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Committee for Medicinal Products for Human Use (CHMP)

Bexsero

(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)

Procedure No: EMEA/H/C/002333/P46/011

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

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

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I. INTRODUCTION

On February 27, 2014, the MAH submitted completed paediatric studies 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 studies do not influence the benefit risk for Bexsero and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the studies

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

II.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- V72P6E1 A Phase 2, Open-Label, Single-Center, Extension Study Evaluating Antibody Persistence compared to Naive Children and Safety, Tolerability and Immunogenicity of Booster Doses of Novartis rMenB±OMV NZ Vaccine in Healthy UK Children Who Previously Received One or Four Doses of the Novartis Vaccine as Infants in Study V72P6
- V72_41 A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with OMV Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years.

2. Clinical studies

V72P6E1: A Phase 2, Open-Label, Single-Center, Extension Study Evaluating Antibody Persistence compared to Naive Children and Safety, Tolerability and Immunogenicity of Booster Doses of Novartis rMenB±OMV NZ Vaccine in Healthy UK Children Who Previously Received One or Four Doses of the Novartis Vaccine as Infants in Study V72P6

➢ **Description**

This study was an extension of study V72P6. It was conducted as an open-label, single center 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 four doses of rMenB or rMenB+OMV NZ at 2, 4, 6 and 12 months of age in parent study V72P6.

Secondary

a) To explore bactericidal antibody persistence in children at 40 months of age who previously received a single dose of rMenB or rMenB+OMV NZ at 12 months of age in parent study V72P6.

b) 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 four doses of the same vaccine as infants in parent study V72P6.

c) To characterize the bactericidal antibody response of a booster dose of rMenB or MenB+OMV NZ administered at 40 months of age and a second booster dose administered at 42 months

of age to children who previously received a single dose of the same vaccine as infants in parent study V72P6.

d) 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.

e) To explore bactericidal antibody persistence in children at 60 months of age who received one or two booster doses of rMenB or rMenB+OMV NZ, or a two-dose catch-up regimen of rMenB+OMV NZ starting at 40 months of age in the present extension study.

f) For all immunogenicity objectives, responses will also be determined to vaccine antigen 287-953 by ELISA.

Safety Objectives:

Primary

To assess the safety and tolerability of one or two booster doses of rMenB or rMenB+OMV NZ administered to children starting at 40 months of age who previously received one or four doses of the same vaccine in parent study V72P6.

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 V72P6. It was conducted as an open-label, single center study (Oxford Vaccine Group, Oxford University Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, UK).

- Study population /Sample size

A maximum number of 126 subjects from parent study V72P6 were eligible to participate in this extension study. These were the subjects who successfully completed study V72P6 at the Oxford Vaccine Group study site. This number excluded V72P6 subjects from the Gloucester Vaccine Evaluation Unit, as this center did not participate in the extension study. The actual number of subjects enrolled from the parent study was 70, and all subjects were exposed to the study vaccine.

Two groups of around 50 newly recruited, naive subjects, 40 and 60 months of age, were also to be enrolled into the study: 43 subjects aged 40 months were actually enrolled and 42 were exposed to the study vaccine; 50 subjects aged 60 months were enrolled and 50 were exposed to the study vaccine. In total, 163 subjects were enrolled in this study.

Individuals eligible to be enrolled in the study were healthy 40-44 months old children:

▫ who participated and completed the V72P6 study (or naive subjects 40 or 60 months of age);

▫ for whom a parent/legal guardian had given written informed consent after the nature of the study had been explained;

▫ were available for all the visits scheduled in the study;

▫ were in good health as determined by: medical history, physical examination and clinical judgment of the investigator.

- Treatments

Subjects who completed study V72P6 at the Oxford Vaccine Group study site and who met all other enrollment criteria were eligible to participate in this extension study.

These subjects were treated as follows:

- **Group 5rMenB** (referred to as Group I in protocol): Subjects who were vaccinated at 2, 4, 6, and 12 months of age with rMenB vaccine in study V72P6 were vaccinated with a single booster vaccination of the same vaccine at 40 months of age.
- **Group 5rMenB+OMV** (referred to as Group II in protocol): Subjects who were vaccinated at 2, 4, 6, and 12 months of age with rMenB+OMV NZ vaccine in Study V72P6 were vaccinated with a single booster vaccination of the same vaccine at 40 months of age.
- **Group 3rMenB** (referred to as Group III in study protocol): Subjects who were vaccinated with a single dose of rMenB vaccine in Study V72P6 were vaccinated with 2 vaccinations of the same vaccine at 40 and 42 months of age.
- **Group 3rMenB+OMV** (referred to as Group IV in study protocol): Subjects who were vaccinated with a single dose of rMenB+OMV NZ vaccine in study V72P6 were vaccinated with 2 vaccinations1 of the same vaccine at 40 and 42 months of age.

Two additional vaccine groups, each consisting of 50 newly recruited, naive subjects, 40 and 60 months of age, were enrolled in the study. These subjects were treated as follows:

- **Group Naive_4042** (referred to as Group V in the protocol): Naive subjects recruited at 40 months of age were vaccinated with 2 vaccinations of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age.
- **Group Naive_6062** (referred to as Group VI in the protocol): Naive subjects recruited at 60 months of age were vaccinated with 2 vaccinations 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 indicator strains H44/76, 5/99, NZ98/254 and M10713. Data was summarized by calculating hSBA geometric mean titers (GMTs), percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8, and percentage of subjects with four-fold increase over baseline. Antibody response to vaccine antigen 287-953 was also to be determined by enzyme linked immunosorbant assay (ELISA) and summarized by geometric mean concentrations (GMCs) and four-fold rises.

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

- Baseline antibody levels measured in naive subjects at 40 months of age (group Naive_4042) served as a descriptive comparator to evaluate antibody persistence at 40 months of age for groups 5rMenB, 5rMenB+OMV, 3rMenB, and 3rMenB+OMV.
- Responses to the first and second catch-up vaccinations of rMenB+OMV NZ administered to naive subjects at 40 and 42 months of age (group Naive_4042) served as a descriptive comparator to evaluate booster responses and, in turn, the presence of immunological memory in groups 5rMenB, 5rMenB+OMV, 3rMenB, and 3rMenB+OMV.
- Baseline antibody levels measured in naive subjects at 60 months of age (group Naive_6062) served as a descriptive comparator to evaluate antibody persistence at 60 months of age postbooster vaccination in groups 5rMenB, 5rMenB+OMV, 3rMenB, and 3rMenB+OMV, and post-2 dose catch-up in group Naive_4042.

Safety Endpoints

All subjects who received at least one vaccination of rMenB±OMV NZ and provided some safety data postvaccination with rMenB±OMV NZ (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 AEs (ie, pain, erythema, induration, swelling) and systemic AEs (ie, fever [defined as axillary temperature ≥ 38°C], change in eating habits, sleepiness, irritability, vomiting, diarrhoea, arthralgia, headache and rash) occurring during the 7 days following each study vaccination were summarized by maximal severity and vaccine group. Additionally, the numbers of subjects who used analgesic or antipyretic medication (prophylactically or therapeutically) within 7 days of study 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 ≥ 40°C. All other systemic AEs were categorized as present or not present, and if present as mild, moderate or severe.

Unsolicited Adverse Events

All unsolicited AEs that occurred during the 7 days following each study vaccination were collected. All SAEs, as well as AEs that required a medical visit and/or resulted in premature withdrawal from the study were collected throughout the study period, except for the 7 days after each vaccination with rMenB±OMV NZ in which all AEs were collected.

All reported unsolicited AEs, as well as AEs that were at least possibly related to rMenB±OMV NZ were summarized according to system organ class and preferred term within each system organ class. These summaries were presented by vaccine group. When an AE occurred more than once for a subject, the maximal severity and strongest relationship to the vaccine were counted. Additionally, separate summaries of AEs were generated as follows: (i) SAEs, (ii) AEs that were possibly or probably related to vaccine, and (iii) AEs that were 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 size in each vaccine group, the analyses of safety and immunogenicity were purely descriptive. As such, no statistical tests were performed. The primary analysis 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

A total of 163 subjects were enrolled in this extension study and 162 received at least one study vaccination. Of the 126 subjects that were eligible from the parent study 70 were enrolled in this extension study. Two groups of newly recruited, naive subjects were enrolled; a total of 43 subjects aged 40 months and 50 subjects aged 60 months.

A summary of the number of subjects who were enrolled, who completed or discontinued the study, by vaccination group, is provided in Table 10.1-1. Among enrolled subjects, a total of 23 (14%) discontinued the study. Most subjects who discontinued withdrew consent or were lost to follow-up. Three (3) subjects discontinued due to protocol violations (moved out of area) and one (1) subject discontinued due to inappropriate enrolment.

Table 10.1-1: Summary of Study Terminations – Enrolled Population

	rMenB vaccine at 2, 4, 6, and 12 months	rMenB+ OMV NZ vaccine at 2,4,6, and 12 months	rMenB vaccine at 12 months	rMenB+ OMV NZ vaccine at 12 months	Naive subjects at 40 month	Naive subjects at 60 month	
Groups	**5rMenB**	**5rMenB+ OMV**	**3rMenB**	**3rMenB+ OMV**	**Naive_4042**	**Naive_6062**	**Total**
Enrolled	29	19	14	8	43	50	163
Completed study	26 (90%)	18 (95%)	13 (93%)	6 (75%)	32 (74%)	45 (90%)	140 (86%)
Premature withdrawals	3 (10%)	1 (5%)	1 (7%)	2 (25%)	11 (26%)	5 (10%)	23 (14%)
Withdrew consent	1 (3%)	0	1 (7%)	0	3 (7%)	5 (10%)	10 (6%)
Lost to follow-up	1 (3%)	1 (5%)	0	1 (13%)	6 (14%)	0	9 (6%)
Inappropriate enrollment	0	0	0	0	1 (2%)	0	1 (<1%)
Protocol deviations	1 (3%)	0	0	1 (13%)	1 (2%)	0	3 (2%)

Source: Table 14.1.1.2
Note: Categorical parameters: N(%), noncategorical parameters: mean±std.

The immunogenicity MITT analyses for persistence at 40 months included 108 subjects, while the MITT population for analysing persistence at 60 months included 134 subjects. One hundred and sixty (160) subjects were included for the MITT booster analyses and 82 were part of the MITT 2-dose catch-up analyses (table 11.1-1)

Table 11.1-1: Overview of Subject Analysis Sets, by Vaccine Groups and Overall

	5rMenB	5rMenB+ OMV	3rMenB	3rMenB+ OMV	Naive_4042 [a]	Naive_6062 [b]	Total
	N=29	N=19	N=14	N=8	N=43	N=50	N=163
Population:							
Enrolled	29 (100%)	19 (100%)	14 (100%)	8 (100%)	43 (100%)	50 (100%)	163 (100%)
Exposed	29 (100%)	19 (100%)	14 (100%)	8 (100%)	42 (98%)	50 (100%)	162 (99%)
Safety	29 (100%)	19 (100%)	14 (100%)	8 (100%)	42 (98%)	50 (100%)	162 (99%)
	N=29	N=19	N=14	N=8	N=43	N=0	N=113
Population							
MITT Persistence 40 months	29 (100%)	17 (89%)	14 (100%)	8 (100%)	40 (93%)		108 (96%)
PP Persistence 40 months	28 (97%)	17 (89%)	14 (100%)	8 (100%)	38 (88%)		105 (93%)
	N=29	N=19	N=14	N=8	N=43	N=50	N=163
Population:							
MITT Persistence 60 months	24 (83%)	16 (84%)	13 (93%)	5 (63%)	29 (67%)	47 (94%)	134 (82%)
MITT Booster	29 (100%)	19 (100%)	14 (100%)	8 (100%)	40 (93%)	50 (100%)	160 (98%)
PP Persistence 60 months	19 (66%)	11 (58%)	13 (93%)	5 (63%)	28 (65%)	47 (94%)	123 (75%)
PP Booster	29 (100%)	19 (100%)	14 (100%)	8 (100%)	40 (93%)	50 (100%)	160 (98%)
	N=0	N=0	N=0	N=0	N=43	N=50	N=93
Population:							
MITT 2 Dose catch-up					40 (93%)	42 (84%)	82 (88%)
PP 2 Dose catch-up					25 (58%)	42 (84%)	67 (72%)

Source: Table 14.1.1.1
Abbreviation: PP – per protocol, MITT – modified intention-to-treat, NA, not applicable.
a. Naive subjects recruited at 40 months of age were vaccinated with 2 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 2 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 less than half of the eligible subjects from the parent study were enrolled into this extension study. 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

Demographic and other baseline characteristics were similar across groups, except for gender differences. A higher percentage of male subjects were enrolled in groups 5rMenB+OMV (53%) and 3rMenB+OMV (63%), while a higher percentage of females were enrolled in groups Naive_4042 (53%) and Naive_6062 (54%).

