follow-on subjects and after first and second dose in vaccine naïve subjects.

Safety:

Solicited local and systemic adverse events: Frequencies and percentages of subjects experiencing each AE are presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point are also presented.

Unsolicited adverse events: The original verbatim terms used by investigators to identify AEs in the case report forms (CRFs) were mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The AEs were then grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, are summarized according to system organ class and preferred term within system organ class. These summaries are presented by vaccination group.

Results

Recruitment / Number analysed

A total of 242 follow-on subjects from groups B+R246 (12/18/24; N=38+ 41+ 43) and B246 (12/18/24; N=47+36+37) from V72P12E1 study were assigned to nonvaccination subset 1 in this extension study V72P12E2 for persistence analysis only. All subjects enrolled in the nonvaccination subset 1 completed the study.

A total of 563 subjects were enrolled in the extension study V72P12E2 (Table 10.1-2).

Table 10.1-2: Summary of Study Terminations Across Vaccine Groups with rMenB+OMV NZ Vaccination at 4 Years of Age (for Antibody Persistence and Response Analyses) – Enrolled Population

	rMenB+OMV NZ + Routine vaccines at 2, 4 and 6 months of age			rMenB+OMV NZ at 2, 4 and 6 months, Routine vaccines at 3, 5 and 7 months of age			rMenB+OMV NZ + Routine vaccines at 2, 3 and 4 months of age			rMenB+OMV NZ catch-up doses at 12 to 26 months of age			Naive
Groups	B+R246 12_48 N=29	B+R246 18_48 N=20	B+R246 24_48 N=17	B246 12_48 N=19	B246 18_48 N=28	B246 24_48 N=18	B+R234 12_48 N=43	B+R234 18_48 N=29	B+R234 24_48 N=28	B12 14_48 N=100	B18 20_48 N=11	B24 26_48 N=12	B48_50 N=209
Enrolled	29 (100%)	20 (100%)	17 (100%)	19 (100%)	28 (100%)	18 (100%)	43 (100%)	29 (100%)	28 (100%)	100 (100%)	11 (100%)	12 (100%)	209 (100%)
Completed study	29 (100%)	19 (95%)	16 (94%)	19 (100%)	27 (96%)	17 (94%)	41 (95%)	28 (97%)	26 (93%)	99 (99%)	11 (100%)	12 (100%)	190 (91%)
Premature withdrawals	0	1 (5%)	1 (6%)	0	1 (4%)	1 (6%)	2 (5%)	1 (3%)	2 (7%)	1 (1%)	0	0	19 (9%)
Withdrew consent	0	1 (5%)	1 (6%)	0	1 (4%)	0	2 (5%)	1 (3%)	2 (7%)	1 (1%)	0	0	18 (9%)
Lost to follow-up	0	0	0	0	0	1 (6%)	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0	1 (<1%)

Immunogenicity results

Antibody Persistence at 4 Years of Age

Antibody persistence was explored in 2 main groups of subjects in study V72P12E2:

Subjects who had received a 3-dose primary series of rMenB+OMV NZ at 2, 3, 4 or 2, 4, 6 months of age in parent study V72P12, followed by a 4th dose boost at 12, 18 or 24 months of age in 1st extension study V72P12E1 (groups B+R246 12, B+R246 18, B+R246 24, B+R246 12_48, B+R246 18_48, B+R246 24_48, B246 12, B246 18, B246 24, B246 12_48, B246 18_48, B246 24_48, B+R234 12_48, B+R234 18_48, and B+R234 24_48; see Table 2.5.4.2-1) (Primary objective).

Subjects who had received 2 catch-up doses of rMenB+OMV NZ at 12 and 14, 18 and 20, or 24 and 26 months of age in 1st extension study V72P12E1 (groups B12 14_48, B18 20_48, and B24 26_48; see Table 2.5.4.2-2) (Secondary objective).

Assessor's comment: The antibody persistence data show that for strain 5/99 most subjects have remaining titres, wile for strainsNZ98/254 (OMV) and H44/76 (fHBP) the seropositivity rates have declined substantially. The results for strain M10713 are similar to what has been seen in other studies, i.e. the baseline titres are very high, making it more difficult to interpret results.

The results for the 3-dose primed groups and the 2-dose catch-up groups were overall similar. For the catch-up groups the confidence intervals were wide in the smaller groups.

Table 2.5.4.2-1 Percentages of Subjects (95% CI) With hSBA Titers ≥ 5 at 4 Years of Age in Vaccine Groups That Received a 3-Dose Primary Series of rMenB+OMV NZ as Infants and a Booster as Toddlers – FAS (Persistence)

		rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age			Vaccine-naïve
		B+R246 12(_48)[a]	B+R246 18(_48)[a]	B+R246 24(_48)[a]	B246 12(_48)[a]	B246 18(_48)[a]	B246 24(_48)[a]	B+R234 12_48	B+R234 18_48	B+R234 24_48	B48_50
H44/76	Persistence at 4 Years of Age[b]	**N=67** 12% (5%-22%)	**N=60** 18% (10%-30%)	**N=59** 24% (14%-37%)	**N=65** 20%) (11%-32%)	**N=63** 27% (17%-40%)	**N=54** 35% (23%-49%)	**N=42** 12% (4%-26%)	**N=28** 25% (11%-45%)	**N=28** 21% (8%-41%)	**N=206** 0% (0.012%-3%)
5/99	Persistence at 4 Years of Age[b]	**N=67** 93% (83%-98%)	**N=60** 98% (91%-100%)	**N=58** 97% (88%-100%)	**N=64** 97% (89%-100%)	**N=62** 100% (94%-100%)	**N=54** 100% (93%-100%)	**N=42** 90% (77%-97%)	**N=28** 89% (72%-98%)	**N=28** 96% (82%-100%)	**N=200** 5% (2%-8%)
NZ98/254	Persistence at 4 Years of Age[b]	**N=67** 9% (3%-18%)	**N=60** 8% (3%-18%)	**N=60** 12% (5%-23%)	**N=66** 9% (3%-19%)	**N=63** 11% (5%-22%)	**N=54** 9% (3%-20%)	**N=42** 10% (3%-23%)	**N=28** 11% (2%-28%)	**N=28** 11% (2%-28%)	**N=206** 0% (0.012%-3%)
M10713	Persistence at 4 Years of Age[b]	**N=65** 54% (41%-66%)	**N=59** 68% (54%-79%)	**N=58** 74% (61%-85%)	**N=62** 55% (42%-68%)	**N=60** 53% (40%-66%)	**N=54** 80% (66%-89%)	**N=40** 68% (51%-81%)	**N=28** 75% (55%-89%)	**N=28** 75% (55%-89%)	**N=192** 60% (53%-67%)

