EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/CHMP/181821/2017
Human Medicines Evaluation Division

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

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/022

Note

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

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1. Introduction

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

The MAH stated that the generated data do not influence the benefit-risk balance for Bexsero. A type II variation addressing potential amendments to the Product Information will be submitted in 2017.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study 'A phase IIIb, open label, multi center extension study of V72_28 to assess antibody persistence, and the safety and tolerability of a booster dose after the completion of the vaccination course in study V72_28.' is a stand-alone study to evaluate the safety and tolerability of a booster dose after completion of the vaccination course in study V72_28.

2.2. Information on the pharmaceutical formulation used in the study

Meningococcal meningitis and sepsis are diseases that can result in death within hours, despite the availability of effective antibiotics. The diseases are caused by *Neisseria meningitidis* (*N meningitidis*), a gram-negative, encapsulated bacterium classified into 5 major pathogenic serogroups (A, B, C, Y, and W-135) on the basis of the chemical composition of distinctive capsular polysaccharides. The reported annual incidence of meningococcal disease in the US varies from 0.5 to 10 per 100 000 population. The overall incidence in Canada varies from 0.5 to 2.1 per 100 000 population (PHA Canada, 2005). Each year, there are an estimated 1400-2800 cases of meningococcal disease in the US (Goldschneider et al, 1969), and in the year 2002 more than 5500 cases were reported in Europe (Muros et al, 2004). The case-fatality rate ranges from 5% to 15%, and up to 25% of survivors are left with neurological sequelae, limb loss or hearing loss. The disease is most common in children and young adults. The serogroup B in the year 2002 accounted for 36% of all reported meningococcal disease in the US, 28% in Canada, and from 41% to 90% of reported cases in Europe (Connolly and Noah, 1999; HPA 2006; Muros et al, 2004; Raghunathan et al, 2004).

In the 1960s, meningococcal vaccines consisting of purified polysaccharide antigens were developed against 4 (A, C, Y, and W-135) of the 5 pathogenic serogroups. Currently, there are no commercial vaccines available in North America or Europe for the prevention of disease caused by serogroup B of *N meningitidis*. Actually, the use of capsular polysaccharide as the basis of a vaccine for prevention of meningococcal B diseases has proven problematic. The meningococcal B capsular polysaccharide is identical to a widely distributed human carbohydrate (α[2→8] N-acetyl neuraminic acid or polysialic acid), which, being a self-antigen, is a poor immunogen in humans. An alternative approach to meningococcal B vaccine development has used surface-exposed proteins contained in outer membrane vesicles (OMV). These vaccines have been shown both to elicit serum bactericidal antibody responses and to be efficacious against developing meningococcal disease in clinical trials.

2.3. Clinical aspects

2.3.1. Introduction

The present study, V72_28E1, is a phase 3b extension of study V72_28 which evaluated the safety and immunogenicity of the Novartis Vaccines and Diagnostics meningococcal B recombinant vaccine with

outer membrane vesicles produced from *N meningitides* serogroup B strain NZ98/254 (rMenB+OMV NZ) when administered alone without routine infant vaccines to healthy infants in their first year of life according to different 2 and 3 dose immunization schedules. The V72_28 study was also aimed at investigating the antibody persistence after primary series and administration of a subsequent booster dose of rMenB+OMV NZ at 11 months of age. In the V72_28 study the safety and immunogenicity of 2 catch-up doses of rMenB+OMV NZ when administered to healthy children 2 to 10 years of age were also assessed.

The aim of this extension study was to explore the antibody persistence 24-36 months, after the last dose of rMenB+OMV NZ in children, who previously received a 2 or 3 dose primary series plus a booster dose at 11 months of age of rMenB+OMV NZ, as infants. This study was also to explore the antibody persistence 24-36 months, after 2 catch-up doses of rMenB+OMV NZ administered to children (2-10 years old).

In addition, this study also evaluated the antibody response (safety and immunogenicity) to an additional dose boost in a subset of subjects who received 2 catch-up doses or ii) a 2 or 3 dose primary series plus a booster dose of rMenB+OMV NZ in parent trial V72_28, and iii) the safety and immunogenicity of 2 catch-up doses of rMenB+OMV NZ administered 1 month apart to healthy vaccine-naïve subjects of similar age of follow-on subjects.