- Efficacy results

Primary endpoint.

To explore bactericidal antibody persistence in children at 40 months of age who previously received four doses of rMenB or rMenB+OMV NZ at 2, 4, 6 and 12 months of age in parent study V72P6.

Table 2-2: Geometric Mean hSBA Titers (GMTs, 95% CI) for Persistence at 40 Months of Age - MITT Population

		5rMenB	5rMenB+OMV	Naive_4042[a]
Strain H44/76		N=29	N=17	N=40
	Baseline in P6	1.4 (1-1.95) N=27	1.35 (0.88-2.09) N=16	NA
	1 month post-3rd vaccination in P6	12 (7.63-20) N=28	31 (16-58)	
	Prebooster in P6 (12 months)	5.94 (4.26-8.3) N=28	3.69 (2.4-5.66)	
	Postbooster in P6 (13 months)	66 (46-94)	104 (65-168)	
	Prebooster in P6E1 (40 months)	3.24 (2.33-4.52)	5.34 (3.47-8.23)	4.25 (3.22-5.6)
Strain 5/99		N=28	N=17	N=40
	Baseline in P6	1.21 (0.93-1.57) N=26	1.05 (0.74-1.48) N=15	NA
	1 month post-3rd vaccination in P6	106 (56-203) N=26	157 (71-349)	
	Prebooster in P6 (12 months)	37 (22-63) N=28	20 (9.78-42) N=15	
	Postbooster in P6 (13 months)	233 (133-406)	906 (438-1872)	
	Prebooster in P6E1 (40 months)	5.11 (2.33-11) N=28	28 (10-77)	1.11 (0.9-1.36)
Strain NZ98/254		N=29	N=17	N=40
	Baseline in P6	1.29 (0.96-1.75) N=27	1.28 (0.88-1.86)	NA
	1 month post-3rd vaccination in P6	1.13 (0.76-1.69) N=28	23 (14-39)	
	Prebooster in P6 (12 months)	1.05 (0.76-1.46) N=28	3.22 (2.08-4.98) N=16	
	Postbooster in P6 (13 months)	1 (0.68-1.47)	25 (15-42)	
	Prebooster in P6E1 (40 months)	1.09 (0.79-1.51)	2.77 (1.81-4.23)	1 (1-1)
Strain M10713		N=28	N=15	N=40
	Baseline in P6	NA	NA	NA
	1 month post-3rd vaccination in P6			
	Prebooster in P6 (12 months)			
	Postbooster in P6 (13 months)			
	Prebooster in P6E1 (40 months)	9.15 (5.01-17)	5.34 (2.35-12)	8.75 (5.22-15)

Source: Table 14.2.1.5.1

Abbreviation: NA, not applicable.

a. Group Naive_4042 consisted of naive subjects recruited at 40 months of age; results for Naive_4042 are baseline values.

Table 2-3: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, for Persistence at 40 Months of Age - MITT Population

		5rMenB	5rMenB+OMV	Naive_4042[a]
Strain H44/76		N=29	N=17	N=40
	Baseline in P6	3 (11%) (2-29) N=27	2 (13%) (2-38) N=16	
	1 month post-3rd vaccination in P6	22 (79%) (59-92) N=28	16 (94%) (71-100)	NA
	Prebooster in P6 (12 months)	21 (75%) (55-89) N=28	11 (65%) (38-86)	
	Postbooster in P6 (13 months)	29 (100%) (88-100)	17 (100%) (80-100)	
	Prebooster in P6E1 (40 months)	13 (45%) (26-64)	11 (65%) (38-86)	25 (63%) (46-77)
Strain 5/99		N=28	N=17	N=40
	Baseline in P6	1 (4%) (0.097-20) N=26	0 (0%) (0-22) N=15	
	1 month post-3rd vaccination in P6	25 (96%) (80-100) N=26	16 (94%) (71-100)	NA
	Prebooster in P6 (12 months)	26 (93%) (76-99) N=28	14 (93%) (68-100) N=15	
	Postbooster in P6 (13 months)	28 (97%) (82-100)	17 (100%) (80-100)	
	Prebooster in P6E1 (40 months)	12 (43%) (24-63) N=28	13 (76%) (50-93)	1 (3%) (0.063-13)
Strain NZ98/254		N=29	N=17	N=40
	Baseline in P6	2 (7%) (1-24) N=27	3 (18%) (4-43)	
	1 month post-3rd vaccination in P6	1 (4%) (0.09-18) N=28	15 (88%) (64-99)	NA
	Prebooster in P6 (12 months)	1 (4%) (0.09-18) N=28	8 (50%) (25-75) N=16	
	Postbooster in P6 (13 months)	0 (0%) (0-12)	15 (88%) (64-99)	

		5rMenB	5rMenB+OMV	Naive_4042[a]
	Prebooster in P6E1 (40 months)	1 (3%) (0.087-18)	7 (41%) (18-67)	0 (0%) (0-9)
		N=28	**N=15**	**N=40**
Strain M10713	Baseline in P6 1 month post-3rd vaccination in P6 Prebooster in P6 (12 months) Postbooster in P6 (13 months)	NA	NA	NA
	Prebooster in P6E1 (40 months)	19 (68%) (48-84)	10 (67%) (38-88)	27 (68%) (51-81)

Source: Table 14.2.1.1.1
Abbreviation: NA, not applicable.
a. Group Naive_4042 consisted of naive subjects recruited at 40 months of age; results for Naive_4042 are baseline values.

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 naïve group for all reference strains except strain 5/99. For strain 5/99 vaccinated subjects had a mean GMT of 28 (10-77) compared to 1.11 (0.9-1.36) of naive subjects, and 76% of vaccinated subjects were seropositive whereas 3% (one individual) of naïve 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 explore bactericidal antibody persistence in children at 40 months of age who previously received a single dose of rMenB or rMenB+OMV NZ at 12 months of age in parent study V72P6*

At 40 months of age GMTs and the proportion of seropositive subjects had decreased to approximately baseline levels.

Assessor´s comment: During initial assessment for market authorization this vaccination regime was considered insufficient to provide relevant protection, and the persistence antibodies at 40 weeks of age is therefore regarded to be of limited interest.

b. *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 four doses of the same vaccine as infants in parent study V72P6.*

Table 11.4.1-5: Geometric Mean hSBA Titers (GMTs; 95% CI) and Geometric Mean Ratio (GMR; 95% CI) at 1 Month after 40-Month Booster or First Vaccination Administered at 40 Months of Age- MITT Population

		5rMenB	5rMenB+OMV	Naive_4042[a]
Strain H44/76		N=29	N=19	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	3.24 (2.33-4.52)	5.34 (3.47-8.23) N=17	3.9 (3-5.08)
	1 Month postbooster or post-1st vaccination in P6E1	99 (67-145) N=28	89 (56-141)	12 (7.96-19)
	1 Month postbooster or post-1st vaccination/ prebooster or pre-1st vaccination	30 (19-47) N=28	17 (9.6-30) N=17	3.23 (2.1-4.96) N=37
Strain 5/99		N=28	N=18	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	5.11 (2.33-11)	28 (10-77) N=17	1.11 (0.9-1.38)
	1 Month postbooster or post-1st vaccination in P6E1	778 (448-1349)	1708 (859-3396)	22 (12-40)
	1 Month postbooster or post-1st vaccination/ prebooster or pre-1st vaccination	148 (85-257) N=27	70 (34-142) N=16	19 (10-36) N=37
Strain NZ98/254		N=29	N=19	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	1.09 (0.79-1.51)	2.77 (1.81-4.23) N=17	1 (1-1)
	1 Month postbooster or post-1st vaccination in P6E1	1.64 (0.95-2.85) N=28	47 (24-91)	7.73 (4.62-13)
	1 Month postbooster or post-1st vaccination/ prebooster or pre-1st vaccination	1.5 (0.86-2.62) N=28	20 (9.67-40) N=17	7.59 (4.47-13) N=37
Strain M10713		N=28	N=18	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	9.15 (5.01-17)	5.34 (2.35-12) N=15	8.24 (4.87-14)
	1 Month postbooster or post-1st vaccination in P6E1	38 (24-59)	39 (22-67)	11 (6.7-19)
	1 Month postbooster or post-1st vaccination/ prebooster	4.66 (2.41-9.01) N=27	10 (4.2-25) N=15	1.26 (0.88-1.8) N=37

Source: Table 14.2.1.5.4

Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint

a. Naive subjects recruited at 40 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age.

Table 11.4.1-6: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, at 1 Month After 40-Month Booster or First Vaccination Administered at 40 Months of Age - MITT Population

		5rMenB	5rMenB+OMV	Naive_4042[a]
Strain 44/76-SL		N=29	N=19	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	13 (45%) (26-64)	11 (65%) (38-86) N=17	23 (61%) (43-76)
	1 Month postbooster or 1 month post-1st vaccination in P6E1	28 (100%) (88-100) N=28	19 (100%) (82-100)	34 (89%) (75-97)
Strain 5/99		N=28	N=18	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	12 (43%) (24-63)	13 (76%) (50-93) N=17	1 (3%) (0.067-14)
	1 Month postbooster or 1 month post-1st vaccination in P6E1	28 (100%) (88-100)	18 (100%) (81-100)	29 (76%) (60-89)
Strain NZ98/254		N=29	N=19	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	1 (3%) (0.087-18)	7 (41%) (18-67) N=17	0 (0%) (0-9)
	1 Month postbooster or 1 month post-1st vaccination in P6E1	4 (14%) (4-33) N=28	17 (89%) (67-99)	25 (66%) (49-80)
Strain M10713		N=28	N=18	N=38
	Prebooster or pre-1st vaccination in P6E1 (40 months)	19 (68%) (48-84)	10 (67%) (38-88) N=15	25 (66%) (49-80)
	1 Month postbooster or 1 month post-1st vaccination in P6E1	27 (96%) (82-100)	17 (94%) (73-100)	29 (76%) (60-89)

Source: Table 14.2.1.1.4
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.
a. Naive subjects recruited at 40 months of age were vaccinated with 2 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 individuals receiving booster vaccinations had higher levels of GMTs and a greater proportion of subjects were seropositive as compared to naïve 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 higher than those induced by the previous booster vaccination at 12 months of age.

c. *To characterize the bactericidal antibody response of a booster dose of rMenB or MenB+OMV NZ administered at 40 months of age and a second booster dose administered at 42 months of age to children who previously received a single dose of the same vaccine as infants in parent study V72P6.*

