23 July 2015
EMA/549048/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Bexsero

International non-proprietary name: meningococcal group b vaccine (rdna, component, adsorbed)

Procedure No. EMEA/H/C/002333/P46 015

Note

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

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1. Introduction

On April 16, 2015, the MAH submitted a completed paediatric study for Bexsero, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Bexsero and therefore no amendments to the product information have been identified.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study V72_42 "A Phase 3, Randomized, Observer-blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Novartis rMenB+OMV NZ Vaccine in Healthy Subjects Aged 11 to 17 years in Korea" The study is intended to support licensure of rMenB0OMV NZ vaccine in Korea.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

2.3.2. V72_42 "A Phase 3, Randomized, Observer-blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Novartis rMenB+OMV NZ Vaccine in Healthy Subjects Aged 11 to 17 years in Korea". Clinical study

V72_42 "A Phase 3, Randomized, Observer-blind, Multicenter Study to Evaluate the *Im*munogenicity and Safety of Novartis rMenB+OMV NZ Vaccine in Healthy Subjects Aged 11 to 17 years in Korea"

Description

Methods

Objective(s)

Primary

To assess the immunogenicity following 2 doses (day 1 and day 31) of the rMenB+OMV NZ vaccine and control vaccines in healthy adolescents, as measured by the percentage of subjects with serum bactericidal assay (SBA) titer ≥1:4 against indicator strains H44/76, 5/99 and NZ298/254 1 month after the second dose (day 61).

Secondary

a. To assess the immunogenicity following 2 doses (day 1 and day 31) of rMenB+OMV NZ vaccine and control vaccines as measured by SBA geometric mean titers (GMTs) against indicator strains H44/76, 5/99 and NZ98/254 at baseline (day 1, prior to vaccination) and 1 month after the second dose (day 61); and the geometric mean ratio (GMR) of postvaccination to prevaccination (baseline) GMTs against the 3 indicator strains.

b. To assess the immunogenicity following 2 doses (day 1 and day 31) of rMenB+OMV NZ vaccine and control vaccines as measured by the percentage of subjects with a 4- fold rise in SBA titers against indicator strains H44/76, 5/99 and NZ98/254 from baseline.

c. To evaluate the immune response following 2 doses (day 1 and day 31) of rMenB+OMV NZ vaccine and control vaccines as measured by enzyme- linked immunosorbent assay (ELISA) geometric mean concentration (GMC); and the GMR of ELISA postvaccination to prevaccination (baseline) GMCs against vaccine antigen 287-953.

Safety Objectives

To assess the safety profile following the administration of rMenB+OMV NZ vaccine and control vaccines in terms of percentages and numbers of subjects with:

a. Local and systemic adverse events (AEs) reported from day 1 (day of vaccination) through day 7 postvaccination.

b. All other AEs reported from day 1 through day 7 postvaccination.

c. Serious AEs (SAEs), medically attended AEs and AEs leading to premature withdrawal throughout the entire study.

Study design

This was a phase 3, observer-blind, multicenter, randomized, controlled study in healthy subjects 11 to 17 years of age in Korea. Two hundred and sixty four healthy subjects 11 to 17 years of age were randomized in a 2:1 ratio to receive 2 doses of rMenB+OMV NZ (rMenB group; Group I in the protocol) OR 1 dose of saline placebo at day 1 followed by 1 dose of MenACWY-CRM at day 31 (Placebo/MenACWY-CRM group; Group II in the protocol) 1.

Study population

Main inclusion criteria:

1. 11-17 years of age inclusive who have given their written assent and whose parent or legal guardian has given written informed consent at the time of enrollment.
2. In good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator;
3. With a negative urine pregnancy test (for female subjects only).

Main exclusion criteria:

1. History of any meningococcal vaccine administration;
2. Current or previous, confirmed or suspected disease caused by N meningitidis;

Treatments

Patients were randomized in a 2:1 ratio to receive 2 doses of rMenB+OMV NZ (rMenB group; Group I in the protocol) OR 1 dose of saline placebo at day 1 followed by 1 dose of MenACWY-CRM at day 31 (Placebo/MenACWY-CRM group; Group II in the protocol).