Figure 1. Abbreviations: CI = confidence interval. hSBA = serum bactericidal assay using human complement. FAS = full analysis set.

[a] (_48) means that both the nonvaccination groups (subset #1, without the suffix "_48") and the vaccinated groups (subset #2, with suffix "_48") are included.

[b] Baseline for vaccine-naïve subjects (group B48_50).

Table 2.5.4.2-2 Percentages of Subjects (95% CI) With hSBA Titers ≥ 5 at 4 Years of Age in Vaccine Groups That Received 2 Catch-up Doses of rMenB+OMV NZ as Toddlers – FAS (Persistence)

		rMenB+OMV NZ Catch-up Doses at 12 to 26 Months of Age			Vaccine-Naive
		B12 14_48	B18 20_48	B24 26_48	B48_50
H44/76		N=96	N=11	N=11	N=206
	Persistence at 4 Years of Age[a]	11% (6%-20%)	9% (0%-41%)	9% (0%-41%)	0%[b] (0.012%-3%)
5/99		N=96	N=11	N=11	N=200
	Persistence at 4 Years of Age[a]	84% (76%-91%)	100% (72%-100%)	100% (72%-100%)	5% (2%-8%)
NZ98/254		N=96	N=11	N=11	N=206
	Persistence at 4 Years of Age[a]	3% (1%-9%)	18% (2%-52%)	0% (0%-28%)	0%[b] (0.012%-3%)
M10713		N=96	N=10	N=10	N=192
	Persistence at 4 Years of Age[a]	59% (49%-69%)	60% (26%-88%)	60% (26%-88%)	60% (53%-67%)

[a] Baseline for vaccine-naïve subjects (group B48_50).

[b] Percentages in this tables are rounded off. Actual value was 0.0049%.

Antibody Response to Booster Dose at 4 Years of Age

indicator strains H44/76, 5/99, NZ98/254 and M10713.

Antibody response to booster vaccination was characterized in 2 main groups of subjects in study V72P12E2:

Subjects who had received a 3-dose primary series of rMenB+OMV NZ at 2, 3, 4 or 2, 4, 6 months of age in parent study V72P12, followed by a 4th dose boost at 12, 18 or 24 months of age in study V72P12E1, and a 5th dose boost at 4 years of age in study V72P12E2 (groups B+R246 12_48, B+R246 18_48, B+R246 24_48, B246 12_48, B246 18_48, B246 24_48, B+R234 12_48, B+R234 18_48, and B+R234 24_48; see Table 2.5.4.3-1) (Secondary objective).

Subjects who had received 2 catch-up doses of rMenB+OMV NZ at 12 and 14, 18 and 20, or 24 and 26 months of age in study V72P12E1 and a 3rd dose boost at 4 years of age in study V72P12E2 (groups B12 14_48, B18 20_48, and B24 26_48; see Table 2.5.4.3-2) (Secondary objective).

Table 2.5.4.3-1 Percentages of Subjects With hSBA Titers ≥ 5 (95% CI) at 4 Years of Age Before and After a 5th Dose Boost of rMenB+OMV NZ in Vaccine Groups That Received a 3-Dose Primary Series as Infants and a Booster as Toddlers – FAS

		rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age			Vaccine-Naive
		B+R246 12(_48)[a]	B+R246 18(_48)[a]	B+R246 24(_48)[a]	B246 12(_48)[a]	B246 18(_48)[a]	B246 24(_48)[a]	B+R234 12_48	B+R234 18_48	B+R234 24_48	B48_50
H44/76		**N=64**	**N=59**	**N=59**	**N=62**	**N=62**	**N=52**	**N=41**	**N=26**	**N=28**	**N=183**
	Persistence at 4 Years of Age[b]	13% (6%-23%)	17% (8%-29%)	24% (14%-37%)	19% (10%-31%)	27% (17%-40%)	35% (22%-49%)	12% (4%-26%)	27% (12%-48%)	21% (8%-41%)	1% (0.014%-3%)
	1 Month After 5th Dose Boost in V72P1E2[c]	100% (87%-100%) N=26	100% (81%-100%) N=18	100% (79%-100%) N=16	100% (79%-100%) N=16	100% (87%-100%) N=26	100% (78%-100%) N=15	97% (87%-100%) N=39	100% (87%-100%)	100% (87%-100%) N=26	71% (64%-78%) N=175
5/99		**N=64**	**N=59**	**N=58**	**N=61**	**N=61**	**N=52**	**N=41**	**N=26**	**N=28**	**N=180**
	Persistence at 4 Years of Age[b]	92% (83%-97%)	98% (91%-100%)	97% (88%-100%)	97% (89%-100%)	100% (94%-100%)	100% (93%-100%)	90% (77%-97%)	92% (75%-99%)	96% (82%-100%)	4% (2%-9%)
	1 Month After 5th Dose Boost in V72P12E2[c]	100% (87%-100%) N=26	100% (81%-100%) N=18	100% (79%-100%) N=16	100% (79%-100%) N=16	100% (87%-100%) N=26	100% (78%-100%) N=15	100% (91%-100%) N=38	100% (87%-100%)	100% (87%-100%) N=26	90% (85%-94%) N=171

		rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age			Vaccine-Naive
		B+R246 12(_48)[a]	**B+R246 18(_48)[a]**	**B+R246 24(_48)[a]**	**B246 12(_48)[a]**	**B246 18(_48)[a]**	**B246 24(_48)[a]**	**B+R234 12_48**	**B+R234 18_48**	**B+R234 24_48**	**B48_50**
NZ98/254		**N=64**	**N=59**	**N=60**	**N=63**	**N=62**	**N=52**	**N=41**	**N=26**	**N=28**	**N=183**
	Persistence at 4 Years of Age[b]	9% (4%-19%)	8% (3%-19%)	12% (5%-23%)	10% (4%-20%)	11% (5%-22%)	10% (3%-21%)	10% (3%-23%)	12% (2%-30%)	11% (2%-28%)	0% (0%-2%)
	1 Month After 5th Dose Boost in V72P12E2[c]	92% (75%-99%) N=26	83% (59%-96%) N=18	94% (70%-100%) N=16	81% (54%-96%) N=16	88% (70%-98%) N=26	80% (52%-96%) N=15	95% (83%-99%) N=40	92% (75%-99%)	92% (75%-99%) N=26	24% (18%-31%) N=173
M10713		**N=62**	**N=58**	**N=58**	**N=60**	**N=59**	**N=52**	**N=39**	**N=26**	**N=28**	**N=172**
	Persistence at 4 Years of Age[b]	52% (39%-65%)	67% (54%-79%)	74% (61%-85%)	53% (40%-66%)	53% (39%-66%)	81% (67%-90%)	67% (50%-81%)	73% (52%-88%)	75% (55%-89%)	61% (53%-68%)
	1 Month after 5th Dose Boost in V72P12E2[c]	84% (64%-95%) N=25	89% (65%-99%) N=18	88% (62%-98%) N=16	93% (66%-100%) N=14	96% (80%-100%) N=25	93% (68%-100%) N=15	97% (85%-100%) N=36	100% (86%-100%) N=25	100% (86%-100%) N=25	77% (70%-83%) N=167

Abbreviations: CI = confidence interval. FAS = full analysis set.

[a] (_48) means that both the nonvaccination groups (subset #1, without the suffix "_48") and the vaccinated groups (subset #2, with suffix "_48") are included.

[b] Baseline for vaccine-naïve subjects (group B48_50).

[c] One month after 1st dose of rMenB+OMV NZ administered for vaccine-naïve subjects (group B48_50).

Source: CSR V72P12E2 Table 11.4.1-5.

Table 2.5.4.3-2 Percentages of Subjects with hSBA Titers ≥ 5 (95% CI) at 4 Years of Age Before and After a 3rd Dose Boost with rMenB+OMV NZ in Vaccine Groups That Received 2 Catch-up Doses as Toddlers - FAS

		rMenB+OMV NZ Catch-up Doses at 12 to 26 Months of Age			Vaccine-Naive
		B12 14_48	**B18 20_48**	**B24 26_48**	**B48_50**
H44/76		**N=97**	**N=10**	**N=12**	**N=183**
	Persistence at 4 Years of Age[a]	11% (5%-19%) N=95	10% (0%-45%)	9% (0%-41%) N=11	1% (0.014%-3%)
	1 Month After 3rd Dose Boost in V72P1E2[b]	100% (96%-100%)	100% (69%-100%)	100% (74%-100%)	71% (64%-78%) N=175
5/99		**N=95**	**N=10**	**N=12**	**N=180**
	Persistence at 4 Years of Age[a]	84% (75%-91%)	100% (69%-100%)	100% (72%-100%) N=11	4% (2%-9%)
	1 Month After 3rd Dose Boost in V72P12E2[b]	100% (96%-100%) N=94	100% (69%-100%)	100% (74%-100%)	90% (85%-94%) N=171
NZ98/254		**N=95**	**N=10**	**N=12**	**N=183**
	Persistence at 4 Years of Age[a]	2% (0%-7%)	20% (3%-56%)	0% (0%-28%) N=11	0% (0%-2%)
	1 Month after 3rd Dose Boost in V72P12E2[b]	96% (90%-99%)	70% (35%-93%)	100% (74%-100%)	24% (18%-31%) N=173
M10713		**N=95**	**N=9**	**N=10**	**N=172**
	Persistence at 4 Years of Age[a]	59% (48%-69%)	67% (30%-93%)	60% (26%-88%)	61% (53%-68%)
	1 Month after 3rd Dose Boost. in V72P12E2[b]	93% (86%-98%) N=90	100% (66%-100%)	90% (55%-100%)	77% (70%-83%) N=167

Abbreviations: CI = confidence interval. FAS = full analysis set.
[a] Baseline for vaccine-naïve subjects (group B48_50).
[b] One month after 1st dose of rMenB+OMV NZ administered for vaccine-naïve subjects (group B48_50).

Assessor's comment: The responses to a single booster dose resulted in higher proportions of responders in the previously primed groups, regardless of schedule, compared to the previously naïve children. These results indicate that all priming schedules induce immunological memory. The results for strain M10713 are more difficult to interpret, due to a high proportion of seropositive subjects prevaccination.

Safety results

Solicited Local and Systemic AEs

Incidences of solicited local AEs and systemic AEs occurring during the 7 days following each study vaccination were summarized by maximal severity and study group. Additionally, the numbers of

subjects who used antipyretic medication (prophylactically or therapeutically) and those who experienced medically attended fever within 7 days of study vaccination were summarized.

