



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 November 2014
EMA/646697/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

Bexsero

International non-proprietary name: **recombinant Neisseria meningitidis group-B NHBA fusion protein / recombinant Neisseria meningitidis group-B NadA protein / recombinant Neisseria meningitidis group B fHbp fusion protein / outer membrane vesicles from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4**

Procedure Number: EMEA/H/C/2333/P46/012

Note

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



1. INTRODUCTION

On April 1, 2014 the MAH submitted a completed paediatric study for Bexsero in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Bexsero and that there is no consequential regulatory action.

2. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

The commercial formulation of Bexsero was used in the clinical studies.

Clinical aspects

Introduction

The MAH submitted a final report for:

- V72P9E1: A Phase 2, Open-Label, Single-Center, Extension Study Evaluating Antibody Persistence Compared to Naive Children and Safety, Tolerability and Immunogenicity of a Booster Dose of Novartis rMenB±OMV NZ Vaccine in Healthy UK Children Who Previously Received a Three-Dose Series of the Novartis Vaccine as Infants in Study V72P9

Clinical study

V72P9E1: A Phase 2, Open-Label, Single-Center, Extension Study Evaluating Antibody Persistence Compared to Naive Children and Safety, Tolerability and Immunogenicity of a Booster Dose of Novartis rMenB±OMV NZ Vaccine in Healthy UK Children Who Previously Received a Three-Dose Series of the Novartis Vaccine as Infants in Study V72P9

➤ **Description**

This study was an extension of study V72P9. It was conducted as an open-label, single centre study (Oxford Vaccine Group, Oxford University Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, UK).

➤ **Methods**

- Objectives

Immunogenicity objectives

Primary

To explore bactericidal antibody persistence in children at 40 months of age who previously received three doses of rMenB or rMenB+OMV NZ as infants in parent study V72P9.

Secondary

- a) To characterize the bactericidal antibody response of a booster dose of rMenB or rMenB+OMV NZ administered at 40 months of age to children who previously received three doses of the same vaccine as infants in parent study V72P9.
- b) To explore bactericidal antibody persistence in children at 60 months of age who received a booster dose of rMenB or rMenB+OMV NZ at 40 months of age in the present extension study.
- c) To assess the bactericidal antibody response of a two-dose catch-up regimen of rMenB+OMV NZ administered to naive children at 40 and 42 months of age or at 60 and 62 months of age.
- d) To explore bactericidal antibody persistence in children at 60 months of age who received a two-dose catch-up regimen of rMenB+OMV NZ administered to naive children at 40 and 42 months of age in the present extension study.
- e) For all immunogenicity objectives, responses were also determined to vaccine antigen 287-953 by Enzyme Linked Immunosorbent Assay (ELISA).

Safety objectives

Primary

To assess the safety and tolerability of a booster dose of rMenB or rMenB+OMV NZ administered to children at 40 months of age who previously received three doses of the same vaccine as infants in parent study V72P9.

Secondary

To assess the safety and tolerability of a two-dose catch-up regimen of rMenB+OMV NZ administered to naive children starting at 40 and 60 months of age.

- Study design

This study was an extension of study V72P9. It was conducted as an open-label, single centre study (Oxford Vaccine Group, Oxford University Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, UK).

- Study population /Sample size

57 subjects completed parent study V72P9 and were potentially eligible for the extension study. Of these, 16 and 14 subjects were enrolled into groups 4rMenB and 4rMenB+OMV NZ respectively.

Two groups of newly recruited, naive subjects, 40 months and 60 months of age, were also enrolled into the study. 50 subjects were to be enrolled in each group. 41 subjects were enrolled in group III and 49 subjects were enrolled in group IV.

Subjects eligible to be enrolled in the study were healthy 40-44 months old children who participated and completed the V72P9 study; naive subjects aged 40 to 44 months and 60 to 62 months; for whom a parent/legal guardian has given written informed consent after the nature of the study has been explained; available for all the visits scheduled in the study; in good health as determined by: medical history, physical examination and clinical judgment of the investigator.

- Treatments

Subjects who completed study V72P9 and who met all other enrollment criteria were eligible to participate in this extension study. These subjects were treated as follows:

- **Group I (4rMenB)**: Subjects who were vaccinated at 6-8 months of age, two months later and at 12 months of age with rMenB vaccine in Study V72P9 were vaccinated with a single booster dose of rMenB at 40 months of age.
- **Group II (4rMenB+OMV)**: Subjects who were vaccinated at 6-8 months of age, two months later, and at 12 months of age with rMenB+OMV NZ vaccine in study V72P9 were vaccinated with a single booster dose of rMenB+OMV NZ at 40 months of age.
- **Group III (Naive_4042) and Group IV (Naive_6062)**: Two groups of naive subjects were recruited at 40 and 60 months of age and were vaccinated with two doses of rMenB+OMV NZ, given two months apart (see below). The pre vaccination antibody level for the group recruited at 40 months of age (group III) served as a baseline to assess antibody persistence at 40 months of age for groups I and II. Responses following the first injection of this group also served as a comparator to evaluate booster responses and the presence of immunological memory for groups I and II. The prevaccination antibody level for the group recruited at 60 months of age (group IV) was to serve as a baseline to evaluate antibody persistence at 60 months of age for groups I through III.

Both groups III and IV also provided data on two-dose catch-up vaccinations in children 40 and 60 months of age, as described below.