The MAH submitted reports for:

- 'A phase IIIb, open label, multi center extension study of V72_28 to assess antibody persistence, and the safety and tolerability of a booster dose after the completion of the vaccination course in study V72_28.'

2.3.2. Clinical study

In what way?Methods

Objective(s)

Primary Immunogenicity Objective
To evaluate the antibody persistence 24 to 36 months after the completion of the vaccination course, in subjects who participated in the V72_28 study in Groups I to IV.

Secondary Immunogenicity Objectives

- To evaluate the immune response at 1 month after a booster dose administered 24 to 36 months after completion of the vaccination course in the parent study (Groups A, C, E, G and I).

- To evaluate the immune response of 2 catch-up doses of meningococcal B recombinant vaccine with outer membrane vesicles produced from *N meningitides* serogroup B strain NZ98/254 (rMenB+OMV NZ) administered 1 month apart to vaccine-naïve children (Group K, L and M).

Safety Objectives:
To assess the safety and tolerability of rMenB+OMV NZ when given as a booster dose administered 24 to 36 months after completion of the vaccination course in the parent study, and to assess the safety and tolerability of rMenB+OMV NZ when given as a 2 dose regimen (0, 1 month schedule) to vaccine-naïve subjects.

Study design and treatments

This trial is an extension of study V72_28. It was conducted as a multicenter study and enrolled subjects who completed the vaccination course of study V72_28 (follow-on subjects enrolled in groups I to IV), and who met all other enrollment criteria for this extension study.

Following are the vaccine groups and vaccination schedule in the parent study V72_28 and in the present study V72_28E1:

- Group I: This group received 3 doses of rMenB+OMV NZ at 2½, 3½ and 5 months of age and a booster at 11 months of age. In this extension study, this group was randomized to 1:2 ratio to nonvaccination and vaccination subsets, respectively. The vaccination subset received a fifth dose boost in this study.

- Group II: This group received 2 doses of rMenB+OMV NZ at 3½ and 5 months of age and a booster dose at 11 months of age. In this extension study, this group was randomized to 1:2 ratio to nonvaccination and vaccination subsets, respectively. The vaccination subset received a fourth dose boost in this study.

- Group III: This group received 2 doses of rMenB+OMV NZ at 6 and 8 months of age and a booster dose at 11 months of age. In this extension study, this group was randomized to 1:2 ratio to nonvaccination and vaccination subsets, respectively. The vaccination subset received a fourth dose boost in this study.

- Group IVa: This group constituted of subjects aged 2-5 years and received 2 doses of rMenB+OMV NZ at a 0, 2 month schedule. In this extension study, this group was randomized to 1:1 ratio to nonvaccination and vaccination subsets. The vaccination subset received third dose boost in this study.

- Group IVb: This group constituted of subjects aged 6-10 years and received 2 doses of rMenB+OMV NZ at a 0, 2 month schedule. In this extension study, this group was randomized to 1:2 ratio to nonvaccination and vaccination subsets. The vaccination subset received a third dose boost in this study. Subjects in nonvaccination subset were evaluated for antibody persistence only. Subjects assigned to vaccination subset with a fifth (Group A) or fourth (Group C and E) or third (Group G and I) dose boost of rMenB+OMV NZ were evaluated for both antibody persistence and antibody response.

- In addition, 3 groups of vaccine-naïve subjects (Groups K, L and M) of similar age to the enrolled subjects in groups A to F (vaccine-naïve Group K: 35-47 months of age), Groups G to H (vaccine-naïve Group L: 4-7 years old) and in Groups I to J (vaccine-naïve Group M: 8-12 years old), not previously enrolled in the parent study V72_28, were recruited at the same study sites and received 2 catch-up doses of rMenB+OMV NZ administered 1 month apart. These subjects served as a baseline descriptive comparison for antibody persistence in the above mentioned groups and had a blood sample drawn for serological analyses at entry. In addition, their response after the first vaccination served as a descriptive comparison for the booster response in subjects from the parent study.