Table 11.4.1-7: Geometric Mean hSBA Titers (GMTs, 95% CI) and Geometric Mean Ratio (GMR; 95% CI) at 1 Month After Vaccinations at 40 and 42 Months of Age and 2-Dose Catch-up Vaccinations at 40 and 42 Months of Age- MITT Population

		3rMenB	3rMenB+OMV	Naive_4042[a]
Strain H44/76		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	3.59 (1.8-7.15)	3.47 (1.39-8.64)	3.9 (3-5.08)
	1 Month post-40 month booster or 1 month post-1st vaccination	94 (48-185) N=13	76 (30-190) N=7	12 (7.96-19)
	1 Month post-40 month booster or 1 month post-1st vaccination/baseline	27 (12-62) N=13	21 (6.84-67) N=7	3.23 (2.1-4.96) N=37
	1 Month post-42 month booster or 1 month post-2nd vaccination	127 (81-198) N=13	145 (82-255)	88 (66-117) N=36
	1 Month post-42 month booster or 1 month post-2nd vaccination /baseline	37 (19-73) N=13	42 (18-99)	20 (15-28) N=34
Strain 5/99		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	9.57 (3.88-24)	1 (0.3-3.3)	1.11 (0.9-1.38)
	1 Month post-40 month booster or 1 month post-1st vaccination	2379 (1164-4859) N=13	509 (192-1348) N=7	22 (12-40)
	1 Month post-40 month booster or 1 month post-1st vaccination/baseline	299 (139-643) N=13	509 (180-1444) N=7	19 (10-36) N=37
	1 Month post-42 month booster or 1 month post-2nd vaccination	5240 (3082-8911) N=13	2413 (1226-4747)	1019 (762-1362) N=36
	1 Month post-42 month booster or 1 month post-2nd vaccination /baseline	501 (180-1397) N=13	2413 (652-8921)	910 (594-1394) N=34
Strain NZ98/254		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	1.23 (0.96-1.57)	1 (0.72-1.38)	1 (1-1)
	1 Month post-40 month booster or 1 month post-1st vaccination	1.73 (0.86-3.48) N=13	148 (57-384) N=7	7.73 (4.62-13)
	1 Month post-40 month booster or 1 month post-1st vaccination/baseline	1.38 (0.69-2.78) N=13	148 (57-382) N=7	7.59 (4.47-13) N=37
	1 Month post-42 month booster or 1	1.86	65	47

	month post-2nd vaccination	(0.89-3.88) N=13	(25-165)	(31-72) N=36
	1 Month post-42 month booster or 1 month post-2nd vaccination /baseline	1.49 (0.72-3.07) N=13	65 (26-162)	47 (31-74) N=34
		N=13	**N=8**	**N=38**
Strain M10713	Baseline in P6E1 (40 months)	3.26 (1.49-7.11)	3 (1.11-8.11)	8.24 (4.87-14)
	1 Month post-40 month booster or 1 month post-1st vaccination	35 (18-68)	30 (12-74) N=7	11 (6.7-19)
	1 Month post-40 month booster or 1 month post-1st vaccination/baseline	11 (4.22-30) N=12	10 (2.82-36) N=7	1.26 (0.88-1.8) N=37
	1 Month post-42 month booster or 1 month post-2nd vaccination	21 (9.25-47) N=12	36 (13-98)	33 (22-51) N=36
	1 Month post-42 month booster or 1 month post-2nd vaccination /baseline	5.47 (1.72-17) N=11	12 (3.08-47)	3.94 (2.14-7.25) N=34

Source: Table 14.2.1.5.5

Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.

a. Naive subjects recruited at 40 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for Naive_4042 group are baseline.

Table 11.4.1-8: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, at 1 Month After Vaccinations at 40 and 42 Months of Age and 2-Dose Catch-up Vaccinations at 40 and 42 Months of Age- MITT Population

		3rMenB	3rMenB+OMV	Naive_4042
Strain H44/76		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	8 (57%) (29-82)	3 (38%) (9-76)	23 (61%) (43-76)
	1 Month post-40 month booster or 1 month post-1st vaccination	13 (100%) (75-100) N=13	7 (100%) (59-100) N=7	34 (89%) (75-97)
	1 Month post-42 month booster or 1 month post-2nd vaccination	13 (100%) (75-100) N=13	8 (100%) (63-100)	36 (100%) (90-100) N=36
Strain 5/99		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	8 (57%) (29-82)	0 (0%) (0-37)	1 (3%) (0.067-14)
	1 Month post-40 month booster or 1 month post-1st vaccination	13 (100%) (75-100) N=13	7 (100%) (59-100) N=7	29 (76%) (60-89)
	1 Month post-42 month booster or 1 month post-2nd vaccination	13 (100%) (75-100) N=13	8 (100%) (63-100)	36 (100%) (90-100) N=36
Strain NZ98/254		N=14	N=8	N=38
	Baseline in P6E1 (40 months)	1 (7%) (0-34)	0 (0%) (0-37)	0 (0%) (0-9)
	1 Month post-40 month booster or 1 month post-1st vaccination	2 (15%) (2-45) N=13	7 (100%) (59-100) N=7	25 (66%) (49-80)
	1 Month post-42 month booster or 1 month post-2nd vaccination	2 (15%) (2-45) N=13	8 (100%) (63-100)	34 (94%) (81-99) N=36
Strain M10713		N=13	N=8	N=38
	Baseline in P6E1 (40 months)	7 (54%) (25-81)	2 (25%) (3-65)	25 (66%) (49-80)
	1 Month post-40 month booster or 1 month post-1st vaccination	13 (100%) (75-100)	6 (86%) (42-100) N=7	29 (76%) (60-89)
	1 Month post-42 month booster or 1 month post-2nd vaccination	10 (83%) (52-98) N=12	8 (100%) (63-100)	32 (89%) (74-97) N=36

Source: Table 14.2.1.1.5
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.
a. Naive subjects recruited at 40 months of age were vaccinated with2 doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for Naive_4042 group are baseline.

One month post booster at 42 months of age or post second vaccination of naïve individuals both groups showed an increase in GMTs as well as a greater proportion of seropositive subjects indication the presence of immunological memory. The levels were comparable to those of group 5rMenB+OMV one month after the single booster dose (secondary endpoint b).

d. 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 11.4.1-9: Geometric Mean hSBA Titers (GMTs) and Geometric Mean Ratio (GMR; 95 CI) for Catch-up Groups- MITT Population

	Strain H44/76		Strain 5/99		Strain NZ98/254		Strain M10713	
	Naive_4042 N=38	Naive_6062 N=42	Naive_4042 N=38	Naive_6062 N=42	Naive_4042 N=38	Naive_6062 N=42	Naive_4042 N=38	Naive_6062 N=41
Baseline in P6E1[a]	3.9 (2.57-5.93)	2.96 (1.95-4.5) N=38	1.11 (0.85-1.45)	1.17 (0.9-1.52) N=38	1 (0.93-1.07)	1.05 (0.98-1.13) N=38	8.24 (5.05-13)	19 (11-30) N=38
1 Month post-1st vaccination[b]	12 (7.96-19)	NA	22 (12-40)	NA	7.73 (4.62-13)	NA	11 (6.7-19)	NA
1 Month post 1st vaccination/ baseline	3.23 (2.1-4.96) N=37		19 (10-36) N=37		7.59 (4.47-13) N=37		1.26 (0.88-1.8) N=37	
1 Month post -2nd vaccination[c]	88 (63-123) N=36	34 (25-47)	1019 (688-1510) N=36	865 (601-1244)	47 (32-69) N=36	29 (20-41)	33 (24-47) N=36	43 (31-59)
1 Month post 2nd vaccination/ baseline	20 (12-36) N=34	12 (6.96-20) N=38	910 (588-1409) N=34	702 (465-1062) N=38	47 (32-70) N=34	27 (19-40) N=38	3.94 (2.37-6.55) N=34	2.24 (1.39-3.63) N=38
18 Months post-2nd vaccination[d]	12 (6.27-23) N=28	NA	44 (29-67) N=28	NA	2.42 (1.59-3.66) N=29	NA	8.52 (5.09-14) N=27	NA
18 Months post-2nd vaccination/ baseline	3.01 (1.68-5.38) N=26		40 (24-66) N=26		2.43 (1.56-3.77) N=27		1.17 (0.64-2.14) N=26	

Source: Table 14.2.1.5.6;
Abbreviations: NA, not applicable.
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.
a. Baseline was at 40 months of age for subjects in Naive_4042 and at 60 months of age for subjects in Naive_6062.
b. Results at 1 month post-1st vaccination given at 40 months of age to subjects in group Naive_4042.
c. Results at 1 month post-2nd vaccination given at 42 months of age to subjects in group Naive_4042 and at 62 months of age to subjects in group Naive_6062.
d. Results at 18 months post-2nd vaccination given at 42 months of age to subjects in group Naive_4042.

Table 11.4.1-10: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, for Catch-up Groups - MITT Population

		Naive_4042	Naive_6062
Strain H44/76		N=38	N=42
	Baseline in P6E1[a]	23 (61%) (43-76)	12 (32%) (18-49) N=38
	1 Month post-1st vaccination[b]	34 (89%) (75-97)	NA
	1 Month post-2nd vaccination[c]	36 (100%) (90-100) N=36	39 (93%) (81-99)
	18 Months post-2nd vaccination[d]	20 (71%) (51-87) N=28	NA
Strain 5/99		N=38	N=42
	Baseline in P6E1[a]	1 (3%) (0.067-14)	1 (3%) (0.067-14) N=38
	1 Month post-1st vaccination[b]	29 (76%) (60-89)	NA
	1 Month post-2nd vaccination[c]	36 (100%) (90-100) N=36	42 (100%) (92-100)
	18 Months post-2nd vaccination[d]	28 (100%) (88-100) N=28	NA
Strain NZ98/254		N=38	N=42
	Baseline in P6E1[a]	0 (0%) (0-9)	1 (3%) (0.067-14) N=38
	1 Month post-1st vaccination[b]	25 (66%) (49-80)	NA
	1 Month post -2nd vaccination[c]	34 (94%) (81-99) N=36	42 (100%) (92-100)
	18 Months post-2nd vaccination[d]	9 (31%) (15-51) N=29	NA
Strain M10713		N=38	N=41
	Baseline in P6E1[a]	25 (66%) (49-80)	32 (84%) (69-94) N=38
	1 Month post-1st vaccination[b]	29 (76%) (60-89)	NA

	Naive_4042	Naive_6062
1 Month post-2nd vaccination[c]	32 (89%) (74-97) N=36	41 (100%) (91-100)
18 Months post-2nd vaccination[d]	22 (81%) (62-94) N=27	NA

Source: Table 14.2.1.1.6
Abbreviations: NA, not applicable.
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.
a. Baseline was at 40 months of age for subjects in Naive_4042 and at 60 months of age for subjects in Naive_6062.
b. Results at 1 month post-1st vaccination given at 40 months to subjects in group Naive_4042.
c. Results at 1 month post-2nd vaccination given at 42 months to subjects in group Naive_4042 and at 62 months to subjects in group Naive_6062.
d. Results at 18 months post-2nd vaccination given at 42 months to subjects in group Naive_4042.