All study vaccines were administered intramuscularly (IM) only.

Outcomes/endpoints

Immunogenicity Endpoints

The measures of immunogenicity include the following:

- The percentage of subjects with SBA titer ≥1:4 at baseline (day 1) and 1 month after the second vaccination (day 61) for each of the 3 indicator strains (H44/76, 5/99, and NZ98/254).

- SBA GMTs at baseline (day 1) and 1 month after the second vaccination (day 61) and GMRs of postvaccination to prevaccination (baseline) GMTs for each of the 3 indicator strains (H44/76, 5/99, and NZ98/254).

- The percentage of subjects with a 4-fold rise in SBA titers from baseline (day 1) to 1 month after the second vaccination (day 61) for each of the 3 indicator strains (H44/76, 5/99, and NZ98/254).

- ELISA GMCs at baseline (day 1) and at 1 month after the second vaccination (day 61) and GMRs for postvaccination to prevaccination (baseline) GMCs for vaccine antigen 287-953.

Safety Endpoints

Local (ie, injection site pain, erythema, induration and swelling) and systemic (ie, loss of appetite, fever [axillary temperature ≥38.0°C], nausea, fatigue, myalgia, arthralgia, headache) AEs were assessed for 7 days (including the day of vaccination) after each vaccination. All AEs occurring during the 7 days (including the day of vaccination) after each vaccination were collected on a diary card.

Serious AEs, medically attended AEs and AEs that resulted in a subject's withdrawal from the study were collected throughout the study period.

Statistical Methods

Both FAS and PPS were used for assessing the primary objective (so they refer to FAS-1 and PPS-1). Analysis of secondary immunogenicity objectives were to be presented in the FAS population (refer to FAS-2), but because FAS and PPS differed by more than 10%, secondary immunogenicity analysis were also to be repeated in the PPS (PPS-2).

For each meningococcal B strain for which SBA titer was measured, the percentage of subjects with a titer ≥1:4 was presented as point estimates along with the associated 95% Clopper-Pearson confidence intervals (CIs) at all the stipulated time-points, for both rMenB+OMV NZ and MenACWY-CRM groups.

The percentage of subjects with at least a 4-fold rise in SBA titer over the prevaccination titer and the associated 95% CIs were calculated for each of the 3 indicator strains and for each vaccine group.

For each indicator strain (H44/76, 5/99, NZ98/254) and vaccine antigen 287-953, the GMT (for SBA titers against the 3 indicator strains) or GMC (for ELISA assay of vaccine antigen 287-953), and the postvaccination to prevaccination (baseline) GMRs and their associated 95% CIs, median, minimal and maximal values were determined using descriptive analyses and presented together with N (number of subjects).

Recruitment / Number analysed

In total 264 subjects (176 subjects in the rMenB+OMV NZ group and 88 subjects in the Placebo/MenACWY-CRM group) were enrolled in this study. Of these, 262 subjects (174 subjects from the rMenB+OMV NZ group and 88 subjects from the Placebo/MenACWYCRM group) completed the study

Table 10.1-1 Summary of Study Terminations - Enrolled Dataset

Groups	rMenB	Placebo/MenACWY-
Enrolled	176	88
Exposed	175 (99%)	88 (100%)
Completed study	174 (99%)	88 (100%)
Premature Withdrawals:	2 (1%)	0
Adverse event	1 (<1%)	0
Withdrew consent	1 (<1%)	0

Source: Table 14.1.1.2.

Abbreviations: rMenB – rMenB+OMV NZ, MenACWY-CRM – Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.

Two subjects from the rMenB+OMV NZ group were prematurely withdrawn from the study. The reasons for early termination were:

- One subject (Subject ID: 03029) withdrew consent on study day 1, before being vaccinated.
- Another subject (Subject ID: 04002) withdrew consent on study day 32 due to an AE 'histiocytic necrotizing lymphadenitis' (Kikuchi disease). Study vaccine was withdrawn and prescription drug therapy was started to treat the AE. Finally the subject recovered from the AE. In the opinion of the investigator the AE was not related to the study vaccine.