- **Group III (Naive_4042)**: Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age.
 - **Group IV (Naive_6062)**: Naive subjects recruited at 60 months of age were to be vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age.
- Outcomes/endpoints

Immunogenicity endpoints

Serum bactericidal activity was measured against *N. meningitidis* serogroup B strains H44/76, 5/99, NZ98/254 and M10713. Data were summarized by calculating hSBA geometric mean titers (GMTs), percentage of subjects with hSBA $\geq 1:4$ and $\geq 1:8$, and additionally $\geq 1:5$ and percentage of subjects with fourfold increase over baseline. Antibody responses to vaccine antigen 287-953 were also determined by ELISA and summarized by geometric mean concentrations (GMCs) and four-fold rises.

Antibody persistence and immune responses were interpreted using data from the naive groups of children recruited at 40 months and 60 months of age, as indicated below.

- Baseline antibody levels measured in naive subjects at 40 months of age (Group III) served as a descriptive comparator to evaluate antibody persistence at 40 months of age for Groups I and II.
- Responses to the first catch-up dose of rMenB+OMV NZ administered to naive subjects at 40 months of age (Group III) served as a descriptive comparator to evaluate the booster response and, in turn, the presence of immunological memory in Groups I and II.
- Baseline antibody levels measured in naive subjects at 60 months of age (Group IV) served as a descriptive comparator to evaluate antibody persistence at 60 months of age post-boost in Groups I and II and post-two catch-up doses in Group III.

Safety endpoints

All subjects who received at least one dose of investigational vaccine and provided post vaccination safety data (defined as the safety population) were included in the safety and tolerability analyses. All safety analyses were descriptive

Local and Systemic Adverse Events

Incidences of local adverse events (i.e., pain, erythema, induration, swelling) and systemic reactions (i.e., fever [defined as axillary temperature $\geq 38^{\circ}\text{C}$], change in eating habits, sleepiness, irritability, vomiting, diarrhea, arthralgia, headache and rash) occurring during the 7 days following each rMenB±OMV NZ vaccination were summarized by maximal severity and study group. Additionally, the numbers of subjects who used antipyretic medication (prophylactically or therapeutically) within 7 days of rMenB±OMV NZ vaccination were summarized. Erythema, induration and swelling were categorized as none, 0 < -10 mm, 10- < 25 mm, 25- < 50 mm, 50 -< 100 mm and ≥ 100 mm. Temperature taken by the axillary route were categorized as < 38°C , 38- < 38.5°C , 38.5- < 39°C , 39 -< 39.5°C , 39.5- < 40°C and $\geq 40^{\circ}\text{C}$. All other systemic reactions were categorized as none, mild, moderate or severe.

Unsolicited Adverse Events (AEs)

All AEs occurring during the 7 days following each study vaccination were collected. AEs that require a medical visit and/or resulting in premature withdrawal from the study, as well as serious adverse events (SAEs), were collected throughout the study period, except for the 7 days after each study vaccination in which all AEs were collected.

All reported AEs, as well as AEs at least possibly related to rMenB±OMV NZ vaccine were summarized according to system organ class and preferred term within each system organ class. These summaries were presented by treatment group. When an AE occurred more than once for a subject, the maximal severity and strongest relationship to the vaccine was counted. Additionally, three separate summaries of AEs were generated as follows: (i) SAEs, (ii) AEs that are possibly or probably related to vaccine, and (iii) AEs that are unrelated to vaccine. Data listings of all AEs were provided by subject. In addition, a summary of the primary termination reasons, a listing of subjects withdrawn from the study because of an AE, and a listing of all termination reasons were presented.

- Statistical Methods

Due to the small sample sizes, the analyses of safety and immunogenicity were purely descriptive. As such, no statistical tests were performed.

The primary analyses of the immunogenicity results were based on the modified Intention-to-treat population (MITT). All safety analyses were based on the safety population.

➤ Results

- Recruitment/ Number analysed

In total, 120 subjects were enrolled in this extension study. This included 16 subjects in the 4rMenB vaccine group, 14 subjects in the 4rMenB+OMV NZ vaccine group, 41 subjects in the Naive_4042 vaccine group and 49 subjects in the Naive_6062 vaccine group. Of these, a total of 102 subjects (85%) from all the vaccine groups completed the study, as per the criteria specified in the protocol. The primary reason for withdrawal of subjects was “Withdrawal of Consent” (10 subjects), followed by “Lost to Follow-up” (6 subjects). A summary of reasons for study termination in all vaccine groups is presented in Table 10.1-1. 115 subjects were part of immunogenicity MITT analysis for persistency and 108 subjects were part of the immunogenicity PP analysis for persistency (table 11.1-1).

Of the 120 subjects enrolled in the study, 119 subjects received at least one study injection and were thus included in the safety analyses.

	Number (%) of Subjects				
	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a	Naive_6062 ^b	TOTAL
Enrolled	16	14	41	49	120
Completed protocol	15 (94%)	12 (86%)	29 (71%)	46 (94%)	102 (85%)
Premature Withdrawal	1 (6%)	2 (14%)	12 (29%)	3 (6%)	18 (15%)
AE or Death	0	0	0	1 (2%)	1 (< 1%)
Withdrawal of consent	0	1 (7%)	7 (17%)	2 (4%)	10 (8%)
Lost to follow-up	1 (6%)	1 (7%)	4 (10%)	0	6 (5%)
Inappropriate enrollment	0	0	1 (2%)	0	1 (< 1%)

Source: Table 14.1.1.2; ^aNaive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age.