Table 2-1 **Summary of Study Groups and Blood Sampling for Subjects Who Completed the Vaccination Course in Study V72_28 (Groups A to F)**

V72_28		V72_28E1			
Groups (Planned No. of Subjects)	Vaccination Schedule with rMenB+OMV NZ	Groups (Planned No. of Subjects)	Vaccine Group Labels	Study Month	
				0*	1
I (250)	2½ , 3½, 5 + booster at 11 months of age	A (up to 167)	2H3H511_V	Blood draw Vaccination	Blood draw
		B (up to 83)	2H3H511_NV	Blood draw	
II (250)	3½, 5 + booster at 11 months of age	C (up to 167)	3H5_11_V	Blood draw Vaccination	Blood draw
		D (up to 83)	3H5_11_NV	Blood draw	
III (250)	6, 8 + booster at 11 months of age	E (up to 167)	68_11_V	Blood draw Vaccination	Blood draw
		F (up to 83)	68_11_NV	Blood draw	

Source: Table 3.1-1 of protocol v4.0, dated 28 NOV 13.

Abbreviation: rMenB+OMV NZ, meningococcal B recombinant vaccine with outer membrane vesicles produced from *N meningitidis* serogroup B strain NZ98/254.

*24-36 months after the last vaccination in V72_28.

Table 2-2 **Summary of Study Groups and Blood Sampling for Subjects Who Completed the Vaccination Course in Study V72_28 (Groups G to J)**

V72_28		V72_28E1			
Groups (Planned No. of Subjects)	Vaccination Schedule with rMenB+OMV NZ	Groups (Planned No. of Subjects)	Vaccine Group Labels	Study Month	
				0*	1
IVa (100)	0, 2 month schedule Subjects 2-5 years of age	G (up to 50)	02_2_5_V	Blood draw Vaccination	Blood draw
		H (up to 50)	02_2_5_NV	Blood draw	
IVb (300)	0, 2 month schedule Subjects 6-10 years of age	I (up to 200)	02_6_10_V	Blood draw Vaccination	Blood draw
		J (up to 100)	02_6_10_NV	Blood draw	

Source: Table 3.1-2 of protocol v4.0, dated 28 NOV 13.

Abbreviation: rMenB+OMV NZ, meningococcal B recombinant vaccine with outer membrane vesicles produced from *N meningitidis* serogroup B strain NZ98/254.

*24-36 months after the last vaccination in V72_28.

Table 2-3 Summary of Study Groups and Blood Sampling for Newly Enrolled, Vaccine-Naïve subjects (groups K, L and M)

V72_28E1	Groups (Planned No. of Subjects)	Vaccine Group Labels	Study Month		
			0	1	2
Vaccine-Naïve Subjects (35-47 Months of Age)	K (100)	NAIVE_123	Blood draw Vaccination	Blood draw Vaccination	Blood draw
Vaccine-Naïve Subjects (4-7 Years of Age)	L (50)	NAIVE_4A	Blood draw Vaccination	Blood draw Vaccination	Blood draw
Vaccine-Naïve Subjects (8-12 Years of Age)	M (50)	NAIVE_4B	Blood draw Vaccination	Blood draw Vaccination	Blood draw

Source: Table 3.1-3 of protocol v4.0, dated 28 NOV 13.

- Groups A to J: All subjects in Group A to J had a blood drawn at study month 0. Subjects randomized to the vaccination subset (Groups A, C, E, G and I) received a booster dose of rMenB+OMV NZ and an additional sample was drawn at study month 1 (1 month after the booster dose - last study visit; Table 2-1; Table 2-2).

- Groups K, L and M: All subjects in Groups K to M had a blood drawn at study month 0, 1 and 2 and received 2 catch up doses of rMenB+OMV NZ, at study month 0 and 1. These subjects also served as baseline descriptive comparison for antibody persistence in the follow-on subjects. In addition, their response after the first vaccination served as a descriptive comparison for the booster response in subjects from the parent study (Table 2-3).