Table 11.1-1 Overview of Datasets Analyzed for Immunogenicity – As Randomized		
Group	**rMenB**	**Placebo/MenACWY-CRM**
Enrolled	176	88
Full Analysis Set Primary Objective (FAS 1):	174 (99%)	88 (100%)
H44/76[11] (SBA)	174 (99%)	88 (100%)
5/99 (SBA)	174 (99%)	88 (100%)
NZ98/254 (SBA)	174 (99%)	88 (100%)
Full Analysis Set Secondary Objective (FAS 2):	174 (99%)	88 (100%)
H44/76 (SBA)	174 (99%)	88 (100%)
5/99 (SBA)	174 (99%)	88 (100%)
NZ98/254 (SBA)	174 (99%)	88 (100%)
Antigen 287-953 (ELISA)	172 (98%)	88 (100%)
Per Protocol Set Primary Objective (PPS 1):	158 (90%)	77 (88%)
H44/76 (SBA)	158 (90%)	77 (88%)
5/99 (SBA)	158 (90%)	77 (88%)
NZ98/254 (SBA)	158 (90%)	77 (88%)
Per Protocol Set Secondary Objective (PPS 2):	158 (90%)	77 (88%)
H44/76 (SBA)	158 (90%)	77 (88%)
5/99 (SBA)	158 (90%)	77 (88%)
NZ98/254 (SBA)	158 (90%)	77 (88%)
Antigen 287-953 (ELISA)	156[a] (89%)	77 (88%)

Abbreviations: rMenB – rMenB+OMV NZ, MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM 197 conjugate vaccine, SBA - serum bactericidal assay, ELISA – enzymelinked immunosorbent assay, FAS – full analysis set; PPS – per protocol set.
[a] serological results (ELISA test) were not available for 2 subjects
Source: case study report v72_42, table 11.1-1.

Baseline data

Overall the demographic and other baseline characteristics for the enrolled population in the rMenB+OMV NZ group and Placebo/MenACWY-CRM group were well matched. Within each vaccine group the percentage of males were higher when compared to females (rMenB+OMV NZ group: 56% vs. 44% respectively; Placebo/MenACWY-CRM group: 59% vs. 41% respectively).

Of the total 264 subjects enrolled, 260 subjects (98%) met entry criteria. There were 4 subjects who actually did not satisfy entry criteria, developed withdrawal criteria but were not withdrawn from the study.

Immunogenicity results

Primary Objective

Percentage of subjects achieving SBA titer ≥1:4 at one month after second vaccination (day 61) in FAS-1 dataset:

At baseline (day 1), percentages of subjects with SBA titer ≥1:4 against 3 *N meningitidis* serogroup B indicator strains (H44/76, 5/99, and NZ98/254) were similar in the rMenB+OMV NZ and Placebo/MenACWY-CRM vaccine groups.

At 1 month after second vaccination, the percentages of subjects achieving an SBA titer ≥ 1:4 after 2 doses of rMenB+OMV NZ vaccine against 3 *N meningitidis* serogroup B indicator strains were much higher compared to the Placebo/MenACWY-CRM group (Table 11.4.1-1).

Table 11.4.1-1 Number (%) (95%CI) of Subjects with SBA Titer ≥ 1:4 at Baseline and 1 Month After Second Vaccination, by Strain – FAS 1[a]

Vaccine Group	rMenB	Placebo/MenACWY-CRM
H44/76	**N=174**	**N=88**
Day 1[b]	45 (26%) (20%-33%)	21 (24%) (15%-34%)
Day 61	170 (98%) (94%-99%)	24 (27%) (18%-38%)
5/99	**N=174**	**N=88**
Day 1[b]	21 (12%) (8%-18%)	9 (10%) (5%-19%)
Day 61	169 (97%) (93%-99%)	14 (16%) (9%-25%)
NZ98/254	**N=174**	**N=88**
Day 1[b]	27 (16%) (10%-22%)	13 (15%) (8%-24%)
Day 61	168 (97%) (93%-99%)	15 (17%) (10%-27%)