One month post second vaccination an increase in GMTs and the proportion of seropositive subjects against all strains was demonstrated compared to baseline in both groups. In naïve subjects vaccinated at 40 and 42 weeks of age the magnitude of GMTs were comparable to those 5rMenB+OMV one month after the booster dose at 40 weeks of age (secondary endpoint b) whereas levels appeared slightly lower in naïve subjects vaccinated at 60 and 62 weeks of age. The proportions of seropositive subjects one month after second vaccination were comparable to those of 5rMenB+OMV one month after the booster dose at 40 weeks of age for both groups of naïve subjects. 18 months after the second vaccination GMTs and proportions of seropositive subjects in group Naïve_4042 had decreased and approached the levels at baseline for all antigens except strain 5/99.

Assessor´s comments: It is noted that it appears that older children (60 months of age) had a lower response than 40 month old children. The clinical relevance of this is, however, unclear.

e. *To explore bactericidal antibody persistence in children at 60 months of age who received one or two booster doses of rMenB or rMenB+OMV NZ, or a two-dose catch-up regimen of rMenB+OMV NZ starting at 40 months of age in the present extension study.*

Table 11.4.1-11: Geometric Mean hSBA Titers (GMTs) (95% CI) for Persistence at 60 Months in Booster/40-, 42-Month Vaccination Groups- MITT Population

		5rMenB[a]	5rMenB+OMV[a]	3rMenB[b]	3rMenB+OMV[b]	Naive_6062[c]
Strain H44/76		N=24	N=16	N=13	N=5	N=46
	60 month persistence or baseline in P6E1	3.13 (1.75-5.59)	4.68 (2.3-9.52)	18 (8.08-39)	13 (3.52-45)	2.98 (1.86-4.78)
Strain 5/99		N=23	N=16	N=13	N=5	N=46
	60 month persistence or baseline in P6E1	43 (19-99)	136 (51-365)	369 (123-1103)	210 (36-1227)	1.14 (0.88-1.47)
Strain NZ98/254		N=24	N=16	N=13	N=5	N=46
	60 month persistence or baseline in P6E1	1.05 (0.8-1.38)	4.95 (3.54-6.92)	1 (0.69-1.45)	11 (5.93-20)	1.04 (0.96-1.14)
Strain M10713		N=22	N=16	N=12	N=5	N=46
	60 month persistence or baseline in P6E1	12 (7.22-20)	10 (5.67-19)	12 (5.85-24)	25 (8.47-74)	18 (12-28)

Source: Table 14.2.1.5.7
Note: N in the headers denotes the total number of subjects evaluated for each strain.
a. Subjects who received 1 booster vaccination of rMenB or rMenB+OMV NZ at 40 months of age; results for these groups were 20 months postbooster vaccination.
b. Subjects who received 2 booster vaccinations of rMenB or rMenB+OMV NZ at 40 and 42 months of age; results for these groups were 18 months post-42 month booster vaccination.
c. Naive subjects recruited at 60 months of age were vaccinated with 2doses of rMenB+OMV NZ, given two months apart at 60 and 62 months of age; results for Naive_6062 group were baseline values.

Table 11.4.1-12: Geometric Mean hSBA Titers (GMTs) (95% CI) for Persistence at 60 Months of Age in Catch-Up Groups- MITT Population

		Naive_4042[a]	Naive_6062[b]
Strain H44/76		N=28	N=46
	60 month persistence or baseline in P6E1	12 (6.27-23)	2.98 (1.86-4.78)
Strain 5/99		N=28	N=46
	60 months persistence or baseline in P6E1	44 (29-67)	1.14 (0.88-1.47)
Strain NZ98/254		N=29	N=46
	60 months persistence or baseline in P6E1	2.42 (1.59-3.66)	1.04 (0.96-1.14)
Strain M10713		N=27	N=46
	60 months persistence or baseline in P6E1	8.52 (5.09-14)	18 (12-28)

Source: Table 14.2.1.5.8

Note: N in the headers denotes the total number of subjects evaluated for each strain.

a. Naive subjects recruited at 40 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 40 and 42 months of age; results for Naive_4042 group are at 60 months (18 months post-2nd catch-up vaccination).

b. Naive subjects recruited at 60 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for Naive_6062 group are baseline.

Table 11.4.1-13: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, for Persistence at 60 Months in Booster/40-, 42-Month Vaccination Groups- MITT Population

		5rMenB[a]	5rMenB+OMV[a]	3rMenB[b]	3rMenB+OMV[b]	Naive_6062[c]
Strain H44/76		N=24	N=16	N=13	N=5	N=46
	60 months persistence or baseline in P6E1	11 (46%) (26-67)	7 (44%) (20-70)	11 (85%) (55-98)	4 (80%) (28-99)	15 (33%) (20-48)
Strain 5/99		N=23	N=16	N=13	N=5	N=46
	60 months persistence or baseline in P6E1	19 (83%) (61-95)	14 (88%) (62-98)	13 (100%) (75-100)	5 (100%) (48-100)	1 (2%) (0.055-12)
Strain NZ98/254		N=24	N=16	N=13	N=5	N=46
	60 months persistence or baseline in P6E1	0 (0%) (0-14)	11 (69%) (41-89)	0 (0%) (0-25)	4 (80%) (28-99)	1 (2%) (0.055-12)
Strain M10713		N=22	N=16	N=12	N=5	N=46
	60 months persistence or baseline in P6E1	17 (77%) (55-92)	14 (88%) (62-98)	11 (92%) (62-100)	5 (100%) (48-100)	38 (83%) (69-92)

Source: Table 14.2.1.1.7

Note: N in the headers denotes the total number of subjects evaluated for each strain.

a. Subjects who received 1 booster vaccination of rMenB or rMenB+OMV NZ at 40 months of age; results for these groups are 20 months postbooster vaccination.

b. Subjects who received 2 booster vaccinations of rMenB or rMenB+OMV NZ at 40 and 42 months of age; results for these groups are 18 months post-42 month booster vaccination.

c. Naive subjects recruited at 60 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for Naive_6062 group are baseline.

Table 11.4.1-14: Proportion of subjects with hSBA ≥ 1:4 (95% CI) by Vaccine Group and Meningococcal Strain, for Persistence at 60 Months of Age in Catch-up Groups- MITT Population

		Naive_4042[a]	Naive_6062[b]
Strain H44/76		N=28	N=46
	60 months persistence or baseline in P6E1	20 (71%) (51-87)	15 (33%) (20-48)
Strain 5/99		N=28	N=46
	60 months persistence or baseline in P6E1	28 (100%) (88-100)	1 (2%) (0.055-12)
Strain NZ98/254		N=29	N=46
	60 months persistence or baseline in P6E1	9 (31%) (15-51)	1 (2%) (0.055-12)
Strain M10713		N=27	N=46
	60 months persistence or baseline in P6E1	22 (81%) (62-94)	38 (83%) (69-92)

Source: Table 14.2.1.1.7;
Note: N in the headers denotes the total number of subjects evaluated for each strain.
a. Naive subjects recruited at 40 months of age were vaccinated with 2 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-2nd catch-up vaccination.
b. Naive subjects recruited at 60 months of age were vaccinated with 2 doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age; results for Naive_6062 group are baseline.

At 60 months of age a decrease in GMTs and proportions of seropositive subjects were demonstrated in groups 5rMenB+OMV, 3rMenB+OMV and Naïve_4042 as compared to one month after the last vaccination (secondary endpoints b, c and d). In group 5rMenB+OMV GMTs had returned to similar levels as baseline in the extension study (prior to the booster dose at 40 months of age). In group 3rMenB+OMV, GMT levels decreased but were still above baseline.

f. Immune response for vaccine antigen 287-953 for all immunogenicity objectives (ELISA)

Table 11.4.1-15: Geometric Mean ELISA Concentration (GMC) for Vaccine Antigen 287-953 in Booster/40-, 42-Month Vaccination Groups - MITT Population

	5rMenB	5rMenB+OMV	3rMenB	3rMenB+OMV	Naive_4042	Naive_6062
	N=28	N=19	N=14	N=8	N=38	N=47
Prebooster or baseline in P6E1 (at 40 months)	82 (59-113)	62 (41-94) N=17	32 (21-49)	28 (16-50)	23 (19-26)	NA
1 Month post-40 month booster or post-1st vaccination	5592 (3900-8017)	3934 (2540-6093)	2100 (1100-4007) N=13	1764 (731-4256) N=7	64 (44-94)	NA
1 Month post-42 month booster or post-2nd vaccination	NA	NA	3790 (2265-6342) N=13	3660 (1899-7055)	3464 (2782-4313) N=36	
60 months persistence or18 months post 2nd vaccination or baseline (at 60 months)	670 (443-1013) N=24	320 (193-530) N=16	280 (159-495) N=13	250 (100-626) N=5	121 (84-173) N=28	25 (21-30)

Source: Table 14.2.1.6.2, Table 14.2.1.6.3
Abbreviations: NA, not applicable.
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.

Table 11.4.1-16: Geometric Mean ELISA Concentration (GMC; 95% CI) for Vaccine Antigen 287-953 in Catch-up Groups- MITT Population

	Naive_4042	Naive_6062
	N=38	N=42
Baseline in P6E1[a]	23 (19-26)	24 (20-28) N=39
1 Month post-1st vaccination	64 (44-94)	NA
1 Month post-2nd vaccination	3464 (2672-4489) N=36	1744 (1372-2218)
18 Months post-2nd vaccination	121 (84-173) N=28	NA

Source: Table 14.2.1.6.4;
Abbreviations: NA, not applicable;
Note: N in the headers denotes the total number of subjects evaluated for each strain. Individual N's in each cell denote the number of subjects from each group who were evaluated at that timepoint.
a. Baseline was at 40 months of age for subjects in Naive_4042 and at 60 months of age for subjects in Naive_6062.

Booster doses/repeated doses resulted in a substantial increase in GMCs across all groups. At 60 months of age in groups 5rMenB+OMV, 3rMenB+OMV and Naive_4042, levels of GMCs had been reduced about 10-fold but remained above baseline.

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. During initial assessment for market authorisation it was noted that immune responses to vaccination with rMenB+OMV NZ in the parent study V72P6 were lower than those of other studies, including the pivotal study V72P13. Responses presented in this extension study are also comparatively low, but considering the levels of the parent study and the limited sample size, there is not enough concern to indicate reduced immunogenicity of vaccination from the data presented here.
It is also 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 occurring by vaccination group is provided in tables 2-4 and 2-5, respectively. Unsolicited reported adverse events are summarized in table 12.2.3-3

Table 12.2.1-1: Summary of Subjects With at Least One Solicited Adverse Event, by Vaccination

	Number (%) of Subjects With Solicited Adverse Events					
	5rMenB	5rMenB+ OMV	3rMenB	3rMenB+ OMV	Naive_4042	Naive_6062
Any vaccination	**N=29**	**N=19**	**N=14**	**N=8**	**N=42**	**N=50**
Any	29 (100%)	19 (100%)	14 (100%)	8 (100%)	42 (100%)	49 (98%)
Local	28 (97%)	19 (100%)	14 (100%)	8 (100%)	42 (100%)	49 (98%)
Systemic	19 (66%)	13 (68%)	11 (79%)	8 (100%)	38 (90%)	42 (84%)
Other[a]	10 (34%)	12 (63%)	5 (36%)	7 (88%)	31 (74%)	33 (66%)
Vaccination 1	**N=29**	**N=19**	**N=14**	**N=8**	**N=42**	**N=50**
Any	29 (100%)	19 (100%)	13 (93%)	8 (100%)	42 (100%)	49 (98%)
Local	28 (97%)	19 (100%)	12 (86%)	8 (100%)	42 (100%)	49 (98%)
Systemic	19 (66%)	13 (68%)	8 (57%)	7 (88%)	36 (86%)	35 (70%)
Other[a]	10 (34%)	12 (63%)	3 (21%)	6 (75%)	22 (52%)	24 (48%)
Vaccination 2			**N=14**	**N=8**	**N=41**	**N=46**
Any	NA	NA	14 (100%)	8 (100%)	41 (100%)	45 (98%)
Local			14 (100%)	8 (100%)	41 (100%)	45 (98%)
Systemic			9 (64%)	5 (63%)	31 (76%)	35 (76%)
Other[a]			3 (21%)	6 (75%)	23 (56%)	25 (54%)

Source: Table 14.3.1.1.1, Table 14.3.1.1.1.1
Abbreviation: NA, not applicable.
a. Other indicators of reactogenicity such as body temperature, use of antipyretics and medically attended fever.