	4rMenB	4rMenB+OMV	Naive_4042 ^a	Naive_6062 ^b	TOTAL
Population	N=16	N=14	N=41	N=49	N=120
Enrolled	16(100%)	14(100%)	41(100%)	49(100%)	120(100%)
Exposed	16(100%)	14(100%)	41(100%)	48(98%)	119(99%)
Safety	16(100%)	14(100%)	41(100%)	48(98%)	119(99%)
MITT persistence	15(94%)	14(100%)	40(98%)	46(94%)	115(96%)
MITT prebooster /persistence of booster	14(88%)	14(100%)	0	46(94%)	74 (62%)
MITT 2 dose catch up	0	0	39(95%)		85(71%)
PP persistence	13(81%)	13(93%)	36(88%)	46(94%)	108(90%)
PP prebooster /persistence of booster	12(75%)	13(93%)	0	46(94%)	71 (59%)
PP 2 dose catch up	0	0	29(71%)	46(94%)	75(63%)

Source: Table 14.1.1.1; PP – per protocol; MITT – modified intention-to-treat; ^aNaive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age

Assessor’s comment: It is noted that the number of enrolled subjects is limited and that about half of the eligible subjects from the parent study were enrolled into this extension study. It is also noted that the proportion of withdrawals was considerably higher in group Naive_4042 than in other groups. The study groups are small and interpretation of data and comparisons between groups should therefore be made with caution. Due to the limited sample size, no firm conclusions are drawn from the data presented from this study.

- Baseline data

Overall the demographic and other baseline characteristics for the enrolled population in all four vaccine groups were similar, except for the gender differences. There was an unequal distribution of males and females in the 4rMenB+OMV NZ, Naive_4042 and Naive_6062 vaccine groups. Higher percentages of females were enrolled in the 4rMenB+OMV NZ vaccine group (79%) and Naive_4042 vaccine group (54%). In the Naive_6062 vaccine group, higher percentages of males (57%) were enrolled.

- Efficacy results

Primary endpoint

To explore bactericidal antibody persistence in children at 40 months of age who previously received three doses of rMenB or rMenB+OMV NZ as infants in parent study V72P9

Table 11.4.1.1-1: Geometric Mean Titer's (GMTs) (95% CI) All Timepoints in V72P9 and Persistence at 40 Months of Age in V72P9E1 - MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a
	N=14	N=14	N=39
Strain H44/76	P9 baseline	1.31 (0.88-1.93)	2.33 (1.2-4.49)
	P9 1 month post 2 nd injection	94 (49-179)	281 (179-439) N=11
	P9 1 month post 3 rd injection	112 (66-192)	234 (170-322) N=11
	P9E1 40 months of age persistence	1.26 (0.9-1.76)	2.55 (1.15-5.66)
	N=14	N=14	N=40
Strain 5/99	P9 baseline	1 (1-1)	1 (1-1) N=11
	P9 1 month post 2 nd injection	658 (413-1048)	562 (362-873) N=11
	P9 1 month post 3 rd injection	1080 (739-1578)	1143 (732-1783) N=11
	P9E1 40 months of age persistence	41 (18-95)	29 (18-47)
	N=15	N=14	N=39
Strain NZ98/254	P9 baseline	1 (1-1) N=14	1 (1-1) N=11
	P9 1 month post 2 nd injection	1 (1-1) N=13	26 (14-50) N=10
	P9 1 month post 3 rd injection	1.14 (0.86-1.5) N=14	56 (33-95) N=11
	P9E1 40 months of age persistence	1 (1-1)	1.74 (0.91-3.33)
	N=14	N=14	N=40
Strain M10713	P9 baseline		
	P9 1 month post 2 nd injection		
	P9 1 month post 3 rd injection		
P9E1 40 months of age persistence	3.6 (1.32-9.84)	7.11 (3.61-14)	4.82 (2.9-8)

Source: [Table 14.2.1.5.1](#); hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for naive_4042 group are baseline.

Table 11.4.1.1-2: Percentage of Subjects with hSBA \geq 1:4 (95% CI) All Timepoints in V72P9 and Persistence at 40 Months of Age in V72P9E1 - MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a
	N=14	N=14	N=39
Strain H44/76	P9 Baseline	2 (14%) (2%-43%)	5 (45%) (17%-77%) N=11
	P9 1 Month Post 2 nd Injection	14 (100%) (77%-100%)	11 (100%) (72%-100%) N=11
	P9 1 Month Post 3 rd Injection	14 (100%) (77%-100%)	11 (100%) (72%-100%) N=11
	P9E1 40 Months of Age Persistence	2 (14%) (2%-43%)	5 (36%) (13%-65%)
	N=14	N=14	N=40
Strain 5/99	P9 Baseline	0 (0%) (0%-23%)	0 (0%) (0%-28%) N=11
	P9 1 Month Post 2 nd Injection	14 (100%) (77%-100%)	11 (100%) (72%-100%) N=11
	P9 1 Month Post 3 rd Injection	14 (100%) (77%-100%)	11 (100%) (72%-100%) N=11
	P9E1 40 Months of Age Persistence	13 (93%) (66%-100%)	14 (100%) (77%-100%)
	N=15	N=14	N=39
Strain NZ98/254	P9 Baseline	0 (0%) (0%-23%) N=14	0 (0%) (0%-28%) N=11
	P9 1 Month Post 2 nd Injection	0 (0%) (0%-25%) N=13	9 (90%) (55%-100%) N=10
	P9 1 Month Post 3 rd Injection	1 (7%) (0%-34%) N=14	11 (100%) (72%-100%) N=11
	P9E1 40 Months of Age Persistence	0 (0%) (0%-22%)	2 (14%) (2%-43%)
	N=14	N=14	N=40
Strain M10713	P9 Baseline		
	P9 1 Month Post 2 nd Injection		
Strain M10713	P9 1 Month Post 3 rd Injection		
	P9E1 40 Months of Age Persistence	4 (29%) (8%-58%)	11 (79%) (49%-95%)

Source: Table 14.2.1.1.1; hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for naive_4042 group are baseline.