Abbreviations: CI – Confidence interval; FAS – full analysis set; N – number of subjects; rMenB – rMenB+OMV NZ; MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM 197 conjugate vaccine; SBA – serum bactericidal assay.
[a] FAS 1 includes all subjects who received at least one vaccination in the study and had immunogenicity data at day 61.
[b] Prevaccination.
Source: case study report v72_42, table 11.4.1-1.

Primary immunogenicity analyses were repeated in the per protocol set (PPS-1) and the immunogenicity results were comparable to those observed in FAS-1 (source: case study report V72_42, table 11.4.1-2).

CHMP comment: Robust functional antibody responses against bacterial strains specific for three of the antigenic components of the vaccine are demonstrated in the studied population of subjects aged 11-17 years in Korea. The SBA responses are in agreement with previously reported results.

Secondary Objectives

Percentage of subjects with 4-fold rise in SBA titers at one month after second vaccination (day 61) in FAS-2 dataset:

At 1 month after second vaccination (day 61), a higher percentage of subjects achieved a 4- fold rise in SBA titers, in the rMenB+OMV NZ group, against 3 *N meningitidis* serogroup B indicator strains, compared to the Placebo/MenACWY-CRM group (Table 11.4.1-3).

Table 11.4.1-3 Numbers (%) (95%CI) of Subjects with 4-Fold Rise in SBA Titers at 1 Month After Second Vaccination, by Strain – FAS 2[a]

Vaccine Group	rMenB	Placebo/MenACWY-CRM
	N=174	N=88
H44/76	161 (93%) (88%-96%)	7 (8%) (3%-16%)
5/99	168 (97%) (93%-99%)	5 (6%) (2%-13%)
NZ98/254	144 (83%) (76%-88%)	5 (6%) (2%-13%)

Abbreviations: CI – Confidence interval; FAS – full analysis Set; N – number of subjects; rMenB – rMenB+OMV NZ; MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM 197 conjugate vaccine; SBA – serum bactericidal assay.
[a] FAS 2 includes all subjects who received at least one vaccination in the study and had immunogenicity data at both day 1 (prevaccination) and day 61 (postvaccination).
Source: case study report v72_42, table 11.4.1-3.

CHMP comment: The difference in SBA response frequency 1 month after second vaccination between the groups is significant.

GMT and GMRs at one month after second vaccination (day 61)in FAS- 2 dataset:

At baseline (day 1), SBA GMTs against the 3 *N meningitidis* serogroup B indicator strains (H44/76, 5/99, and NZ98/254) were similar in the rMenB+OMV NZ and placebo/MenACWY-CRM vaccine groups.

At one month after second vaccination (day 61), SBA GMTs against 3 *N meningitidis* serogroup B indicator strains in the rMenB+OMV NZ group were higher than in the placebo/MenACWY-CRM group (Table 11.4.1-4).

Geometric mean ratios (GMRs; day61/day 1) against 3 *N meningitidis* serogroup B indicator strains in the rMenB+OMV NZ group were also higher than in the placebo/MenACWY-CRM group (Table 11.4.1-4).

Table 11.4.1-4 SBA GMTs and GMRs and 95% CIs at Baseline and 1 Month After Second Vaccination, by Strain – FAS 2[a]

Vaccine Group	rMenB	Placebo/MenACWY-CRM
	N=174	N=88
H44/76	**174**	**88**
Day 1[b]	2.31 (1.94-2.74)	2.18 (1.72-2.77)
Day 61	91 (74-112)	2.56 (1.91-3.43)
Day 61/Day 1	40 (32-49)	1.18 (0.92-1.51)
5/99	**N=174**	**N=88**
Day 1[b]	1.5 (1.31-1.72)	1.37 (1.16-1.61)
Day 61	351 (284-432)	1.84 (1.34-2.52)
Day 61/Day 1	234 (181-301)	1.34 (1-1.81)
NZ98/254	**N=174**	**N=88**
Day 1[b]	1.71 (1.45-2.02)	1.59 (1.27-1.99)
Day 61	32 (26-40)	1.77 (1.35-2.32)
Day 61/Day 1	19 (15-23)	1.11 (0.92-1.35)