Table 12.2.1-2: Overview of Unsolicited Adverse Events Following Any Vaccination

	Number (%) of Subjects with Unsolicited Adverse Events					
	5rMenB	5rMenB+OMV	3rMenB	3rMenB+OMV	Naive_4042	Naive_6062
	N=29	N=19	N=14	N=8	N=42	N=50
Any unsolicited AEs	15 (52%)	7 (37%)	10 (71%)	4 (50%)	22 (52%)	21 (42%)
At least possibly related unsolicited AEs	2 (7%)	1 (5%)	4 (29%)	1 (13%)	7 (17%)	8 (16%)
Any SAEs	1 (3%)	1 (5%)	0	1 (13%)	2 (5%)	2 (4%)

Source: Table 14.3.1.1.10, Table 14.3.1.1.13, Table 14.3.1.1.6
Abbreviation: AE, adverse event; SAE, serious adverse event.

Table 2-4: Numbers (%) of Subjects With Any (and Severe/>100 mm) Solicited Local Adverse Events, by Vaccination – Safety Population

		Number (%) of Subjects with Solicited Local Adverse Events					
		5rMenB	5rMenB+ OMV	3rMenB	3rMenB+ OMV	Naive_4042	Naive_6062
Vaccination 1		**N=29**	**N=19**	**N=14**	**N=8**	**N=42**	**N=50**
Pain	Any	17 (59%)	14 (74%)	3 (21%)	8 (100%)	39 (93%)	40 (80%)
	Severe	1 (3%)	2 (11%)	0	1 (13%)	9 (21%)	6 (12%)
Erythema	Any	28 (97%)	19 (100%)	12 (86%)	8 (100%)	41 (98%)	47 (94%)
	> 100 mm	4 (14%)	0	0	0	0	0
Induration	Any	14 (48%)	9 (47%)	3 (21%)	5 (63%)	14 (33%)	23 (46%)
	> 100 mm	2 (7%)	0	0	0	0	0
Swelling	Any	13 (45%)	5 (26%)	3 (21%)	2 (25%)	20 (48%)	19 (38%)
	> 100 mm	2 (7%)	0	0	0	0	0
Vaccination 2		**N=29**	**N=19**	**N=14**	**N=8**	**N=41**	**N=46**
Pain	Any	NA	NA	7 (50%)	7 (88%)	35 (85%)	39 (85%)
	Severe			2 (14%)	2 (25%)	6 (15%)	2 (4%)
Erythema	Any	NA	NA	14 (100%)	8 (100%)	38 (93%)	40 (87%)
	> 100 mm			0	0	0	0
Induration	Any	NA	NA	7 (50%)	6 (75%)	20 (49%)	19 (41%)
	> 100 mm			1 (7%)	0	0	0
Swelling	Any	NA	NA	8 (57%)	4 (50%)	26 (63%)	19 (41%)
	> 100 mm			2 (14%)	0	0	0

Source: Table 14.3.1.1.2.1
Abbreviation: NA, not applicable. Note: The numbers (N) in the header is the total number of subjects with documented reactions

Table 2-5: Numbers (%) of Subjects With Any (and Severe) Solicited Systemic Adverse Events, by Vaccination – Safety Population

		Number (%) of Subjects with Solicited Systemic Adverse Events					
		5rMenB	5rMenB+ OMV	3rMenB	3rMenB+ OMV	Naive_4042	Naive_6062
Vaccination 1		**N=29**	**N=19**	**N=14**	**N=8**	**N=42**	**N=50**
Systemic							
Change in eating habits	Any	5 (17%)	10 (53%)	3 (21%)	2 (25%)	16 (38%)	17 (34%)
	Severe	0	0	1 (7%)	0	1 (2%)	0
Sleepiness	Any	13 (45%)	12 (63%)	5 (36%)	4 (50%)	20 (48%)	18 (36%)
	Severe	0	0	0	0	2 (5%)	0
Vomiting	Any	1 (3%)	3 (16%)	2 (14%)	0	1 (2%)	5 (10%)
	Severe	0	0	0	0	0	0
Diarrhea	Any	3 (10%)	1 (5%)	2 (14%)	0	6 (14%)	4 (8%)
	Severe	0	0	0	0	0	0
Irritability	Any	14 (48%)	10 (53%)	4 (29%)	5 (63%)	32 (76%)	24 (48%)
	Severe	0	1 (5%)	0	0	3 (7%)	0
Headache	Any	1 (3%)	0	1 (7%)	0	4 (10%)	5 (10%)
	Severe	0	0	0	0	0	0
Arthralgia	Any	0	6 (32%)	1 (7%)	2 (25%)	13 (31%)	10 (20%)
	Severe	0	1 (5%)	0	0	3 (7%)	1 (2%)
Rash	Any	3 (10%)	0	0	1 (13%)	1 (2%)	2 (4%)
	Urticarial	0	0	0	0	1 (2%)	0
Fever (≥38°C)[a]	Yes	1 (3%)	1 (5%)	1 (7%)	0	4 (10%)	5 (10%)
Other							
Axillary temperature	<38°C	28 (97%)	18 (95%)	13 (93%)	8 (100%)	38 (90%)	45 (90%)
	≥40°C	0	0	0	0	0	0
Antipyretic preventive medications used	Yes	10 (34%)	12 (63%)	2 (14%)	6 (75%)	22 (52%)	23 (46%)
Antipyretic treatment medications used	Yes	1 (3%)	2 (11%)	1 (7%)	0	4 (10%)	5 (10%)
Medically attended fever	Yes	0	0	0	0	0	0
Vaccination 2		**N=29**	**N=19**	**N=14**	**N=8**	**N=41**	**N=46**
Systemic							
Change in eating habits	Any	NA	NA	4 (29%)	2 (25%)	14 (34%)	16 (35%)
	Severe			0	0	0	1 (2%)
Sleepiness	Any	NA	NA	6 (43%)	3 (38%)	15 (37%)	15 (33%)
	Severe			0	0	1 (2%)	1 (2%)
Vomiting	Any	NA	NA	1 (7%)	0	0	4 (9%)
	Severe			1 (7%)	0	0	1 (2%)
Diarrhea	Any	NA	NA	1 (7%)	1 (13%)	1 (2%)	4 (9%)
	Severe			0	0	0	0
Irritability	Any	NA	NA	7 (50%)	5 (63%)	24 (59%)	20 (43%)
	Severe			1 (7%)	0	2 (5%)	1 (2%)
Headache	Any	NA	NA	1 (7%)	1 (13%)	4 (10%)	3 (7%)
	Severe			0	0	1 (2%)	0
Arthralgia	Any	NA	NA	3 (21%)	2 (25%)	9 (22%)	12 (26%)
	Severe			2 (14%)	1 (13%)	3 (7%)	0
Rash	Any	NA	NA	2 (14%)	0	2 (5%)	3 (7%)

		Number (%) of Subjects with Solicited Systemic Adverse Events					
		5rMenB	5rMenB+ OMV	3rMenB	3rMenB+ OMV	Naive_4042	Naive_6062
	Urticarial			0	0	0	0
Fever (≥38°C)[a]	Yes	NA	NA	3 (21%)	0	5 (12%)	2 (4%)
Other							
Axillary temperature	<38°C	NA	NA	11 (79%)	8 (100%)	36 (88%)	44 (96%)
	≥40°C			0	0	0	0
Antipyretic preventive medications used	Yes	NA	NA	2 (14%)	6 (75%)	21 (51%)	25 (54%)
Antipyretic treatment medications used	Yes	NA	NA	3 (21%)	0	4 (10%)	3 (7%)
Medically attended fever	Yes	NA	NA	1 (7%)	0	0	1 (2%)

Source: Table 14.3.1.1.2.1
Abbreviation: NA, not applicable. Note: The numbers (N) in the header is the total number of subjects with documented reactions.
a. Fever was defined as axillary body temperature ≥ 38°C

Table 12.2.3-3: All and at Least Possibly Related Unsolicited Adverse Events Reported by >5% of Subjects (Preferred Term) by Descending Frequency After any Vaccination – Safety Population

Preferred Term	Number (%) of Subjects with Unsolicited Adverse Events											
	All AEs						At Least Possibly Related AEs					
	5rMenB	5rMen+ OMV	3rMenB	3rMen+ OMV	Naive_4 042	Naive_6 062	5rMenB	5rMenB +OMV	3rMenB	3rMenB +OMV	Naive_4 042	Naive_6 062
	N=29	N=19	N=14	N=8	N=42	N=50	N=29	N=19	N=14	N=8	N=42	N=50
Pyrexia	0	0	4 (29%)	0	0	0	0	0	1 (7%)	0	0	0
Ear Infection	2 (7%)	1 (5%)	2 (14%)	1 (13%)	4 (10%)	1 (2%)	0	0	0	0	0	0
Injection Site Erythema	0	0	2 (14%)	0	2 (5%)	2 (4%)	0	0	2 (14%)	0	2 (5%)	2 (4%)
Rhinitis	0	0	2 (14%)	0	4 (10%)	1 (2%)	0	0	0	0	0	0
Asthma	1 (3%)	0	0	1 (13%)	2 (5%)	0	0	0	0	0	0	0
Cystic Lymphangioma	0	0	0	1 (13%)	0	0	0	0	0	0	0	0
Heat Stroke	0	0	0	1 (13%)	0	0	0	0	0	0	0	0
Localised Infection	1 (3%)	0	0	1 (13%)	0	0	0	0	0	0	0	0
Oedema Peripheral	0	0	0	1 (13%)	0	0	0	0	0	1 (13%)	0	0
Pain	0	0	0	1 (13%)	0	0	0	0	0	0	0	0
Lower Respiratory Tract Infection	3 (10%)	0	0	0	1 (2%)	1 (2%)	0	0	0	0	0	0
Abdominal Pain Upper	1 (3%)	0	1 (7%)	0	0	1 (2%)	1 (3%)	0	1 (7%)	0	0	1 (2%)
Alopecia	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Ear Pain	0	0	1 (7%)	0	0	1 (2%)	0	0	0	0	0	0