Local and Systemic AEs Following a 5th Dose Boost of rMenB+OMV NZ at 4 Years of Age

Across all study groups, most subjects who received a 5th dose boost of rMenB+OMV NZ at 4 years of age reported at least 1 solicited local or systemic AEs during the first 7 days (90% to 100%). Across study groups, 84% to 100% of subjects reported solicited local AEs and 70% to 95% of subjects reported solicited systemic AEs.

The most commonly reported solicited local AE across groups was injection site pain, and severe intensity of injection site pain ranged from 11% to 32% (Table 2.5.5.2-1).

The most commonly reported solicited systemic AE across study groups was irritability and severe intensity ranged from 0% to 12% of subjects. Other commonly reported systemic AEs were sleepiness, change in eating habits and arthralgia (Table 2.5.5.2-1).

Across study groups percentages of subjects reporting fever ranged from 4% to 21% of subjects. One subject from group B+R234 12_48 reported a temperature ≥ 40°C. Medically attended fever was reported in 2 subjects from group B+R246 12_48 and in 1 subject from group B+R234 12_48 (Table 2.5.5.2-1).

Table 2.5.5.2-1 Number (%) of Subjects With Local and Systemic AEs After a 5th Dose Boost of rMenB+OMV NZ in Groups With a 3-Dose Primary Series as Infants and a Booster as Toddlers - Safety Set (Solicited AEs) Days 1 - 7

	rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age		
	B+R246 12_48	**B+R246 18_48**	**B+R246 24_48**	**B246 12_48**	**B246 18_48**	**B246 24_48**	**B+R234 12_48**	**B+R234 18_48**	**B+R234 24_48**
Local AEs									
	N=29	**N=20**	**N=17**	**N=19**	**N=27**	**N=17**	**N=43**	**N=29**	**N=27**
Injection Site Pain[a] (Any)	27 (93%)	18 (90%)	17 (100%)	16 (84%)	23 (85%)	16 (94%)	38 (88%)	28 (97%)	27 (100%)
Severe	5 (17%)	4 (20%)	3 (18%)	6 (32%)	4 (15%)	5 (29%)	10 (23%)	8 (28%)	3 (11%)
Erythema (None)	21 (72%)	15 (75%)	13 (76%)	12 (63%)	13 (48%)	10 (59%)	26 (60%)	17 (59%)	19 (70%)
> 100 mm	1 (3%)	0	0	0	1 (4%)	1 (6%)	2 (5%)	0	0
Induration (None)	25 (86%)	17 (89%) N=19	16 (94%)	16 (84%)	20 (74%)	13 (76%)	34 (79%)	21 (72%)	20 (74%)
> 100mm	1 (3%)	0 N=19	0	0	0	1 (6%)	1 (2%)	0	0
Swelling (None)	26 (90%)	16 (84%) N=19	13 (76%)	13 (68%)	19 (70%)	11 (65%)	28 (65%)	17 (59%)	22 (81%)
> 100 mm	1 (3%)	0 N=19	0	0	0	1 (6%)	1 (2%)	0	0
Systemic AEs									
	N=29	**N=20**	**N=17**	**N=19**	**N=27**	**N=17**	**N=43**	**N=29**	**N=27**
Change in Eating Habits (Any)	12 (41%)	6 (32%) N=19	6 (35%)	12 (63%)	7 (26%)	8 (47%)	20 (47%)	11 (38%)	13 (48%)
Severe	0	0 N=19	0	0	1 (4%)	0	0	0	1 (4%)
Sleepiness (Any)	18 (62%)	7 (37%) N=19	8 (47%)	9 (47%)	12 (44%)	6 (35%)	22 (51%)	21 (72%)	14 (52%)

	rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age		
	B+R246 12_48	**B+R246 18_48**	**B+R246 24_48**	**B246 12_48**	**B246 18_48**	**B246 24_48**	**B+R234 12_48**	**B+R234 18_48**	**B+R234 24_48**
Severe	0	1 (5%) N=19	0	0	1 (4%)	0	0	0	1 (4%)
Vomiting (Any)	0	1 (5%) N=19	0	0	1 (4%)	0	5 (12%)	3 (10%)	2 (7%)
Severe	0	0 N=19	0	0	0	0	0	0	0
Diarrhea (Any)	4 (14%)	1 (5%) N=19	1 (6%)	2 (11%)	4 (15%)	2 (12%)	6 (14%)	4 (14%)	3 (11%)
Severe	0	0 N=19	0	0	0	0	0	0	0
Irritability (Any)	18 (62%)	9 (47%) N=19	11 (65%)	14 (74%)	13 (48%)	8 (47%)	23 (53%)	20 (69%)	16 (59%)
Severe	1 (3%)	1 (5%) N=19	2 (12%)	2 (11%)	0	2 (12%)	1 (2%)	3 (10%)	2 (7%)
Headache (Any)	5 (17%)	1 (5%) N=19	6 (35%)	3 (16%)	2 (7%)	3 (18%)	7 (16%)	5 (17%)	8 (30%)
Severe	1 (3%)	0 N=19	0	0	0	0	0	0	1 (4%)
Arthralgia (Any)	12 (41%)	4 (21%) N=19	6 (35%)	9 (47%)	8 (30%)	5 (29%)	11 (26%)	8 (28%)	12 (44%)
Severe	2 (7%)	1 (5%) N=19	0	3 (16%)	1 (4%)	0	1 (2%)	3 (10%)	2 (7%)
Rash (Any)	2 (7%)	1 (5%) N=19	0	5 (26%)	2 (7%)	4 (24%)	7 (16%)	5 (17%)	2 (7%)
Urticarial	1 (3%)	0 N=19	0	2 (11%)	0	3 (18%)	3 (7%)	3 (10%)	2 (7%)

	rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age		
	B+R246 12_48	**B+R246 18_48**	**B+R246 24_48**	**B246 12_48**	**B246 18_48**	**B246 24_48**	**B+R234 12_48**	**B+R234 18_48**	**B+R234 24_48**
Fever (≥38°C)	6 (21%)	3 (15%)	3 (18%)	2 (11%)	1 (4%) N=26	1 (6%)	5 (12%)	4 (14%)	2 (7%)
Temperature									
< 36.0°C	0	1 (5%)	0	0	1 (4%) N=26	0	0	0	0
≥ 40°C	0	0	0	0	0 N=26	0	1 (2%)	0	0
Antipyretic Use (Prophylactic)	1 (3%)	2 (10%)	1 (6%)	1 (5%)	2 (7%)	1 (6%)	7 (16%)	1 (3%)	1 (4%)
Antipyretic Use (Therapeutic)	5 (17%)	5 (25%)	4 (24%)	3 (16%)	3 (11%)	1 (6%)	10 (23%)	4 (14%)	3 (11%)
Medically-attended Fever	2 (7%)	0	0	0	0	0	1 (2%)	0	0

Abbreviation: AE = adverse event.

[a] Abbreviated to 'Pain' in source table CSR V72P12E2 Table 12.2.3.1.

Assessor's comment: The reactogenicity of Bexsero is in agreement with previously reported results. The rates of adverse events are high compared to many other vaccines. The fever rates in this age group appear to be somewhat lower compared to the fever rates in infants.

Local and Systemic AEs Following a 3rd Dose Boost of rMenB+OMV NZ at 4 Years of Age

The majority of subjects in study groups that received a 3rd dose boost of rMenB+OMV NZ at 4 years of age reported at least 1 solicited AE during the first 7 days postvaccination (90% to 100%). Across study groups, 90% to 95% of subjects reported solicited local AEs and 60% to 79% of subjects reported solicited systemic AEs.

The most commonly reported solicited local AE across study groups was injection site pain and severe intensity was reported in 8% to 19% of subjects. Severe intensity of erythema and induration was reported in 2% and 1% of subjects, respectively, from the study group B12 14_48 (Table 2.5.5.2-2).

Most commonly reported solicited systemic AE across study groups was irritability and severe intensity was reported by 6% of subjects from the study group B12 14_48. Other commonly reported systemic AEs were sleepiness, change in eating habits (0%-42%), arthralgia and headache (Table 2.5.5.2-2).

Percentages of subjects reporting fever across study groups ranged from 16% to 42% of subjects. None of the subjects reported fever ≥40°C. Medically attended fever was reported in 2 subjects from group B12 14_48 and 1 subject from group B18 20_48 (Table 2.5.5.2-2).

Table 2.5.5.2-2 Number (%) of Subjects With Local and Systemic AEs After a 3rd Dose Boost of rMenB+OMV NZ in Groups That Received 2 Catch-up Doses as Toddlers - Safety Set (Solicited AEs) Days 1-7

	rMenB+OMV NZ Catch-up Doses at 12 to 26 Months of Age		
	B12 14_48	**B18 20_48**	**B24 26_48**
Local AEs			
	N=99	**N=10**	**N=12**
Injection Site Pain[a] (Any)	94 (95%)	9 (90%)	11 (92%)
Severe	19 (19%)	1 (10%)	1 (8%)
Erythema (mm) (None)	78 (79%)	7 (70%)	12 (100%)
>100mm	2 (2%)	0	0
Induration (mm) (None)	90 (91%)	9 (90%)	12 (100%)
>100mm	1 (1%)	0	0
Swelling (None)	79 (80%)	8 (80%)	8 (67%)
>100mm	0	0	0
Systemic AEs			
	N=99	**N=10**	**N=12**
Change in eating habits (Any)	42 (42%)	0	3 (25%)
Severe	2 (2%)	0	1 (8%)
Sleepiness (Any)	52 (53%)	3 (30%)	3 (25%)
Severe	3 (3%)	0	0
Vomiting (Any)	6 (6%)	2 (20%)	1 (8%)
Severe	0	0	0
Diarrhea (Any)	5 (5%)	0	2 (17%)
Severe	0	0	0
Irritability (Any)	53 (54%)	4 (40%)	5 (42%)
Severe	6 (6%)	0	0
Headache (Any)	20 (20%)	2 (20%)	4 (33%)
Severe	1 (1%)	0	0
Arthralgia (Any)	28 (28%)	1 (10%)	6 (50%)
Severe	10 (10%)	0	1 (8%)

	rMenB+OMV NZ Catch-up Doses at 12 to 26 Months of Age		
	B12 14_48	**B18 20_48**	**B24 26_48**
Rash (Any)	13 (13%)	0	0
Urticarial	4 (4%)	0	0
Fever (≥ 38°C)	16 (16%)	4 (40%)	5 (42%)
Temperature (°C)			
<36.0°C	0	0	0
≥40°C	0	0	0
Antipyretic use (Prophylactic)	5 (5%)	2 (20%)	2 (17%)
Antipyretic use (Therapeutic)	18 (18%)	4 (40%)	5 (42%)
Medically-attended fever	2 (2%)	1 (10%)	0

Abbreviation: AE = adverse event.

[a] Abbreviated to 'Pain' in source table CSR V72P12E2 Table 12.2.3.1.

Assessor's comment: The frequencies and severity of AEs did not differ substantially between the different vaccination schedules, i.e. following the 5th or 3rd dose.