Abbreviations: CI – confidence interval; FAS – full analysis set; GMR – geometric mean ratio; GMT – geometric mean titer; N – number of subjects; rMenB – rMenB+OMV NZ; MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM 197 conjugate vaccine; SBA – serum bactericidal assay.
[a] FAS 2 includes all subjects who received at least one vaccination in the study and had immunogenicity data at both day 1 and day 61.
[b] Prevaccination.
GMTs and GMRs are unadjusted.
Source: case study report v72_42, table 11.4.1-4.

CHMP comment: The GMTs after two doses of study vaccine are clearly higher than for the placebo/MenACWY-CRM treatment. The GMTs prevaccination are rather similar between treatment groups though, consequently resulting in higher GMRs in the rMenB group for all strains. The results are in agreement with previous reports.

ELISA GMCs and GMRs against antigen 287-953 at one month after second vaccination (day 61) in FAS-2 dataset:

At baseline (day 1), ELISA GMCs against antigen 287-953 were similar in the rMenB+OMV NZ and Placebo/MenACWY-CRM vaccine groups.

At 1 month after second vaccination (day 61), ELISA GMCs for rMenB+OMV NZ group was higher than for the placebo/MenACWY-CRM group (Table 11.4.1-5).

Geometric mean ratio (GMR; day 61/day 1) in the rMenB+OMV NZ vaccine group against antigen 287-953 was also higher than in the Placebo/MenACWY-CRM group (Table 11.4.1-5).

Table 11.4.1-5 ELISA GMCs and GMRs and 95% CIs at Baseline and 1 Month After Second Vaccination, Antigen 287-953 – FAS 2[a]

Vaccine Group	rMenB	Placebo/MenACWY-CRM
	N=172	N=88
Day 1[b]	23 (22-24)	26 (23-29)
Day 61	1208 (1025-1423)	27 (23-32)
Day 61/Day 1	52 (44-62)	1.05 (0.9-1.22)

Abbreviations: CI – Confidence interval; ELISA – enzyme-linked immunosorbent assay; FAS – full analysis set; GMC – geometric mean concentration; GMR – geometric mean ratio; N – number of subjects; rMenB – rMenB+OMV NZ; MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM 197 conjugate vaccine.
[a] FAS 2 includes all subjects who received at least one vaccination in the study and had immunogenicity data at both day 1 and day 61.
[b] Prevaccination.
GMCs and GMRs are unadjusted.
Source: case study report v72_42, table 11.4.1-5.

CHMP comment: The GMCs and GMRs in the rMenB group are higher than in the control group, supporting the previous results that the present vaccine has a good effect on immunogenicity. The data presented in the present study do not raise any concerns regarding the immunogenicity of vaccination with rMenB+OMV NZ.

Safety results

A summary of local and systemic solicited (ie., AEs collected using a predefined checklist in a diary card) and unsolicited AEs during the 7-day period after each vaccination and any vaccination is provided below in several tables. .

Table 12.2.1-1 Numbers (%) of Subjects With Solicited Local and Systemic AEs and Other Solicited Data for 7 Days After Any and Each Vaccination – Solicited Safety Set

Vaccine Group	rMenB	Placebo/MenACWY-CRM
Any Vaccination	**N=174**	**N=88**
Any[a]	166 (95%)	55 (63%)
Local	166 (95%)	44 (50%)
Systemic[b]	114 (66%)	37 (42%)
Day 1 (Vaccination 1)	**N=174**	**N=87**
Any[a]	161 (93%)	37 (43%)
Local	160 (92%)	22 (25%)
Systemic[b]	89 (51%)	31 (36%)
Day 31 (Vaccination 2)	**N=173**	**N=88**
Any[a]	149 (86%)	42 (48%)
Local	145 (84%)	36 (41%)
Systemic[b]	74 (43%)	21 (24%)

Abbreviations: AE – Adverse event; rMenB – rMenB+OMV NZ, MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.