Prior to booster vaccination at 40 months of age, GMTs and proportions of seropositive subjects in the vaccinated group had decreased to low levels approaching baseline and were comparable to those of the naive group for all reference strains except strain 5/99. For strain 5/99 vaccinated subjects had a

mean GMT of 29 (18-47) compared to 1 (1-1) of naive subjects, and 100% of vaccinated subjects were seropositive whereas none of the naive subjects were seropositive.

Assessor's comment: The decrease in GMTs and proportion of seropositive subjects was not unexpected and could indicate the need for a booster vaccination at 40 months of age. However, the number of subjects is very small, and confirmation is needed from larger studies.

Secondary endpoints

- a. To characterize the bactericidal antibody response of a booster dose of rMenB or rMenB+OMV NZ administered at 40 months of age to children who previously received three doses of the same vaccine as infants in parent study V72P9.

Table 11.4.1.2-1: Geometric Mean hSBA Titers (GMTs; 95% CI) and Geometric Mean Ratio (GMR; 95% CI) – One Month after Booster or First Injection Administered at 40 Months of Age- MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a	
	N=13	N=14	N=39	
Strain H44/76	P9E1 (prebooster/ 40 months of age)	1.28 (0.89-1.85)	2.55 (1.15-5.66)	1.08 (0.97-1.21) N=38
	P9E1 (1 month post booster or 1 st injection)	100 (50-200)	114 (59-222)	8.89 (5.83-14)
	P9E1 (1 month post booster or 1 st injection)/ pre booster/40 months of age)	85 (52-140) N=11	45 (21-94)	8.09 (5.22-13) N=37
Strain 5/99	N=14	N=14	N=39	
	P9E1 (prebooster/ 40 months of age)	39 (16-95) N=13	29 (18-47)	1 (1-1)
	P9E1 (1 month post booster or 1 st injection)	1007 (445-2277)	926 (432-1988)	27 (16-44)
P9E1 (1 month post booster or 1 st injection)/ pre booster/40 months of age)	32 (18-56) N=12	32 (18-58)	26 (16-43) N=38	
Strain NZ98/254	N=14	N=14	N39	
	P9E1 (prebooster/ 40 months of age)	1 (1-1)	1.74 (0.91-3.33)	1 (1-1) N=38
	P9E1 (1 month post booster or 1 st injection)	2.15 (0.88-5.23)	32 (14-71)	1.91 (1.35-2.71)
P9E1 (1 month post booster or 1 st injection)/ pre booster/40 months of age)	2.28 (0.87-5.95) N=13	18 (7.17-46)	1.98 (1.37-2.85) N=37	
Strain MI0713	N=13	N=14	N=39	
	P9E1 (prebooster/ 40 months of age)	3.51 (1.18-10)	7.11 (3.61-14)	4.76 (2.83-8)
	P9E1 (1 month post booster or 1 st injection)	10 (3.43-30)	23 (13-41)	6.04 (3.73-9.79)
P9E1 (1 month post booster or 1 st injection)/ pre booster/40 months of age)	2.46 (0.95-6.34) N=11	3.25 (1.67-6.31)	1.4 (0.96-2.04) N=38	

Source: Table 14.2.1.5.2; Table 14.2.1.5.3; hSBA - human serum bactericidal assay; GMT – geometric mean titer; GMR – geometric mean ratios; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age.

Table 11.4.1.2-2: Percentages of Subjects with hSBA \geq 1:4 (95% CI) – 1 Month after Booster or First Injection Administered at 40 Months of Age - MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a
Strain 44/76 -SL	N=13	N=14	N=39
	P9E1 (1 month post booster at 40 months of age)	13 (100%) (75%-100%)	14 (100%) (77%-100%)
Strain 5/99	N=14	N=14	N=39
	P9E1 (1 month post booster at 40 months of age)	14 (100%) (77%-100%)	14 (100%) (77%-100%)
Strain NZ98/254	N=14	N=14	N=39
	P9E1 (1 month post booster at 40 months of age)	3 (21%) (5%-51%)	13 (93%) (66%-100%)
Strain M10713	N=13	N=14	N=39
	P9E1 (1 month post booster at 40 months of age)	9 (69%) (39%-91%)	13 (93%) (66%-100%)

Source: [Table 14.2.1.1.2](#); [Table 14.2.1.1.3](#); hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age;

One month post booster or first vaccination in the extension study subjects receiving booster vaccinations had higher levels of GMTs and a greater proportion of subjects were seropositive as compared to naive individuals indicating the presence of immunological memory. The levels of GMTs after booster at 40 months of age were at the same level or slightly lower than those induced by the third vaccination dose at 12 months of age (table 11.4.1.1-1, primary endpoint).

- b. To explore bactericidal antibody persistence in children at 60 months of age who received a booster dose of rMenB or rMenB+OMV NZ at 40 months of age in the present extension study.