Local and Systemic AEs Following Two Catch-up Doses of rMenB+OMV NZ at 4 Years of Age

The majority of subjects in group B48_50 that received 2 catch-up doses of rMenB+OMV NZ 2 months apart at 4 years of age reported at least 1 solicited AE during the first 7 days after any vaccination (97%). Most subjects (94%) reported solicited local AEs and 78% of subjects reported solicited systemic AEs.

The most commonly reported solicited local AE was injection site pain. Severe intensity of pain was reported in 13% and 11% of subjects post-1st and -2nd vaccination, respectively. (Table 2.5.5.2-3).

Most commonly reported solicited systemic AE was sleepiness, with severe intensity reported in 2% and 1% of subjects post-1st and 2nd vaccination, respectively. Other commonly reported systemic AEs were irritability, change in eating habits and arthralgia (Table 2.5.5.2-3).

Percentages of subjects reporting fever in study group B48_50 post-1st and 2nd vaccination were 10% and 8% of subjects, respectively. Two subjects reported temperature ≥ 40°C post-1st vaccination. Medically attended fever was reported in 2 subjects post-1st vaccination and 4 subjects post-2nd vaccination (Table 2.5.5.2-3).

Table 2.5.5.2-3 Number (%) of Subjects With Local and Systemic AEs After the 1st and 2nd rMenB+OMV NZ Vaccination in Vaccine-naïve Subjects - Safety Set (Solicited AEs) Days 1-7

	B48_50	
	1st Vaccination	**2nd Vaccination**
Local AEs		
	N=205	**N=194**
Injection Site Pain[a] (Any)	185 (90%)	157 (81%)
Severe	27 (13%)	21 (11%)
Erythema (mm) (None)	161 (79%) N=204	160 (82%)
>100mm	1 (<1%) N=204	0
Induration (mm) (None)	178 (87%) N=204	174 (90%)
>100mm	0 N=204	0
Swelling (None)	174 (85%) N=204	170 (88%)
>100mm	1 (<1%) N=204	0
Systemic AEs		
	N=205	**N=194**
Change in eating habits (Any)	49 (24%) N=203	43 (22%)
Severe	3 (1%) N=203	2 (1%)
Sleepiness (Any)	74 (36%)	67 (35%) N=193
Severe	5 (2%)	2 (1%) N=193
Vomiting (Any)	8 (4%)	6 (3%)
Severe	0	0
Diarrhea (Any)	11 (5%) N=204	8 (4%) N=193
Severe	1 (<1%) N=204	0 N=193
Irritability (Any)	67 (33%) N=204	58 (30%) N=193
Severe	8 (4%) N=204	5 (3%) N=193
Headache (Any)	25 (12%) N=204	24 (12%)
Severe	1 (<1%) N=204	1 (1%)

	B48_50	
	1st Vaccination	2nd Vaccination
Arthralgia (Any)	45 (22%) N=203	40 (21%) N=192
Severe	6 (3%) N=203	2 (1%) N=192
Rash (Any)	15 (7%) N=201	10 (5%) N=192
Urticarial	6 (3%) N=201	2 (1%) N=192
Fever (≥ 38°C)	20 (10%) N=204	16 (8%) N=189
Temperature (°C)		
< 36.0°C	5 (2%) N=204	5 (3%) N=189
≥ 40°C	2 (1%) N=204	0 N=189
Antipyretic use (Prophylactic)	17 (8%) N=204	23 (12%) N=192
Antipyretic use (Therapeutic)	22 (11%) N=204	24 (12%) N=193
Medically-attended fever	2 (1%) N=204	4 (2%) N=192

Abbreviation: AE = adverse event.

[a] Abbreviated to 'Pain' in source table CSR V72P12E2 Table 12.2.3.1.

Assessor's comment: The AEs reporting is genereally in agreement in the previously unvaccinated group compared to the previously primed groups.

Unsolicited AEs Following a 5th Dose Boost of rMenB+OMV NZ at 4 Years of Age

Percentages of subjects with any and possibly or probably related unsolicited AEs during the first 7 days following a 5th dose boost of rMenB+OMV NZ at 4 years of age both ranged from 0% to 37% across study groups.

Unsolicited AEs from day 1 to 7 were reported most commonly in the system organ class (SOC) "General disorders and administration site conditions". Most of these were solicited AEs continuing past 7 days after vaccination and were considered possibly or probably related to the study vaccination.

Percentages of subjects with any unsolicited AEs from day 1 through study termination following a 5th dose of rMenB+OMV NZ at 4 years of age ranged from 18% to 38%, and possibly or probably related AEs ranged from 0% to 37% across groups (Table 2.5.5.3-1).

Injection site induration was the most commonly reported unsolicited AE from day 1 through study termination, reported in 2% to11% of subjects. All of these were considered possibly or probably related to the study vaccination.

None of the subjects reported SAEs or AEs leading to withdrawal or death from day 1 through study termination (Table 2.5.5.3-1).

Table 2.5.5.3-1 Overview of Unsolicited AEs After a 5th Dose Boost of rMenB+OMV NZ From Day 1 Through Study Termination in Groups That Received a 3-Dose Primary Series as Infants and a Booster as Toddlers - Safety Set (Unsolicited AEs)

	rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 Months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age		
	B+R246 12_48	B+R246 18_48	B+R246 24_48	B246 12_48	B246 18_48	B246 24_48	B+R234 12_48	B+R234 18_48	B+R234 24_48
	N=30	N=20	N=17	N=19	N=27	N=17	N=43	N=29	N=28
Any AEs	8 (27%)	4 (20%)	4 (24%)	7 (37%)	7 (26%)	3 (18%)	11 (26%)	11 (38%)	6 (21%)
Possibly/Probably Related AEs	6 (20%)	0	3 (18%)	7 (37%)	5 (19%)	1 (6%)	6 (14%)	5 (17%)	3 (11%)
SAEs	0	0	0	0	0	0	0	0	0
Possibly/Probably Related SAEs	0	0	0	0	0	0	0	0	0
AEs Leading to Withdrawal	0	0	0	0	0	0	0	0	0
AEs Leading to Death	0	0	0	0	0	0	0	0	0

Abbreviation: AE, adverse event.