Preferred Term	Number (%) of Subjects with Unsolicited Adverse Events											
	All AEs						At Least Possibly Related AEs					
	5rMenB	5rMen+ OMV	3rMenB	3rMen+ OMV	Naive_4 042	Naive_6 062	5rMenB	5rMenB +OMV	3rMenB	3rMenB +OMV	Naive_4 042	Naive_6 062
	N=29	N=19	N=14	N=8	N=42	N=50	N=29	N=19	N=14	N=8	N=42	N=50
Eczema	1 (3%)	0	1 (7%)	0	0	1 (2%)	0	0	0	0	0	0
Eczema Infected	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Faeces Discoloured	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Fungal Skin Infection	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Hyperpyrexia	1 (3%)	0	1 (7%)	0	0	0	0	0	1 (7%)	0	0	0
Impetigo	1 (3%)	0	1 (7%)	0	1 (2%)	1 (2%)	0	0	0	0	0	0
Injection Site Swelling	0	0	1 (7%)	0	1 (2%)	2 (4%)	0	0	1 (7%)	0	1 (2%)	2 (4%)
Lethargy	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Overdose	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Rash	1 (3%)	0	1 (7%)	0	0	0	0	0	1 (7%)	0	0	0
Skin Infection	0	0	1 (7%)	0	0	0	0	0	0	0	0	0
Varicella	0	1 (5%)	1 (7%)	0	1 (2%)	0	0	0	0	0	0	0
Constipation	2 (7%)	0	0	0	0	0	0	0	0	0	0	0
Cough	2 (7%)	0	0	0	1 (2%)	2 (4%)	0	0	0	0	0	0
Tonsillitis	2 (7%)	0	0	0	1 (2%)	2 (4%)	0	0	0	0	0	0
Injection Site Induration	0	0	0	0	0	3 (6%)	0	0	0	0	0	3 (6%)
Bronchopneumonia	0	1 (5%)	0	0	0	0	0	0	0	0	0	0
Eating Disorder	0	1 (5%)	0	0	1 (2%)	0	0	1 (5%)	0	0	1 (2%)	0
Fall	0	1 (5%)	0	0	0	0	0	0	0	0	0	0
Irritability	0	1 (5%)	0	0	0	0	0	1 (5%)	0	0	0	0
Lymphadenitis	0	1 (5%)	0	0	1 (2%)	0	0	0	0	0	0	0
Nasopharyngitis	0	1 (5%)	0	0	1 (2%)	0	0	0	0	0	0	0
Oropharyngeal Pain	0	1 (5%)	0	0	1 (2%)	1 (2%)	0	0	0	0	0	0
Otitis Media	0	1 (5%)	0	0	0	0	0	0	0	0	0	0
Somnolence	0	1 (5%)	0	0	0	0	0	1 (5%)	0	0	0	0
Urinary Tract Infection	0	1 (5%)	0	0	2 (5%)	1 (2%)	0	0	0	0	0	0

Source: Table 14.3.1.1.9, Table 14.3.1.1.12.

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.

V72_41 A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with OMV Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years.

- **Description**

- **Methods**

  - Objectives

  Immunogenicity Objectives:

  Primary objective

  ▫ To demonstrate the equivalence of rMenB+OMV NZ lot 1 to rMenB+OMV NZ lot 2 when administered to adolescents, as measured by human serum bactericidal activity (hSBA) geometric mean titers (GMTs) against 3 *N. meningitidis* serogroup B reference strains (H44/76, 5/99, and NZ98/254) and as measured by Enzyme linked immunosorbent assay (ELISA) geometric mean concentrations (GMCs) against vaccine antigen 287-953, approximately 30 days after a primary vaccination course of two doses administered one month apart.

The study was considered a success if, at one month following the second vaccination, the two-sided 95% confidence interval (CI) of the ratio of the hSBA GMTs for each of 3 serogroup B reference strains (H44/76, 5/99, and NZ98/254) and the twosided 95% CI of the ratio of the ELISA GMCs against vaccine antigen 287-953 are contained within the interval (0.5, 2.0).

Secondary objectives:

a) To assess the immune response at one month after a primary vaccination course of two rMenB+OMV NZ doses administered one month apart as measured by the percentage of subjects with hSBA ≥1:5 and as measured by the ratio of hSBA postvaccination to pre-vaccination GMTs [GMR] against 3 *N. meningitidis* serogroup B reference strains (H44/76, 5/99, and NZ98/254).
b) To assess the immune response at one month after a primary vaccination course of two rMenB+OMV NZ doses administered one month apart as measured by the ratio of ELISA post-vaccination to pre-vaccination GMCs [GMR] against vaccine antigen 287-953.
c) To evaluate the immune response at two weeks after a primary vaccination course of two rMenB+OMV NZ doses administered one month apart as measured by hSBA GMT, the ratio of hSBA post-vaccination to pre-vaccination GMTs [GMR], and the percentage of subjects with hSBA ≥1:5 against 3 *N. meningitidis* serogroup B reference strains (H44/76, 5/99, and NZ98/254).
d) To evaluate the immune response at two weeks after a primary vaccination course of two rMenB+OMV NZ doses administered one month apart as measured by ELISA GMC and the ratio of ELISA post-vaccination to pre-vaccination GMCs [GMR] against vaccine antigen 287-953.

Analyses related to the secondary objectives are descriptive only. There are no statistical hypotheses related to the secondary immunogenicity objectives.

Safety Objective:

To evaluate the safety and tolerability of two doses of two rMenB+OMV NZ vaccine lots formulated with OMV manufactured at 2 different manufacturing sites, given one month apart, in healthy adolescents.

- Study design

This was a Phase 3, multicenter (7 sites in Canada and 6 sites in Australia), observer-blind randomized trial in adolescents (11-17 years, inclusive). All subjects received two rMenB+OMV NZ vaccinations one month apart and were followed for a total of 2 months. Subjects were randomized to 1 of 2 treatment arms to receive either two doses of rMenB+OMV NZ vaccine Lot 1 or 2 doses of rMenB+OMV NZ Lot 2. Lot 1 was formulated with OMV manufactured in Novartis Rosia facility and Lot 2 from Novartis Siena facility.

- Study population /Sample size

Overall, 320 subjects were planned to be enrolled, with 160 subjects per lot who were to be randomized in a 1:1 ratio. Estimating a total drop-out rate of 15%, a sample size of 135 evaluable subjects per arm were planned to be vaccinated with rMenB+OMV NZ in the groups Lot 1_Rosia and Lot 2_Siena, respectively. Assuming an underlying GMT (or GMC) ratio of 1.0 and that the results for the three strains and vaccine antigen 287-953 are independent, the overall power to demonstrate immunologic consistency is approximately 93.6%. The power to reject the null hypothesis associated with the primary immunogenicity objective is the probability that, for each strain or vaccine antigen 287-953, the two-sided 95% confidence interval (CI) for the ratio of GMTs (or GMCs) at 1 month after the second vaccination is entirely contained within the interval (0.5, 2.0).

All subjects who received at least one vaccination were to be included in the safety analyses.

Individuals eligible were to be enrolled into this study were male and female subjects:

- 11-17 years of age inclusive who had given their written assent and whose parents or legal guardians provided written informed consent at the time of enrollment;
- who were available for all the visits scheduled in the study (i.e., did not leave the area before the end of the study period);
- in good health as determined by the outcome of medical history, physical examination, and clinical judgment of the investigator.

- Treatments

Enrolled subjects were randomised into two groups and vaccinated with Novartis Meningococcal B Recombinant+OMV NZ vaccine (rMenB+OMV NZ);

  - Group Lot 1_Rosia; Lot 1 formulated with OMV manufactured in Rosia site
  - Group Lot 2_Siena: Lot 2 formulated with OMV manufactured in Siena site

Treatments were given twice one month apart followed by a one month long follow up period. The total study period was two months.

- Outcomes/endpoints

Immunogenicity endpoints

The Serum Bactericidal Assay (SBA) using human serum as the source of exogenous complement (hSBA) was used to measure the induction of functional bactericidal antibodies directed against serogroup B meningococci following vaccination with rMenB+OMV. An Enzyme-Linked Immunosorbent Assay (ELISA) was also used to measure immune response to vaccination.
The primary immunogenicity variables were:

  - The ratio of the vaccine lot hSBA GMTs for each of the three serogroup B reference strains (H44/76, 5/99, and NZ98/254) at one month after the second vaccination.
  - The ratio of the vaccine lot ELISA GMCs for the 287-953 vaccine antigen at one month after the second vaccination.

Equivalence of the immune response of the two lots of rMenB+OMV NZ, each formulated with OMV manufactured at a different sites, assessed at one month after the second vaccination based on the ratio of the vaccine lot hSBA GMTs for each of three serogroup B reference strains (H44/76, 5/99, and NZ98/254) and based on the ratio of ELISA GMCs for vaccine antigen 287-953. The equivalence interval was (0.5, 2.0). An additional blood draw in a subset of subjects at two weeks after the second dose was also collected.
Additional secondary analyses at each time point included the percentage of subjects with hSBA ≥1:5, which is above the historically defined threshold titer (1:4) that correlates to clinical protection, and the GMR to baseline at each time point.

Safety endpoints

All subjects who received at least one vaccination of rMenB+OMV NZ and provided some safety data post vaccination were included in the safety analyses. All safety analyses were descriptive.

Local and Systemic Adverse Reactions

Post-vaccination reactions reported from day 1 to day 7 after each vaccination were summarized by maximal severity and by vaccine group. The severity of local reactions, including injection-site erythema, induration, and swelling was categorized as none (0 mm), 1 to <25 mm, 25 to <50 mm, 50 to <100 mm and ≥100 mm (severe local reactions). The severity of pain and systemic reactions (i.e., nausea, fatigue, myalgia, arthralgia, headache and rash) occurring up to 7 days (including the day of vaccination) after each vaccination was categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity). Rash was categorized as none, urticarial, and other. Frequencies and percentages of subjects experiencing each local and systemic reaction during days 1 to 3 after vaccination were similarly summarized, as well as daily frequencies and the time of onset of the first reactions. Each local and systemic reaction was also categorized as none vs. any. Body temperature (regardless of the route of measurement) was analyzed in 0.5°C increments as follow <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. Additionally, the number and percentage of subjects who used analgesic or antipyretic medication were summarized in addition to the number and percentage of subjects who stayed home due to a reaction.

Other Adverse events

All reported adverse events, as well as adverse events judged as at least possibly related to study vaccine, were summarized according to system organ class and preferred term within system organ class. These summaries were presented by vaccination group. When an adverse event occurred, more than once for a subject, the maximal severity and strongest relationship to the vaccine group was counted. Additionally, three separate summaries were produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events were provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event was presented, as well as a listing of adverse events leading to hospitalization.

- Statistical Methods

The null hypothesis associated with the lot-to-lot immunogenicity objective was that for at least one strain at one month after the second vaccination, the two-sided 95% CI on the ratio of hSBA GMTs (strains H44/76, 5/99, or NZ98/254) or the two-sided 95% CI on the ratio of the ELISA GMCs (vaccine antigen 257-953) was outside the interval (0.5, 2.0).
For each of the three strains and the 287-953 vaccine antigen, lot-to-lot consistency for the 2 lots of rMenB+OMV NZ was assessed in terms of log10-transformed hSBA GMTs or log10-transformed ELISA GMCs at one month after the second vaccination.
Analyses related to the secondary objectives were descriptive only. Therefore, there were no statistical hypotheses related to the secondary immunogenicity objectives.

➢ Results

- Recruitment/ Number analysed

Overall, 344 subjects aged 11 to 17 years were enrolled in the study. Of these, 170 were included in Lot1_Rosia and 174 subjects in Lot2_Siena. The immunogenicity per protocol population (PP) comprised of 299 subjects, 147 subjects from Lot1_Rosia and 152 subjects from Lot2_Siena. An immunogenicity subset PP population of 147 subjects (76 in Lot1_Rosia and 71 in Lot2_Siena) was analyzed at two weeks after second vaccination.
The safety population was composed of 342 subjects; 169 subjects in Lot1_Rosia and 173 subjects in Lot2_Siena. Two of the enrolled subjects (59/001/Lot1_Rosia and 52/023/Lot2_Siena) did not receive any vaccination at all, and were therefore excluded from safety analyses.
A summary of the number of subjects who were enrolled, who completed or discontinued the study, by vaccination group, is provided in table 2-2. Among enrolled subjects, a total of 6 subjects (2%) discontinued the study. Five of the six subjects who discontinued withdrew consent whereas one subject from Lot2_Siena reported an adverse event “Infectious Mononucleosis” with moderate severity which led to premature withdrawal from the study.