Study population /Sample size

Table 2-4 Number of Subjects Planned and Analyzed Across All Groups

Groups	Planned	Enrolled
35-47 Months of Age		
2H3H511_(/V)	167	98
2H3H511_(/NV)	83	47
3H5_11_V	167	89
3H5_11_NV	83	43
68_11_V	167	81
68_11_NV	83	39
NAIVE_123	100	100
4-7 Years of Age		
02_2_5_V	50	32
02_2_5_NV	50	36
NAIVE_4A	50	55
8-12 Years of Age		
02_6_10_V	200	91
02_6_10_NV	100	90
NAIVE_4B	50	50

Source: Table 14.1.1.1.0.1; Table 14.1.1.1.0.2.

Outcomes/endpoints

Criteria for Evaluation:

Immunogenicity Endpoints

Primary Endpoint

Evaluation of antibody persistence on study day 1 (visit 1) - Groups A to J:

At visit 1, Percentage of subjects with the serum bactericidal activity using human plasma as the source of exogenous complement (hSBA) titers ≥ 4 and ≥ 5 directed against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.

Percentage of subjects with hSBA titers ≥ 8 against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.

- hSBA geometric mean titers (GMTs) directed against indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- hSBA geometric mean ratios (GMRs) directed against *N meningitidis* serogroup B, at 24-36 months after the completion of the vaccination course in the parent study (visit 1 of V72_28E1) over:

- Groups A to J: 1 month after the completion of the vaccination course in the parent study (post primary vaccination visit1).

- Group G to J: preprimary vaccination (visit 1 of V72_28).

Secondary Endpoints

Evaluation of immune response at 1 month after a booster dose administration – Groups A, C, E, G, I, K, L and M (vaccination subset):

At visit 1 (pre-vaccination) and visit 2 (1 month after the booster administration [unless indicated otherwise]).

- Percentage of subjects with hSBA titers ≥ 4 and ≥ 5 directed against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- Percentage of subjects with hSBA titers ≥ 8 against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- Percentage of subjects with 4-fold rise in titers from visit 1 to visit 2, from post-primary visit to visit 2, and for Groups G and I, from preprimary vaccination to visit 2 directed against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- hSBA GMTs directed against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain at visit 1 and visit 2.
- hSBA GMRs directed against the indicator strains of *N meningitidis* serogroup B H44/76, 5/99, NZ98/254 and M10713 strain at: visit 2 over visit 1, visit 2 over post-primary vaccination visit and for groups G and I, visit 2 over preprimary vaccination visit (baseline of parent V72_28 study).

Evaluation of immune response at 1 month after a 2 catch-up doses schedule - Groups K, L and M, vaccine-naïve subjects:

At visit 1 (pre-vaccination), visit 2 (1 month post first dose) and visit 3 (1 month post second dose [unless indicated otherwise]).

- Percentage of subjects with hSBA titers ≥ 4 and ≥ 5 directed against the indicator strains of N meningitidis serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- Percentage of subjects with hSBA titers ≥ 8 against the indicator strains of N meningitidis serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- Percentage of subjects with 4-fold rise in titers from visit 1 to visit 2 and from visit 1 to visit 3 directed against the indicator strains of N meningitidis serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- hSBA GMTs directed against the indicator strains of N meningitidis serogroup B H44/76, 5/99, NZ98/254 and M10713 strain.
- hSBA GMRs directed against the indicator strains of N meningitidis serogroup B H44/76, 5/99, NZ98/254 and M10713 strain at: visit 2 over visit 1, visit 3 over visit 1 and visit 3 over visit 2.