Table 11.4.1.2-3: Geometric Mean hSBA Titers (GMTs; 95% CI) (Persistence at 60 Months of Age) - MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_6062 ^a
	N=13	N=14	N=46
Strain H44/76	P9E1 (1 month post booster)	100 (50-200)	114 (59-222)
	P9E1 20 months post booster /baseline	9.37 (2.47-36) N=9	4.69 (1.98-11) N=12
	N=14	N=14	N=46
Strain 5/99	P9E1 (1 month post booster)	1007 (445-2277)	926 (432-1988)
	P9E1 20 months post booster /baseline	334 (186-599) N=9	119 (56-252) N=11
	N=14	N=14	N=46
Strain NZ98/254	P9E1 (1 month post booster)	2.15 (0.88-5.23)	32 (14-71)
	P9E1 20 months post booster /baseline	1 (1-1) N=10	1.63 (0.86-3.08) N=12
	N=13	N=14	N=45
Strain M10713	P9E1 (1 month post booster)	10 (3.43-30)	23 (13-41)
	P9E1 20 months post booster /baseline	4.96 (1.03-24) N=8	5.51 (2.19-14) N=11

Source: Table 14.2.1.5.2; hSBA - serum bactericidal assay; GMT – geometric mean titer; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age. Baseline antibody levels measured in naive subjects at 60 months of age served as a descriptive comparator to evaluate antibody persistence at 60 months of age for the groups which received 4rMenB or 4rMenB+OMV NZ in V72P9 study.

Table 11.4.1.2-4: Percentages of Subjects with hSBA \geq 1:4 (95% CI) – Persistence at 60 Months of Age- MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_6062 ^a
	N=13	N=14	N=46
Strain 44/76 -SL	P9E1 (1 month post booster at 40 months of age)	13 (100%) (75%-100%)	14 (100%) (77%-100%)
	P9E1 20 months post booster /baseline	6 (67%) (30%-93%) N=9	8 (67%) (35%-90%) N=12
	N=14	N=14	N=46
Strain 5/99	P9E1 (1 month post booster at 40 months of age)	14 (100%) (77%-100%)	14 (100%) (77%-100%)
	P9E1 20 months post booster /baseline	9 (100%) (66%-100%) N=9	11 (100%) (72%-100%) N=11
	N=14	N=14	N=46
Strain NZ98/254	P9E1 (1 month post booster at 40 months of age)	3 (21%) (5%-51%)	13 (93%) (66%-100%)
	P9E1 20 months post booster /baseline	0 (0%) (0%-31%) N=10	2 (17%) (2%-48%) N=12
	N=13	N=14	N=45
Strain M10713	P9E1 (1 month post booster at 40 months of age)	9 (69%) (39%-91%)	13 (93%) (66%-100%)
	P9E1 20 months post booster /baseline	4 (50%) (16%-84%) N=8	5 (45%) (17%-77%) N=11

Source: Table 14.2.1.1.2; hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for naive_6062 group are baseline

20 months post booster vaccination at 40 months of age GMTs had decreased for all strains and were approaching the levels prior to the booster dose except for strain 5/99 where a GMT of 119 (56-252) was demonstrated.

- c. To assess the bactericidal antibody response of a two-dose catch-up regimen of rMenB+OMV NZ administered to naive children at 40 and 42 months of age or at 60 and 62 months of age.

Table 11.4.1.2-5: Geometric Mean hSBA Titers (GMTs) and Geometric Mean Ratio (GMR; 95 CI) Two Dose Catch-up Data - MITT Population

	Strain H44/76		Strain 5/99		Strain NZ98/254		Strain M10713	
	Naive_4042 N=39	Naive_6062 N=46	Naive_4042 N=39	Naive_6062 N=46	Naive_4042 N=39	Naive_6062 N=46	Naive_4042 N=39	Naive_6062 N=45
P9E1 Baseline	1.08 (0.97-1.21) N=38	1.09 (0.96-1.25)	1 (1-1)	1.17 (0.96-1.42)	1 (1-1) N=38	1 (1-1)	4.76 (2.83-8)	8.09 (5.13-13)
P9E1 1 month post 1 st injection	8.89 (5.83-14)		27 (16-44)		1.91 (1.35-2.71)		6.04 (3.73-9.79)	
P9E1 1 month post 1 st injection/ P9E1 Baseline	8.09 (5.22-13) N=37		26 (16-43) N=38		1.98 (1.37-2.85) N=37		1.4 (0.96-2.04) N=38	
P9E1 1 month post 2 nd injection	74 (57-94) N=30	83 (67-103) N=34	247 (188-323) N=31	331 (254-432) N=34	16 (11-23) N=31	14 (9.81-21) N=35	8.91 (5.19-15) N=29	44 (33-57) N=33
P9E1 1 month post 2 nd injection/ P9E1 Baseline	66 (49-90) N=29	73 (56-96) N=34	247 (188-323) N=31	277 (198-389) N=34	16 (11-23) N=30	14 (9.81-21) N=35	1.9 (1.12-3.22) N=29	5.79 (3.47-9.66) N=32
P9E1 18 Months Post 2nd	2.73 (1.54-4.84) N=24		24 (16-35) N=24		1 (1-1) N=24		14 (6.78-27) N=23	
P9E1 18 Months Post 2nd Minus P9E1 Baseline	2.42 (1.34-4.36) N=24		24 (16-35) N=24		1 (1-1) N=24		4.33 (1.86-10) N=23	

Source: Table 14.2.1.5.3; hSBA - human serum bactericidal assay; GMT – geometric mean titer; GMR – geometric mean ratios; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age

Table 11.4.1.2-6: Percentages of Subjects with hSBA \geq 1:4 (95% CI) – Two Dose Catch-up - MITT Population