Table 2-2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects		
	Lot 1_Rosia	**Lot 2_Siena**	**Total**
Enrolled	170	174	344
Completed protocol	168 (99%)	170 (98%)	338 (98%)
Premature withdrawal	2 (1%)	4 (2%)	6 (2%)
AE or Death	0	1 (<1%)	1 (<1%)
Withdrawal of consent	2 (1%)	3 (2%)	5 (1%)

- Baseline data

The demographic and other baseline characteristics for the enrolled population in the Lot1_Rosia and Lot2_Siena were well matched, except for gender differences. There was a 5% difference in percentage of males (58% and 53%) and females (42% and 47%) between Lot1_Rosia and Lot2_Siena, respectively. The majority of subjects in the Lot1_Rosia and Lot2_Siena groups were White. These gender differences did not affect the lot consistency conclusions for this study.

- Efficacy results

Primary endpoint:
Equivalence of the immune response of the two lots of rMenB+OMV NZ, each formulated with OMV manufactured at a different sites, assessed at one month after the second vaccination based on the ratio of the vaccine lot hSBA GMTs for each of three serogroup B reference strains (H44/76, 5/99, and NZ98/254) and based on the ratio of ELISA GMCs for vaccine antigen 287-953

Table 2-5: Geometric Mean hSBA Titers (GMTs, 95%CI), Geometric Mean Ratios to Baseline (GMRs - 95% CI) and Vaccine Group Ratios by MenB Reference Strain at One Month after the Second Vaccination – Per Protocol Population

		Lot 1_Rosia	Lot 2_Siena	Total	Lot 1_Rosia : Lot 2_Siena
Men B hSBA 44-76-SL		N=147	N=152	N=299	
	Baseline	1.07 (1-1.14)	1.03 (0.97-1.1)	1.07 (1.02-1.11)	1.04 (0.95-1.13)
	1 month after 2nd vaccination.	111 (96-129)	111 (96-128) N=151	117 (105-130) N=298	1 (0.82-1.23)
	1 month after 2nd vaccination to Baseline	104 (89-121)	107 (92-124) N=151	110 (99-122) N=298	0.97 (0.79-1.19)
Men B hSBA 5/99		N=147	N=152	N=299	
	Baseline	1.17 (1.04-1.31)	1.19 (1.06-1.33)	1.23 (1.13-1.33)	0.98 (0.84-1.15)
	1 month after 2nd vaccination.	183 (160-209)	199 (174-227)	179 (163-197)	0.92 (0.77-1.1)
	1 month after 2nd vaccination to Baseline	156 (133-183)	167 (143-195)	146 (130-164)	0.93 (0.75-1.16)
Men B hSBA NZ98/254		N=147	N=152	N=299	
	Baseline	1.07 (1-1.15)	1.04 (0.97-1.11)	1.06 (1.01-1.11)	1.04 (0.94-1.14)
	1 month after 2nd vaccination.	9.27 (7.44-12)	11 (9.22-14) N=151	10 (8.77-12) N=298	0.81 (0.6-1.09)
	1 month after 2nd vaccination to Baseline	8.63 (6.99-11)	11 (8.99-14) N=151	9.63 (8.35-11) N=298	0.78 (0.59-1.04)

Table 2-6: Geometric Mean ELISA Concentrations (GMCs, 95% CI), Geometric Mean Ratios (GMRs, 95% CI) to Baseline and Vaccine Group Ratios against the 287-953 Vaccine Antigen at One Month after the Second Vaccination – Per Protocol Population

	Lot 1_Rosia	Lot 2_Siena	Total	Lot 1_Rosia : Lot 2_Siena
	N=147	N=152	N=299	
Baseline	24 (22-26)	21 (20-23)	23 (21-24)	1.11 (0.99-1.25)
1 month after 2nd vaccination.	2729 (2338-3186)	3291 (2829-3828)	2875 (2585-3197)	0.83 (0.67-1.02)
1 month after 2nd vaccination to Baseline	115 (96-137)	154 (130-183)	126 (112-143)	0.75 (0.59-0.94)

Table 2-7: Equivalence Criterion Met for Ratio of hSBA GMTs for 3 Serogroup B Reference Strains (H44/76, 5/99, and NZ98/254) and ELISA GMCs against Vaccine Antigen 287-953 at One Month after Second Vaccination– Per Protocol Population

	Lot 1_Rosia Vs Lot 2_Siena		
	Vaccine Group Ratios	Two-Sided 95% CI	Equivalence Criterion CI (0.5, 2.0)
Strain 44/76-SL	1	(0.82-1.23)	+
Strain 5/99	0.92	(0.77-1.1)	+
Strain NZ98/254	0.81	(0.6-1.09)	+
Vaccine Antigen 287-953	0.83	(0.67-1.02)	+

Source: Table 14.2.1.1, Table 14.2.1.3; hSBA - human serum bactericidal activity; GMTs - geometric mean titers; GMCs - geometric mean concentrations; CI - confidence interval; '+' Equivalence criterion met, '-' Equivalence criterion not met.

Assessor's comment: It is unclear how the GMT for the total population can be higher than the GMTs for each group for strain 44/76-SL at one month after the 2nd vaccination, and lower for the total population for strain 5/99 than in each for the groups. This should be clarified.

Post-script: The company responded to the Assessor's request for clarification in August 2014. The apparent mistake is due the use of adjusted and unadjusted GMTs values for different groups in the same Table. The responses were accepted and the submission is considered fulfilled

The primary objective to demonstrate equivalence of rMenB+OMV NZ lot 1 to rMenB+OMV NZ lot 2 at one month after second vaccination was met for the 3 *N. meningitidis* serogroup reference strains H44/76, 5/99, and NZ98/254 and for the vaccine antigen 287-953. The two-sided 95% CI of the ratio of the hSBA GMTs for each of the 3 serogroup B reference strains (H44/76, 5/99, and NZ98/254) and the two-sided 95% CI of the ratio of the ELISA GMCs against vaccine antigen 287-953 were each contained within the interval (0.5, 2.0

Secondary endpoints:
Immune response at one month after second vaccination: Percentage of subjects with hSBA ≥1:5 and as measured by the ratio of hSBA postvaccination to pre-vaccination GMTs [GMR] against 3 N. meningitidis serogroup B reference strains (H44/76, 5/99, and NZ98/254).

Table 11.4.1.2-1: Percentage of Subjects with hSBA ≥1:5 (95% CI) by MenB Reference Strain at One Month after the Second Vaccination – Per Protocol Population

		Lot 1_Rosia	Lot 2_Siena	Total
Men B hSBA 44-76-SL		N=147	N=152	N=299
	Baseline	3 (2%) (0%-6%)	3 (2%) (0%-6%)	6 (2%) (1%-4%)
	1 month after 2nd vaccination	146 (99%) (96%-100%)	150 (99%) (96%-100%) N=151	296 (99%) (98%-100%) N=298
Men B hSBA 5/99		N=147	N=152	N=299
	Baseline	9 (6%) (3%-11%)	11 (7%) (4%-13%)	20 (7%) (4%-10%)
	1 month after 2nd vaccination	147 (100%) (98%-100%)	152 (100%) (98%-100%)	299 (100%) (99%-100%)
Men B hSBA NZ98/254		N=147	N=152	N=299
	Baseline	4 (3%) (1%-7%)	1 (1%) (0.017%-4%)	5 (2%) (1%-4%)
	1 month after 2nd vaccination	103 (70%) (62%-77%)	120 (79%) (72%-86%) N=151	223 (75%) (70%-80%) N=298

Ratio of ELISA post-vaccination to pre-vaccination GMCs (GMR) against vaccine antigen 287-953. Enzyme-linked immunosorbent assay (ELISA) GMR to baseline at one month after second vaccination, against vaccine antigen 287-953, was found to be slightly higher in Lot2_Siena (154) when compared to Lot1_Rosia (115), but the GMRs for each lot had overlapping 95% CIs (Table 2-6).

Immune response at two weeks after second vaccination: Human serum bactericidal assay (hSBA) GMT, the ratio of hSBA post-vaccination to prevaccination GMTs (GMR), and the percentage of subjects with hSBA ≥1:5 against 3 N. meningitidis serogroup B reference strains (H44/76, 5/99, and NZ98/254).

In general, there was a decline in hSBA GMT levels and GMRs measured at one month after the second vaccination when compared to the respective titer levels and GMRs measured at two weeks after the second vaccination, for all three reference strains and for both Lot1_Rosia and Lot2_Siena.
At two weeks and one month after the second vaccination, all subjects (100%) receiving Lot1_Rosia and Lot2_Siena attained hSBA levels ≥1:5, against *N. meningitidis* serogroup B reference strains H44/76 and 5/99. However against reference strain NZ98/254, for both lots, the percentage of subjects with hSBA ≥1:5 was higher at two weeks compared to one month after vaccination (96% and 84% at 2 weeks post vaccination vs. 80% and 64% one month after vaccination, for Lot2_Siena and Lot1_Rosia, respectively.

Table 11.4.1.2-2: Geometric Mean hSBA Titers (GMTs, 95%CI), Geometric Mean Ratios to Baseline (GMRs, 95% CI) by MenB Reference Strain at 2 Weeks and One Month After the Second Vaccination – Immunogenicity Subset - PP Population

		Lot 1_Rosia	Lot 2_Siena	Total
		N=76	N=71	N=147
Men B hSBA 44-76-SL	Baseline	1.08 (0.95-1.22)	1.09 (0.96-1.23)	1.1 (1.01-1.19)
	2 weeks after 2nd Vaccination	187 (152-229)	171 (139-210) N=70	175 (153-199) N=146
	2 weeks after 2nd Vaccination to Baseline	174 (138-219)	157 (124-199) N=70	159 (137-184) N=146
	1 month after 2nd Vaccination	112 (91-138)	108 (87-134) N=70	128 (111-146) N=146
	1 month after 2nd Vaccination to Baseline	104 (83-130)	99 (79-125) N=70	116 (101-134) N=146
Men B hSBA 5/99	Baseline	1.19 (0.96-1.48)	1.39 (1.11-1.74)	1.35 (1.17-1.55)
	2 weeks after 2nd Vaccination	254 (206-314)	339 (273-420)	294 (257-336)
	2 weeks after 2nd Vaccination to Baseline	214 (161-284)	243 (183-325)	218 (183-261)
	1 month after 2nd Vaccination	156 (127-192)	184 (149-227)	153 (134-174)
	1 month after 2nd Vaccination to Baseline	131 (101-171)	132 (101-172)	113 (96-134)
Men B hSBA NZ98/254	Baseline	1.05 (0.97-1.14)	0.99 (0.91-1.08)	1.05 (0.99-1.1)
	2 weeks after 2nd Vaccination	14 (10-18)	20 (15-27)	18 (15-21)
	2 weeks after 2nd Vaccination to Baseline	13 (9.87-17)	20 (15-26)	17 (14-20)
	1 month after 2nd Vaccination	7.61 (5.46-11)	12 (8.83-17) N=70	9.44 (7.61-12) N=146
	1 month after 2nd Vaccination to Baseline	7.25 (5.27-9.96)	12 (9.01-17) N=70	9.02 (7.33-11) N=146

Table 11.4.1.2-3: Percentage of Subjects with hSBA ≥1:5 (95% CI) by MenB Reference Strain at 2 Weeks and One Month After the Second Vaccination – Immunogenicity Subset PP Population

		Lot 1_Rosia	Lot 2_Siena	Total
Men B hSBA 44-76-SL		**N=76**	**N=71**	**N=147**
	Baseline	2 (3%) (0%-9%)	3 (4%) (1%-12%)	5 (3%) (1%-8%)
	2 weeks after 2nd vaccination	76 (100%) (95%-100%)	70 (100%) (95%-100%) N=70	146 (100%) (98%-100%) N=146
	1 month after 2nd vaccination	76 (100%) (95%-100%)	70 (100%) (95%-100%) N=70	146 (100%) (98%-100%) N=146
Men B hSBA 5/99		**N=76**	**N=71**	**N=147**
	Baseline	5 (7%) (2%-15%)	9 (13%) (6%-23%)	14 (10%) (5%-15%)
	2 weeks after 2nd vaccination	76 (100%) (95%-100%)	71 (100%) (95%-100%)	147 (100%) (98%-100%)
	1 month after 2nd vaccination	76 (100%) (95%-100%)	71 (100%) (95%-100%)	147 (100%) (98%-100%)
Men B hSBA NZ98/254		**N=76**	**N=71**	**N=147**
	Baseline	2 (3%) (0%-9%)	0 (0%) (0%-5%)	2 (1%) (0%-5%)
	2 weeks after 2nd vaccination	64 (84%) (74%-92%)	68 (96%) (88%-99%)	132 (90%) (84%-94%)
	1 month after 2nd vaccination	49 (64%) (53%-75%)	56 (80%) (69%-89%) N=70	105 (72%) (64%-79%) N=146

Assessor's comment: See previous comment regarding the results for the two groups and the total results.