Safety Endpoints

- Safety was to be assessed in terms of the number/percentage of subjects reporting adverse events (AEs), and number/percentage of reported AEs for all subjects, including:
- Groups A, C, E, G and I (vaccination subset) and groups K, L and M (vaccine-naïve subjects):

- Day 1-7 after the vaccination:
    - Unsolicited AEs
    - Solicited local AEs:
- Groups A, C, E, G, K and L: erythema, induration, injection site tenderness, swelling.
- Groups I and M: injection site pain, swelling, erythema, and induration.
    - Solicited systemic AEs:
- Groups A, C, E, G, K and L: change in eating habits, diarrhea, irritability, rash, sleepiness, persistent crying and vomiting.
- Groups I and M: arthralgia, chills, headache, malaise, myalgia and nausea, rash.
    - Other solicited data: use of medicine to prevent or to treat fever/pain, body temperature, medically attended fever.
- Entire study period:

  Serious unsolicited AEs, medically attended AEs and AEs leading to withdrawal from the study, associated concomitant medications.

Groups B, D, F, H and J - Nonvaccination subset:

- Entire study period: All unsolicited AEs and related concomitant medications.

Statistical Methods

The analyses of immunogenicity and safety were descriptive. As such, no statistical tests were to be performed. For the immunogenicity endpoints, 95% confidence intervals (CIs) were to be calculated.

The immunogenicity analyses were to be based on the full analysis set (FAS) and the safety analyses, on the safety set.

The percentages of subjects with hSBA titers≥ 4, ≥ 5, ≥ 8 and the associated 2-sided Clopper-Pearson 95% CIs were computed, by vaccine group for each of the *N meningitidis* serogroup B strains.

For analyzing GMTs, the antibody titers and antigen concentrations were logarithmically transformed (log10). GMTs and the associated 2-sided 95% CI were computed by exponentiating (base10) the corresponding least square means of the log10-transformed titers and the associated 95% CI obtained from a 2-way ANOVA with factors for vaccine group and study center.

GMRs and the associated 2-sided 95% CI were obtained from a 2-way Analysis of Variance (ANOVA) with factors for vaccine group and study center.

Results

Recruitment/ Number analysed

Efficacy results

Immunogenicity results

A total of 851 subjects were enrolled in this extension study, 255 subjects were evaluated for antibody persistence only and 596 subjects (follow-on + vaccine-naïve subjects) were evaluated for antibody persistence and booster/first dose response. Majority of the subjects enrolled in the vaccination subset (follow-on + vaccine-naïve subjects) were included in the per protocol set (PPS) and FAS.

Demographic and other baseline characteristics were balanced across the vaccine groups as per the age groups. Most of the subjects were of white race and the gender distribution was similar.

Antibody persistence after 24-36 months of vaccination course in follow-on subjects or at baseline in vaccine-naïve subjects:

35-47 months of age:

Across the vaccine follow-on groups, there was a decline in antibody titers against all strains at 24-36 months after the completion of the vaccination course in V72_28 (visit 1 in V72_28E1) from 1 month after last vaccination in V72_28.

Overall, at 24-36 months after the completion of the vaccination course in V72_28 study, hSBA antibody titers across the 3 follow-on groups (2H3H511, 3H5_11 and 68_11) were higher than NAIVE_123 group except against strain M10713 (Table 2-6). At 24-36 months after the completion of the vaccination course in V72_28 study, GMTs across the 3 follow-on groups were higher than the NAIVE_123 group except against strain M10713 (Table 2-8).

Table 2-8 hSBA GMTs (95% CIs) After 24-36 Months of Vaccination Course in V72_28 in Follow-on Subjects or Baseline in Vaccine-Naïve Subjects in V72_28E1 - FAS Persistence (35-47 Months of Age)

	2H3H511	3H5_11	68_11	NAIVE_123[a]
H44/76 (fHbp)	**N = 140**	**N = 131**	**N = 119**	**N = 100**
	4.17 (3.40-5.13)	4.48 (3.60-5.57)	5.62 (4.48-7.04)	2.79 (2.25-3.45)
5/99 (NadA)	**N = 140**	**N = 131**	**N = 119**	**N = 100**
	44 (32-60)	52 (37-72)	83 (58-117)	1.15 (1.03-1.29)
NZ98/254 (PorA P1.4)	**N = 140**	**N = 131**	**N = 119**	**N = 100**
	3.48 (2.78-4.36)	2.98 (2.35-3.78)	4.86 (3.80-6.22)	1.14 (1.06-1.22)
M10713 (NHBA)	**N = 127**	**N = 111**	**N = 109**	**N = 93**
	2.77 (2.06-3.71)	3.03 (2.20-4.16)	3.17 (2.30-4.38)	3.30 (2.52-4.32)

Source: Table 14.2.1.3.1.