Unsolicited AEs Following a 3rd Dose Boost of rMenB+OMV NZ at 4 Years of Age

Percentages of subjects with any unsolicited AEs during the first 7 days following a 3rd dose boost of rMenB+OMV NZ at 4 years of age ranged from 9% to 25% and possibly or probably related AEs ranged from 8% to 17% across study groups.

Unsolicited AEs from day 1 to 7 were reported most commonly (7% to 17% of subjects, none reported in B18 20_48) in the SOC "General disorders and administration site conditions". Possibly or probably related AEs were reported in 6% and 8% of subjects in these groups. In group B18 20_48 unsolicited AEs were most commonly (9%) in the SOC "Infections and infestations"; all of these were considered possibly related to the study vaccination.

Percentages of subjects with any unsolicited AEs from day 1 through study termination following a 3rd dose of rMenB+OMV NZ at 4 years of age ranged from 18% to 33%, and possibly or probably related AEs ranged from 8% to 17% across groups (Table 2.5.5.3-2).

Pyrexia was the most commonly reported unsolicited AE from day 1 through study termination, reported in 3% to17% of subjects across all 3 groups. One subject (group B24 26_48) reported possibly related pyrexia.

None of the subjects reported SAEs or AEs leading to withdrawal or death from day 1 through study termination (Table 2.5.5.3-2).

Table 2.5.5.3-2 Overview of Unsolicited AEs After a 3rd Dose Boost of rMenB+OMV NZ From Day 1 Through Study Termination in Groups That Received 2 Catch-up Doses as Toddlers - Safety Set (Unsolicited AEs)

	rMenB+OMV NZ Catch-up Doses at 12 to 26 Months of Age		
	B12 14_48	**B18 20_48**	**B24 26_48**
	N=100	**N=11**	**N=12**
Any AEs	25 (25%)[a]	2 (18%)	4 (33%)
Possibly/Probably Related AEs	8 (8%)	1 (9%)	2 (17%)
SAEs	0	0	0
Possibly/Probably Related SAEs	0	0	0
AEs Leading to Withdrawal	0	0	0
AEs Leading to Death	0	0	0

Abbreviations: AE = adverse event. SAE = serious adverse event.

Unsolicited AEs Following Two Catch-up Doses of rMenB+OMV NZ at 4 Years of Age

Following any vaccination at 4 years of age in group B48_50, the percentage of subjects with any unsolicited AE during the first 7 days was 29% and possibly or probably related AEs were reported by 15% of subjects.

Unsolicited AEs from day 1 to 7 were reported most commonly (10% of subjects) in the SOC “General disorders and administration site conditions” and “infections and infestations” after any vaccination. Nearly all of the general disorders and administration site conditions and 1% of reported infections and infestations were considered possibly or probably related to study vaccine.

One subject (467017) reported an SAE, gastroenteritis of moderate intensity on day 67 (7 days post-2nd vaccination at 4 years of age). The event was considered not related to the study vaccination. One subject (017006) was withdrawn from study due to an AE (injection site pain of moderate intensity). The event was considered probably related to the study vaccination.

Percentage of subjects with any unsolicited AEs from day 1 through study termination following any vaccination at 4 years of age in study group B48_50 was 51% and possibly or probably related AEs were reported by 15% of subjects (Table 2.5.5.3-3).

The most commonly reported unsolicited AEs following any vaccination with rMenB+OMV NZ in study group B48_50 were injection site induration; cough and bronchitis reported in 6% 5% and 4% of subjects respectively. All cases with injection site induration were possibly or probably related to study vaccination (Table 12.2.3-9).

Serious adverse events were reported by 3 subjects (1%) after any vaccination from day 1 through study termination. Subject 017025 reported infectious croup, subject 105013 reported concussion, contusion and periorbital haematoma and subject 467017 reported gastroenteritis and dehydration. All these events were considered not related to the study vaccination. As reported earlier, one subject

(subject ID: 017006) was withdrawn from study due to an AE (injection site pain of moderate intensity). The AE, injection site pain was considered probably related to the study vaccination

Table 2.5.5.3-3 Overview of Unsolicited AEs From Day 1 Through Study Termination After Any rMenB+OMV NZ Vaccination in Vaccine-naïve Group

	Vaccine-Naive
	B48_50
	N=206
Any AEs	105 (51%)
Possibly/Probably Related AEs	31 (15%)
SAEs	3 (1%)
Possibly/Probably Related SAEs	0
AEs Leading to Withdrawal	1 (< 1%)
AEs Leading to Death	0

Abbreviation: AE, adverse event; SAE, serious adverse event.

Assessor's comment: No new safety signal was detected from the unsolicited AEs reporting.

Discussion on clinical aspects

These data represent the longest persistence data presented so far in children with a sample size that allows conclusions for most groups. As discussed earlier, the waning antibody titres and seropositivity are of concern for two of the antigens, the OMV and fHBP. The respective roles of persisting antibodies and immunological memory are not fully understood, and the clinical relevance of the waning titres is unclear. It could be discussed whether the persistence data should be included in the SPC, for increased transparency of the data. Considering that the relevance of waning titres to two out of four antigens, in the presence of immunological memory is unclear it is doubtful that this will be of any assistance to the prescribers. Thus, a detailed description of the data is not warranted in the SPC, but a brief description of the persistence data could be useful. The MAH is asked to discuss the need relevance of these findings, together with other persistence data. Considering the limited time since approval, and that the vaccine is only beginning to be used on a larger scale, it is unlikely that effectiveness data from post-marketing experience is available yet.