	Naive_4042 ^a	Naive_6062 ^b	
	N=39	N=46	
Strain H44/76	P9E1 (Baseline)	1 (3%) (0.067%-14%)	2 (4%) (1%-15%)
	P9E1 (1 month post 1 st injection)	28 (72%) (55%-85%)	
	P9E1 ^e (1 month post 2 nd injection)	30 (100%) (88%-100%)	34 (100%) (90%-100%)
	N=38	N=34	
Strain 5/99	P9E1 (Baseline)	0 (0%) (0%-9%)	2 (4%) (1%-15%)
	P9E1 (1 month post 1 st injection)	34 (87%) (73%-96%)	
	P9E1 ^e (1 month post 2 nd injection)	31 (100%) (89%-100%)	34 (100%) (90%-100%)
	N=31	N=34	
Strain NZ98/254	P9E1 (Baseline)	0 (0%) (0%-9%)	0 (0%) (0%-8%)
	P9E1 (1 month post 1 st injection)	9 (23%) (11%-39%)	
	P9E1 ^e (1 month post 2 nd injection)	28 (90%) (74%-98%)	31 (89%) (73%-97%)
	N=31	N=35	
Strain MI0713	P9E1 (Baseline)	20 (51%) (35%-68%)	30 (67%) (51%-80%)
	P9E1 (1 month post 1 st injection)	24 (62%) (45%-77%)	
	P9E1 ^e (1 month post 2 nd injection)	21 (72%) (53%-87%)	32 (97%) (84%-100%)
	N=29	N=33	

Source: Table 14.2.1.1.3; hSBA - human Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for naive_4042 group are baseline, 1 month post 1st injection, and 18 months post 2 dose catch up; results for Naive_6062 are baseline and 1 month post 2nd injection

Following the second vaccination an increase in GMTs was demonstrated for all strains in both groups. Levels were, however lower than those of group 4rMenB+OMV one month after the second the injection at 8-10 months of age for all strains except NZ98/254 (see table 11.4.1.1-1, primary endpoint). At 18 months after the second injection a decrease in GMTs was demonstrated.

Assessor’s comment: although it appears that the levels of GMTs induced after two vaccinations in children aged 40/42 or 60/62 months are lower than those in children vaccinated before 12 months of age the clinical relevance of this is unclear.

- d. To explore bactericidal antibody persistence in children at 60 months of age who received a two-dose catch-up regimen of rMenB+OMV NZ administered to naive children at 40 and 42 months of age in the present extension study

		Naive_4042 ^a	Naive_6062 ^b
Strain H44/76		N=24	N=46
	P9E1 (18 months post 2 nd injection/baseline)	2.73 (1.54-4.84)	1.09 (0.96-1.25)
Strain 5/99		N=24	N=46
	P9E1 (18 months post 2 nd injection/baseline)	24 (16-35)	1.17 (0.96-1.42)
Strain NZ98/254		N=24	N=46
	P9E1 (18 months post 2 nd injection/baseline)	1 (1-1)	1 (1-1)
Strain M10713		N=23	N=45
	P9E1 (18 months post 2 nd injection/baseline)	14 (6.78-27)	8.09 (5.13-13)

Source: Table 14.2.1.5.3.1; hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for naive_4042 group are 18 months post 2 dose catch up; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for Naive_6062 group are baseline

Table 11.4.1.2-8: Percentages of Subjects with hSBA \geq 1:4 (95% CI) – Two Dose Catch-up –Persistence at 60 Months of Age- MITT Population

	Naive_4042 ^a	Naive_6062 ^b
	N=24	N=46
Strain H44/76		
P9E1 (18 months post 2 nd injection/baseline)	9 (38%) (19%-59%)	2 (4%) (1%-15%)
	N=24	N=46
Strain 5/99		
P9E1 (18 months post 2 nd injection/baseline)	24 (100%) (86%-100%)	2 (4%) (1%-15%)
	N=24	N=46
Strain NZ98/254		
P9E1 (18 months post 2 nd injection/baseline)	0 (0%) (0%-14%)	0 (0%) (0%-8%)
	N=23	N=45
Strain M10713		
P9E1 (18 months post 2 nd injection/baseline)	19 (83%) (61%-95%)	30 (67%) (51%-80%)

Source: Table 14.2.1.1.3.1; hSBA - Serum Bactericidal Assay; MenB - *N. meningitidis* serogroup B; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for naive_4042 group are 18 months post 2 dose catch up; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for Naive_6062 group are baseline.

At 18 months post second injections GMT levels had decreased and approached baseline for all strains except for strain 5/99 where levels were slightly higher and 100% of subjects were still seropositive.

Table 11.4.1.3-1: Geometric Mean ELISA Concentration (GMC) for Vaccine Antigen 287-953 - Persistence/Booster - MITT Population

	4rMenB	4rMenB+OMV NZ	Naive_4042 ^a	Naive_6062 ^b
	N=15	N=14	N=39	N=46
GMC (prebooster/ 40 months of age)	86 (43-173) N=14	103 (61-174)	27 (22-35)	
GMC (1 month post booster or 1 st injection)	5187 (2924-9204)	3662 (2065-6491)	83 (52-133)	
GMC (20 months post booster/ 18 months post 2 nd injection/ baseline) ^c	772 (395-1512) N=10	358 (201-640) N=12	87 (63-120) N=24	25 (19-33) N=46

Source: Table 14.2.1.6.2; Table 14.2.1.6.3; ELISA - Enzyme Linked Immunosorbent Assay; GMC – geometric mean concentration; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; ^c results for Naive_6062 are baseline ; results for naive_4042 group are baseline, 1 month post 1st injection, and 18 months post 2nd injection; baseline antibody concentration measured in naive subjects at 60months of age (Naive_6062) served as a descriptive comparator to evaluate antibody persistence at 60 months of age post-boost in groups which received 4rMenB or 4rMenB+OMV and post-two catch-up doses in group Naive_4042.