ELISA GMC and the ratio of ELISA post-vaccination to pre-vaccination GMCs (GMR) against vaccine antigen 287-953

In general, for both lots, there was a decline in ELISA GMC levels and GMRs against vaccine antigen 287-953 measured at one month after second vaccination when compared to the levels measured at two weeks after the second vaccination

Table 11.4.1.2-4: Geometric Mean ELISA Concentrations (GMCs, 95% CI) and Geometric Mean Ratios to Baseline (GMRs, 95% CI) against the 287-953 Vaccine Antigen at 2 Weeks and One Month after the Second Vaccination - Immunogenicity Subset - Per Protocol Population

	Lot 1_Rosia N=76	Lot 2_Siena N=71	Total N=147
Baseline	26 (22-31)	23 (19-27)	24 (21-27)
2 weeks after 2nd vaccination	3782 (3011-4750) N=74	4824 (3839-6061)	4479 (3878-5174) N=145
2 weeks after 2nd vaccination to Baseline	166 (130-213) N=74	217 (169-279)	200 (171-234) N=145
1 month after 2nd vaccination	2463 (1964-3089)	3106 (2467-3910)	2641 (2281-3058)
1 month after 2nd vaccination to Baseline	93 (71-123)	137 (103-182)	110 (92-132)

Assessor´s comment: the primary objective was met and similarity between lots 1 and 2 was demonstrated. Levels of GMTs and GMCs were comparable to those of other studies. A decrease in GMTs and GMCs was demonstrated between the time points two weeks after second vaccination and one month after second vaccination. This was not unexpected. No European centers were included in the study, the lack of data from European adolescents was discussed during initial assessment, and it was concluded that the applicant should provide data on adolescent in the EU.
The data presented from this study gives no reason for concern regarding immunogenicity of vaccination with rMenB+OMV NZ.

- Safety results

An overview of subjects with adverse events is provided in table 2-9 and numbers of subjects with local and systemic reactions, by vaccination, are summarized in tables 2-10 and 2-11, respectively. One subject from Lot2_Siena (51/013) withdrew from the study on day 34 due to an adverse event of infectious mononucleosis that started on day 14, with moderate severity and was judged as unrelated to the study vaccine by the investigator

Table 2-9: Overview of Subjects with Adverse Events

	Number (%) of Subjects with Adverse Events		
	Lot 1_Rosia N=169	Lot 2_Siena N=173	Total N=342
Any AEs	68 (40%)	65 (38%)	133 (39%)
At least possibly related AEs	34 (20%)	38 (22%)	72 (21%)
SAE	0	0	0
Deaths	0	0	0
Withdrawal from study due to AE	0	1 (1%)	1 (<1%)
Dose reduction, interruption or delay due to an AE	2 (1%)	3 (2%)	5 (1%)

Table 2-10: Numbers (%) of Subjects with Any (and Severe/≥100 mm) Local Reactions, by Vaccination

		Number (%) of Subjects With Injection Site Reactions					
		Inj.: 1		Inj.: 2		Inj.: Any	
		Lot1_Rosia	Lot2_Siena	Lot1_Rosia	Lot2_Siena	Lot1_Rosia	Lot2_Siena
		N=169	N=173	N=168	N=170	N=169	N=173
Induration	Any	41/168 (24%)	51 (29%)	47 (28%)	46/169 (27%)	65 (38%)	74 (43%)
	≥100 mm	0	0	0	0	0	0
Pain	Any	159 (94%)	167 (97%)	149 (89%)	158 (93%)	162 (96%)	170 (98%)
	Severe	18 (11%)	19 (11%)	10 (6%)	19 (11%)	24 (14%)	30 (17%)
Erythema	Any	80/168 (48%)	75 (43%)	87/166 (52%)	88/169 (52%)	110 (65%)	111 (64%)
	≥100 mm	1/168 (1%)	0	0	1/169 (1%)	1 (1%)	1 (1%)
Swelling	Any	50/168 (30%)	43 (25%)	59/167 (35%)	57/168 (34%)	80 (47%)	74 (43%)
	≥100 mm	0	0	1/167 (1%)	0	1 (1%)	0

Source: Table 14.3.1.1.2.2; Note: The number (N) in the header is the total number of subjects at risk for local reactions.

Table 2-11: Numbers (%) of Subjects with Any (and Severe) Systemic Reactions, by Vaccination

		Number (%) of Subjects With Systemic Reactions					
		Inj.: 1		Inj.: 2		Inj.: Any	
		Lot1_Rosia	Lot2_Siena	Lot1_Rosia	Lot2_Siena	Lot1_Rosia	Lot2_Siena
		N=169	N=173	N=168	N=170	N=169	N=173
Systemic							
Arthralgia	Any	20 (12%)	29 (17%)	15 (9%)	28 (16%)	28 (17%)	44 (25%)
	Severe	0	0	0	3 (2%)	0	3 (2%)
Fatigue	Any	60 (36%)	61 (35%)	48 (29%)	61 (36%)	75 (44%)	85 (49%)
	Severe	4 (2%)	3 (2%)	1 (1%)	7 (4%)	5 (3%)	10 (6%)
Headache	Any	54 (32%)	63 (36%)	47 (28%)	66 (39%)	75 (44%)	89 (51%)
	Severe	2 (1%)	4 (2%)	4 (2%)	3 (2%)	6 (4%)	6 (3%)
Myalgia	Any	90 (53%)	102 (59%)	62 (37%)	70 (41%)	99 (59%)	118 (68%)
	Severe	9 (5%)	6 (3%)	2 (1%)	9 (5%)	11 (7%)	13 (8%)
Nausea	Any	31 (18%)	33 (19%)	30 (18%)	36 (21%)	49 (29%)	56 (32%)
	Severe	2 (1%)	3 (2%)	1 (1%)	4 (2%)	3 (2%)	7 (4%)
Rash	Any	7 (4%)	7 (4%)	6 (4%)	11 (6%)	11 (7%)	16 (9%)
	Severe	1 (1%)	0	1 (1%)	2 (1%)	1 (1%)	2 (1%)
Fever (≥ 38°C)	Yes	5 (3%)	4 (2%)	4 (2%)	1 (1%)	8 (5%)	5 (3%)
Other							
Temp	< 38°C	164 (97%)	169 (98%)	164 (98%)	169 (99%)	161 (95%)	168 (97%)
	≥ 40°C	0	0	0	0	0	0
Use Analgesic	Yes	71 (42%)	75 (43%)	47 (28%)	59 (35%)	82 (49%)	92 (53%)
Stay Home	Yes	13/165 (8%)	16/170 (9%)	18/167 (11%)	12 (7%)	23/168 (14%)	23/172 (13%)

Source: Table 14.3.1.1.2.2.
Note: The number (N) in the header is the total number of subjects at risk for systemic or other reactions.

Overall, percentages of subjects who reported with solicited systemic reaction appeared to be slightly higher in Lot2_Siena when compared to Lot1_Rosia. The most frequently reported solicited systemic reaction after any vaccination was myalgia, reported in 59% of subjects in Lot1_Rosia and 68% of subjects in Lot2_Siena. The majority of the solicited local reactions reported were of mild to moderate intensity. Severe intensity of pain was reported in 14% of subjects in Lot1_Rosia and 17% of subjects from Lot2_Siena. Fever (≥ 38°C) was an uncommon symptom, reported in 5% of subjects in Lot 1_Rosia and 3% of subjects in Lot 2_Siena.

Table 2-12: Numbers (%) of Subjects with All and Possibly/Probably Related Adverse Events - Safety Set, Sorted by Overall Frequency

Preferred Term	Number (%) of Subjects with Adverse Events					
	All			At Least Possibly Related		
	Lot 1_Rosia	Lot 2_Siena	Total	Lot 1_Rosia	Lot 2_Siena	Total
	N=169	N=173	N=342	N=169	N=173	N=342
Injection Site Pain	10 (6%)	12 (7%)	22 (6%)	10 (6%)	12 (7%)	22 (6%)
Upper Respiratory Tract Infection	8 (5%)	4 (2%)	12 (4%)	4 (2%)	2 (1%)	6 (2%)
Injection Site Induration	3 (2%)	7 (4%)	10 (3%)	3 (2%)	7 (4%)	10 (3%)
Nasopharyngitis	3 (2%)	7 (4%)	10 (3%)	0	0	0
Abdominal Pain Upper	6 (4%)	2 (1%)	8 (2%)	3 (2%)	0	3 (1%)
Dizziness	6 (4%)	2 (1%)	8 (2%)	2 (1%)	1 (1%)	3 (1%)
Myalgia	5 (3%)	6 (3%)	11 (3%)	5 (3%)	6 (3%)	11 (3%)
Swelling	0	6 (3%)	6 (2%)	0	5 (3%)	5 (1%)
Arthralgia	0	5 (3%)	5 (1%)	0	4 (2%)	4 (1%)

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Assessor's comment: Although systemic adverse reactions appeared to be more common in Lot2_Siena, the clinical relevance of this is unclear. Apart from this the data from the two groups were similar and the safety results presented in this study are in agreement with previously presented results. No new safety concerns are raised based on this study.

3. Discussion on clinical aspects

The submitted studies were intended to explore aspects of persistence of immunogenicity and safety following different vaccination schedules in children aged up to 60 months of age as well as the similarity in immunogenicity and safety profile between two lots of vaccine with OMV produced at different sites in adolescents aged 11 to 17 years. The results of the studies generally confirm what is already known regarding immunogenicity and safety of Bexsero, although there is an apparent inconsistency in the results as described in the comments above. This should be clarified. Therefore no further regulatory action regarding Bexsero is required based on the presented results.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

This submission is considered fulfilled and no further action is required, if the below question is adequately responded to.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

1. Study V72_41: There are apparent inconsistencies in tables 2-5 and 11.4.1.2-3. : It is unclear how the GMT for the total population can be higher than the GMTs for each group for strain 44/76-SL at one month after the 2nd vaccination, and lower for the total population for strain 5/99 than in each for the groups. This should be clarified.

Post-script: The requested clarification was submitted in August 2014; the submission is considered fulfilled (see also comment at page 31 of this report).