Additional clarifications requested

1. The MAH is asked to discuss the need relevance of the waning antibody titres and seropositivity rates, together with other persistence data, and discuss the need to include further data in the SPC.

Assessment of responses to additional clarifications.

The MAH is asked to discuss the need relevance of the waning antibody titres and seropositivity rates, together with other persistence data, and discuss the need to include further data in the SPC.

MAH Response

Novartis acknowledges that persistence data from study V72P12E2 show a decline in antibodies against strains NZ98/254 (OMV) and H44/76 (fHbp) in previously primed children 4 years of age. Antibody decline after a primary vaccination course is a common feature of the response to infant vaccines irrespective of the priming schedule. Nevertheless, immunological measurements are surrogates and only indirectly relate to protection. Exposure to the organism (or to a booster dose of the vaccine) induces anamnestic antibody responses in most subjects primed as infants even though prechallenge antibodies may have dwindled demonstrating evidence the vaccine induced immune memory. (see Plotkin, 2008).

Indeed, the responses to a single booster dose in study V72P12E2 resulted in high percentages of subjects achieving protective levels of bactericidal antibodies (hSBA ≥ 1:5) against all 4 indicator strains irrespective of the priming schedule. In particular against the NZ98/254 and H44/76 antigens, for which the antibody titers declined the most, response to booster vaccination was high (and similar to or even higher than responses seen after the 3-dose primary vaccination course (parent study V72P12) and after the 4th dose boost (first extension study V72P12E1)). In addition, the responses to a booster dose elicited much higher antibody levels in previously primed children compared with antibody levels observed in age-matched vaccine naïve children after one dose of rMenB+OMV NZ.

Moreover, bactericidal antibodies against PorA P1.4 and fHbp, and the persistence of antibodies to these antigens will not be the sole predictors of protective activity, as bactericidal activity against other vaccine antigens will also contribute to protection. The likelihood that the vaccine is not protective is thought to be reduced when bactericidal antibodies induced by vaccination are targeting multiple antigens on the surface of the meningococcus.

Antibodies to multiple antigens may act synergistically to enhance bactericidal activity thus underestimating the true protective activity of the vaccine-induced antibodies. For example, there are data indicating that antibodies to NHBA and fHbp can cooperate resulting in enhanced bactericidal activity (Vu et al. 2011). In addition, Donnelly and colleagues have shown that strains are killed more efficiently when targeted by antibodies against two or more antigens (Donnelly et al. 2010).

The observation that a booster dose at 4 years of age restores hSBA ≥ 1:5 percentages to high values suggest powerful anamnestic responses to all 4 indicator strains in children that have been primed as infants and received a 4th dose boost as toddlers as per recommendation in the SmPC, irrespective of the persisting levels of antibodies against the respective strains present at 4 years of age. Together with the argument that bactericidal activity against all 4 indicator strains contribute to protection, and that antibodies to multiple antigens may act synergistically, the relevance of waning titers to 2 out of 4 antigens is unclear.

Based on the above, Novartis agrees with the assessment of the Rapporteur that it is doubtful whether inclusion of additional information regarding persistence of antibodies will be of any assistance to the prescribers and therefore suggests not to include it in the SmPC.

Additional note on safety data from study V72P12E2

Upon review of the data from this study Novartis identified two adverse reactions, headache and arthralgia, that were reported by ≥ 10% of subjects approximately 4 years of age regardless of previous vaccination schedule.

These adverse reactions are not considered a new signal for identified or potential risks that require an update of the Risk Management Plan for rMenB+OMV NZ because they do not impact the positive

benefit-risk profile of the vaccine, as stated in section 2.5.6 of the addendum to the Clinical Overview submitted in support of study V72P12E2 under Article 46 of the Paediatric Regulation.

However, these reactions are currently not listed for children in the relevant age group in the SmPC of rMenB+OMV NZ and based on the data from study V72P12E2 Novartis considers their addition to the SmPC warranted.

Novartis will follow the appropriate procedure to implement these changes to the SmPC.

Assessment: The MAH has provided a discussion on the relevance of the waning antibody titres. The discussion is based on similar arguments as were provided during the approval process. In conclusion, the relevance of waning antibody titres is not known, and whether immunological memory is sufficient to protect can only be speculated on. Likewise, the vaccine composition, i.e. multiple antigens, may reduce the importance of sustained antibody levels to all antigens, but again the relevance is unknown. Therefore, a sentence should be added to section 5.1 of the SPC, stating that antibody levels to the OMV and fHbp antigens have waned at four years of age in children fully vaccinated with a 3+1 vaccination schedule, although the presence of immunological memory is considered demonstrated, and the relevance of this is currently unknown.

The proposed update of section 4.8 is agreed.

3. Rapporteur's overall conclusion and recommendation

The commitment is considered fulfilled, by the submission of the full clinical study report, and the response to the question. However, a SPC change is considered necessary for full transparency of the data. Section 5.1 should include a statement that antibody levels to the OMV and fHbp antigens have waned at four years of age in children fully vaccinated with a 3+1 vaccination schedule, although the presence of immunological memory is considered demonstrated, and the relevance of this is currently unknown, and section 4.8 should be updated according to the MAH suggestion above.

Overall conclusion

Recommendation

☒ Fulfilled:

Type II variation to be requested from the MAH within 3 months to amend the product information as follows:

Section 5.1 should include a statement that antibody levels to the OMV and fHbp antigens have waned at four years of age in children fully vaccinated with a 3+1 vaccination schedule, although the presence of immunological memory is considered demonstrated, and the relevance of this is currently unknown, and section 4.8 should be updated according to the MAH suggestion above.

☐ Not fulfilled:

Additional clarifications requested

Not applicable.