Table 11.4.1.3-2: Geometric Mean ELISA Concentration (GMC; 95% CI) for Vaccine Antigen 287-953 Two Dose Catch-up - MITT Population

	Naive_4042 ^a	Naive_6062 ^b
	N=39	N=46
GMC (Baseline)	27	25
95% CI	(22-35)	(19-33)
GMC(1 month post1 st injection)	83	
95% CI	(52-133)	
GMC (1 month post 2 nd injection)	612	2164
95%CI	(329-1139) N=31	(1663-2817) N=35
GMC (18 months post 2 nd injection)	87	
	(63-120) N=24	

Source: Table 14.2.1.6.3; ELISA - Enzyme Linked Immunosorbent Assay; GMC – geometric mean concentration; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age

Booster vaccination induced a marked increase in GMC levels for all strains. After 20 months levels had declined but were still above baseline. Two vaccinations given to naive subjects induced a clear increase in GMCs, but at a lower level than in subject receiving the full primary vaccination schedule + booster.

Assessor's general comment on efficacy results:

Due to the limited sample size, no firm conclusions are drawn from the data presented from this study and interpretation of data and comparisons between groups should be made with caution. Responses presented in this extension study are comparative to what has been presented from other studies and there is no concern to indicate reduced immunogenicity of vaccination from the data presented here.

It is noted that baseline values for strain M10713 in the newly recruited groups Naive_4042 and Naive_6062 are high. The analytical method for this strain was, however, subject to discussion during initial assessment, and the ELISA was also considered relevant. This issue will not be commented on further in this report.

- Safety results

A summary of local and systemic solicited adverse events and unsolicited adverse events occurring by vaccination group is provided in tables 12.2.3.1-1, 12.2.3.1-2 and 12.2.3.2-1 respectively.

Table 12.2.3.1-1: Numbers (%) of Subjects with Any (And Severe/>100 mm) Local Adverse Event, by Vaccination

		Number (%) of Subjects With Injection Site Reactions							
		Inj.: 1				Inj.: 2			
		4rMenB N=16	4rMenB+OMV NZ N=14	Naive_4042 ^a N=39	Naive_6062 ^b N=48	4rMenB N=0	4rMenB+OMV NZ N=0	Naive_4042 ^a N=37	Naive_6062 ^b N=46
Pain	Any	10(63)	12(86)	34(87)	44(92)			35(95)	41/45(91)
	Severe	0	4(29)	3(8)	5(10)			9(24)	6/45(13)
Erythema	Any	13(81)	14(100)	36(92)	45(94)			36(97)	40(87)
	>100 mm	0	0	0	0			0	0
Induration	Any	11(69)	5(36)	17(44)	19(40)			18(49)	20/45(44)
	>100 mm	0	0	0	0			0	0
Swelling	Any	9(56)	6(43)	10(26)	22(46)			15(41)	20/45(44)
	>100 mm	0	0	0	0			0	0

Source: [Table 14.3.1.1.2.1](#); ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age.

Note: The numbers (N) in the header is the total number of subjects with documented reactions.

Table 12.2.3.1-2: Numbers (%) of Subjects with Any (And Severe/>100 mm) Solicited Systemic Adverse Event, by Vaccination

		Number (%) of Subjects with Solicited Systemic Adverse Events							
		Inj.: 1				Inj.: 2			
		4rMenB N=16	4rMenB+OMV NZ N=14	Naive_4042 ^a N=39	Naive_6062 ^b N=48	4rMenB N=0	4rMenB+OMV N=0	Naive_4042 ^a N=37	Naive_6062 ^b N=46
Systemic									
Change Eat. Habits	Any	5(31)	5(36)	13(33)	10(21)			13(35)	10(22)
	Severe	0	0	1(3)	1(2)			1(3)	1(2)
Sleepiness	Any	6(38)	6(43)	20(51)	19(40)			17(46)	14(30)
	Severe	0	1(7)	3(8)	3(6)			3(8)	0
Vomiting	Any	0	2(14)	1(3)	5(10)			4(11)	3(7)
	Severe	0	1(7)	0	0			0	0
Diarrhea	Any	2(13)	1(7)	2(5)	2(4)			2(5)	2(4)
	Severe	0	0	0	0			0	0
Irritability	Any	8(50)	11(79)	24(62)	21(44)			23(62)	20(43)
	Severe	0	1(7)	0	2(4)			2(5)	1(2)
Headache	Any	2(13)	1(7)	4(10)	6(13)			4(11)	9(20)
	Severe	0	0	0	1(2)			0	0
Arthralgia	Any	2(13)	3(21)	9(23)	15(31)			7(19)	15(33)
	Severe	0	1(7)	1(3)	1(2)			2(5)	1(2)
Rash	Any	2(13)	1(7)	2(5)	3(6)			1(3)	4(9)
	Urticarial	1(6)	0	0	0			0	1(2)
Fever (≥38°C)	Yes	4(25)	1(7)	6(15)	5(10)			4(11)	5(11)
Other									
Temperature	<38°C	12(75)	13(93)	33(85)	43(90)			33(89)	41(89)
	≥40°C	0	0	1(3)	0			0	0
Antipyretic preventive medicines used	Yes	4(25)	9(64)	19(49)	21(44)			13(35)	22/45(49)
Antipyretic treatment medications used	Yes	3(19)	1(7)	5(13)	7(15)			3(8)	7/45(16)
Medically Attended Fever	Yes	0	0	0	0			1(3)	0

Source: Table 14.3.1.1.2.1; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age
Note: The numbers (N) in the header is the total number of subjects with documented reactions.