[a] Any AE refers to a subject reporting either local or systemic AEs.
[b] Includes subjects with body temperature ≥ 38°C irrespective of route of measurement.
Source: case study report v72_42, table 12.2.1-1.

Table 12.2.3-1 Numbers (%) of Subjects with Solicited AEs and Other Solicited Data From Day 1 to Day 7 after Any and Each Vaccination – Solicited Safety Set

Vaccine Group			rMenB			Placebo/MenACWY-CRM		
Vaccination			Any	Day 1	Day 31	Any	Day 1	Day 31
			N=174	N=174	N=173	N=88	N=87	N=88
Local AEs	Pain	Any	165 (95%)	158 (91%)	142 (82%)	39 (44%)	18 (21%)	33 (38%)
		Severe	6 (3%)	4 (2%)	2 (1%)	0	0	0
	Erythema (mm)	Any[a]	74 (43%)	62 (36%)	49 (28%)	22 (25%)	5 (6%)	17 (19%)
		Severe (>100)	0	0	0	0	0	0
	Swelling (mm)	Any[a]	77 (44%)	57 (33%)	47 (27%)	16 (18%)	0	16 (18%)
		Severe (>100)	0	0	0	0	0	0
	Induration (mm)	Any[a]	73 (42%)	55 (32%)	54 (31%) N=172	19 (22%)	3 (3%)	17 (19%)
		Severe (>100)	0	0	0	0	0	0
Systemic AEs	Myalgia	Any	57 (33%)	45 (26%)	29 (17%)	14 (16%)	10 (11%)	9 (10%)
		Severe	3 (2%)	3 (2%)	0	0	0	0
	Arthralgia	Any	26 (15%)	14 (8%)	15 (9%)	10 (11%)	4 (5%)	7 (8%)
		Severe	0	0	0	0	0	0
	Nausea	Any	29 (17%)	20 (11%)	15 (9%)	10 (11%)	7 (8%)	5 (6%)
		Severe	0	0	0	0	0	0
	Headache	Any	75 (43%)	42 (24%)	50 (29%)	27 (31%)	19 (22%)	16 (18%)
		Severe	2 (1%)	0	2 (1%)	0	0	0
	Malaise	Any	76 (44%)	51 (29%)	47 (27%)	17 (19%)	13 (15%)	10 (11%)
		Severe	0	0	0	0	0	0
	Loss of appetite	Any	29 (17%)	15 (9%)	21 (12%)	10 (11%)	8 (9%)	4 (5%)
		Severe	0	0	0	0	0	0

Vaccine Group			rMenB			Placebo/MenACWY-CRM		
Other	Body Temperature. (°C)	≥38.0	15 (9%)	6 (3%)	9 (5%)	2 (2%)	1 (1%)	1 (1%)
		≥40.0	0	0	0	0	0	0
	Analgesic Antipyretic Medication Used	Prophylactic	2 (1%)	1 (1%)	1 (1%)	0	0	0
		Treatment	20 (11%)	11 (6%)	12 (7%)	2 (2%)	1 (1%)	1 (1%)
	Medically Attended Fever[b]		3 (2%)	1 (1%)	2 (1%)	0	0 N=86	0

Abbreviations: AE – Adverse Event; rMenB – rMenB+OMV NZ, MenACWYCRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.
[a] Any refers to erythema or swelling or induration ≥25mm in diameter, including severe solicited local AEs (>100mm).
[b] Fever refers to body temperature ≥38°C.
Note: Day 1 – vaccination 1, Day 31 – Vaccination 2.
Source: case study report v72_42, table 12.2.3-1.