Table 12.2.3.2-1: Summary of All and at Least Possibly Related Unsolicited Adverse Events Reported by >5% of Subjects in Either Treatment Group (Preferred Term) by Descending Frequency after any Vaccination

Preferred Term	Number (%) of Subjects with Adverse Events							
	All				At Least Possibly Related			
	4rMenB N=16	4rMenB+OMV NZ N=14	Naive_4042 ^a N=41	Naive_6062 ^b N=48	4rMenB N=16	4rMenB+OMV NZ N=14	Naive_4042 ^a N=41	Naive_6062 ^b N=48
Injection site induration	3(19)	0	1(2)	3(6)	3(19)	0	1(2)	3(6)
Ear infection	2(13)	1(7)	3(7)	1(2)	0	0	0	0
Erythema	2(13)	1(7)	0	0	2(13)	1(7)	0	0
Swelling	2(13)	1(7)	0	0	2(13)	1(7)	0	0
Tonsillitis	0	1(7)	4(10)	0	0	0	0	0
Cough	1(6)	0	3(7)	0	1(6)	0	0	0
Rhinitis	0	0	3(7)	2(4)	0	0	0	0
Abdominal pain upper	0	1(7)	0	1(2)	0	1(7)	0	1(2)
Conjunctivitis	0	1(7)	0	0	0	1(7)	0	0
Ear tube insertion	0	1(7)	0	0	0	0	0	0
Excoriation	0	1(7)	0	0	0	0	0	0
Gastritis	0	1(7)	0	0	0	0	0	0
Hair follicle tumour benign	0	1(7)	0	0	0	0	0	0
Induration	0	1(7)	2(5)	0	0	1(7)	2(5)	0
Lower respiratory tract infection	1(6)	1(7)	1(2)	0	0	0	0	0
Respiratory disorder	0	1(7)	0	0	0	0	0	0
Upper respiratory tract infection	0	1(7)	1(2)	0	0	0	0	0
Asthma	1(6)	0	0	1(2)	0	0	0	0
Ear pain	1(6)	0	1(2)	0	0	0	0	0
Injection site erythema	0	0	0	3(6)	0	0	0	3(6)
Laceration	1(6)	0	0	0	0	0	0	0
Lymphadenitis	1(6)	0	0	0	0	0	0	0
Lymphadenopathy	1(6)	0	0	0	0	0	0	0
Pain	1(6)	0	1(2)	0	1(6)	0	1(2)	0
Rash macular	1(6)	0	0	0	1(6)	0	0	0
Urinary tract infection	1(6)	0	1(2)	0	0	0	0	0
Varicella	1(6)	0	0	0	0	0	0	0

Source: Table 14.3.1.1.9, Table 14.3.1.1.12; ^a Naive subjects recruited at 40 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; ^b Naive subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age.

A total of 7 subjects experienced at least one SAE. A summary of subjects with SAEs in all the four vaccine groups is presented in Table 12.3.1.2-1. Except for one SAE (febrile convulsion, from the Naive_4042 vaccine group), all other SAEs were considered not to be related to study vaccines.

Subject 01/334 in group Naive_4042 was febrile (39.9 degrees) and developed febrile convulsions lasting few minutes approximately 8 hours post second vaccination. The event resolved completely without hospitalization within two days.

Table 12.3.1.2-1: Listing of Serious Adverse Events

Subject No.	Preferred Term	Onset		Duration (days)	Outcome	Hospitalization	Relationship
		Study day	Phase (day of)				
4rMenB							
01042	Lymphadenitis	3	Injection 1 (3)	15	Recovered	Yes	None
4rMenB+OMV							
01005	Upper Respiratory Tract Infection	275	Injection 1 (275)	2	Recovered	Yes	None
Naive_4042							
01302	Croup Infectious	276	Injection 2 (213)	1	Recovered	Yes	None
01305	Gastroenteritis	378	Injection 2 (321)	7	Recovered	Yes	None
01305	Vomiting	419	Injection 2 (362)	9	Recovered	Yes	None
01333	Encephalitis	80	Injection 1 (80)		AE Persist	Yes	None
01334	Febrile Convulsion	60	Injection 2 (1)	2	Recovered	No	Possibly Related
Naive_6062							
01443	Asthma	121	Injection 2 (15)	6	Recovered	Yes	None

Assessor's comment: The safety results presented in this study are in agreement with previously presented results, and no new safety concerns are raised based on this study.

3. Discussion on clinical aspects

The submitted study was intended to explore aspects of persistence of immunogenicity and safety following different vaccination schedules in children aged up to 60 months of age. The results generally confirm what is already known regarding immunogenicity and safety of Bexsero. Therefore no further regulatory action regarding Bexsero is required based on the presented results.

3. Rapporteur's Overall Conclusion AND RECOMMENDATION

➤ Overall conclusion

This submission is considered fulfilled and no further action is required

➤ Recommendation

Fulfilled –

No further action required

Not fulfilled:

4. ADDITIONAL CLARIFICATIONS REQUESTED

None