Table 12.2.1-2 Numbers (%) of Subjects Reporting Unsolicited AEs for 7 Days After Any and Each Vaccination – Unsolicited Safety Set

Vaccine Group	rMenB	Placebo/MenACWY-CRM
Any Vaccination	**N=174**	**N=88**
Any AEs	45 (26%)	10 (11%)
At least possibly or probably related AEs	30 (17%)	3 (3%)
Day 1 (Vaccination 1)	**N=174**	**N=87**
Any AEs	28 (16%)	4 (5%)
At least possibly or probably related AEs	20 (11%)	0
Day 31 (Vaccination 2)	**N=173**	**N=88**
Any AEs	24 (14%)	7 (8%)
At least possibly or probably related AEs	15 (9%)	3 (3%)

Abbreviations: AE – Adverse event; rMenB – rMenB+OMV NZ, MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.
Source: case study report v72_42, table 12.2.1-2.

Two subjects from the rMenB+OMV NZ group reported SAEs. Subject ID: 04021 experienced right lower abdominal pain and was diagnosed with parovarian cyst and Subject ID: 05006 experienced abdominal pain and was diagnosed with gastroenteritis. In both subjects, SAEs were assessed as not related to the study vaccine. Both events were considered serious as the subjects were hospitalized (Table 12.2.1-3).

One subject from the rMenB+OMV NZ group (Subject ID: 04002) was withdrawn from the study on study day 32 due to an AE 'histiocytic necrotizing lymphadenitis' (Kikuchi disease). Study vaccine was withdrawn and prescription drug therapy was started to treat the AE. Finally the subject recovered from the AE. In the opinion of the investigator the AE was not related to the study vaccine.

Table 12.2.1-3 Number (%) of Subjects Reporting Selected Unsolicited AEs from Day 1 Though Study Termination– Unsolicited Safety Set

Vaccine Group	rMenB	Placebo/MenACWY-CRM
	N=174	N=88
SAEs	2 (1%)	0
At least possibly or probably related SAEs	0	0
Deaths	0	0
Medically attended AEs	45 (26%)	20 (23%)
AEs resulting in premature withdrawal	1 (1%)	0

Abbreviations: AE – Adverse event; SAE – serious adverse event; rMenB – rMenB+OMV NZ, MenACWY-CRM – meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.
Source: case study report v72_42, table 12.2.1-3.

CHMP comment: The results from the present study is in agreement with previous reports. No new safety concerns are raised based on these results.

2.3.3. Discussion on clinical aspects

The submitted study was intended to assess the immunogenicity and safety following 2 doses of rMenB+OMV NZ and control in healthy adolescents aged 11 to 17 years in Korea. The aim of the study was to support licensure of the vaccine in Korea. The results generally confirm what is already known regarding immunogenicity and safety of Bexsero. Consequently, no further regulatory action considering Bexsero is required, based on the presented results.

3. CHMP overall conclusion and recommendation

Overall conclusion

The commitment is regarded as fulfilled, through the submission of the full clinical study report.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

4. Member State Comments

Comments were received from MS 1 who requested a further review of the AE of Kikuchi disease, as following:

One subject withdrew consent on study day 32 due to the AE 'histiocytic necrotizing lymphadenitis' (Kikuchi disease). According to the CSR, this subject received the 1st dose of Bexsero but not the 2nd dose because of the AE (observed 31 days post-vaccination). In the opinion of the investigator this AE was unrelated to study vaccine. Nevertheless, no rationale has been provided.

Despite the 1 month-interval between vaccine dose and symptoms, the AE might at least be potentially related to vaccination since the etiology of Kikuchi disease (autoimmune? infectious?) is still unknown.

The MAH is asked to provide the subject's narrative and a rationale for exclusion of a potential relationship between Bexsero vaccination and Kikuchi disease.

CHMP comment: The comments from MS 1 have been implemented in the RSI of the ongoing PSUSA assessment (EMEA/H/C/2333; PSUR 4) regarding Bexsero.

Comments were received from MS 2 who endorsed the AR and had no additional comments.