Abbreviations: CI, confidence interval; FAS, full analysis set; GMT, geometric mean titer; hSBA, human serum bactericidal assay.

[a]Baseline in V72_28E1 vaccine-naïve subjects: NAIVE_123.

Across the vaccine follow-on groups, at 24-36 months after the completion of the vaccination course in V72_28 study, substantial proportions of subjects retained hSBA antibody titers ≥ 4 against strain 5/99 (84% to 93%). Against strains H44/76 and NZ98/254, the percentages of subjects with hSBA antibody titers ≥ 4 were 51% to 61% and 38% to 56% of subjects, respectively. The percentages of subjects with persisting hSBA antibody titers ≥ 5 against strain M10713 were 31% to 39% (Table 2-6).

In the NAIVE_123 group at baseline, the percentages of subjects with hSBA antibody titers ≥ 4 were 38% against H44/76 and very low against strains 5/99 (3%) and NZ98/254 (2%). The percentages of

subjects with hSBA antibody titers ≥ 5 were comparable to follow-on subjects against strain M10713 (37%; Table 2-6).

The persistence for 2 + 1 schedules (3H5_11 and 68_11) was comparable to the persistence for the 3 + 1 schedule (2H3H5_11; Table 2-6).

Table 2-6 **Number (%) of Subjects (95% CI) With hSBA Titers ≥ 4 or ≥ 5 After 24-36 Months of Vaccination Course in V72_28 in Follow-on Subjects or Baseline in Vaccine-Naïve Subjects in V72_28E1 - FAS Persistence (35-47 Months of Age)**

	2H3H511	3H5_11	68_11	NAIVE_123[a]
	N = 140	N = 131	N = 119	N = 100
H44/76 (fHbp)	72 (51%) (42.8%-60%)	69 (53%) (43.8%-61.5%)	73 (61%) (52%-70.1%)	38 (38%) (28.5%-48.3%)
	N = 140	N = 131	N = 119	N = 100
5/99 (NadA)	118 (84%) (77.2%-89.9%)	115 (88%) (80.9%-92.9%)	111 (93%) (87.2%-97.1%)	3 (3%) (0.6%-8.5%)
	N = 140	N = 131	N = 119	N = 100
NZ98/254 (PorA P1.4)	63 (45%) (36.6%-53.6%)	50 (38%) (29.8%-47.1%)	67 (56%) (46.9%-65.4%)	2 (2%) (0.24%-7%)
	N = 127	N = 111	N = 109	N = 93
M10713 (NHBA)	39 (31%) (22.8%-39.5%)	40 (36%) (27.1%-45.7%)	42 (39%) (29.4%-48.3%)	34 (37%) (26.8%-47.2%)

Source: Table 14.2.1.1.7; Table 14.2.1.1.1.

Abbreviations: CI, confidence interval; FAS, full analysis set; hSBA, human serum bactericidal assay.

[a]Baseline in V72_28E1 vaccine-naïve subjects: NAIVE_123.

Note: Immune response hSBA ≥ 4 was assessed only against strains H44/76, 5/99 and NZ98/254. For hSBA against strain M10713, the cut-off was ≥ 5.

4-7 years of age:

In the 02_2_5 follow-on group, there was a decline in antibody titers against all strains at 24-36 months after the completion of the vaccination course in V72_28 study (visit 1 in V72_28E1) from the baseline in V72_28 and 1 month after last vaccination in V72_28 (Table 2-9)

Overall, at 24-36 months after the completion of the vaccination course in V72_28 study, hSBA antibody titers were higher in the 02_2_5 follow-on group than the NAIVE_4A group against strains H44/76, 5/99 and NZ98/254 and similar against strain M10713 (Table 2-7).

At 24-36 months after the completion of the vaccination course in V72_28 study, GMTs were higher in the 02_2_5 follow-on group than the NAIVE_4A group against strains 5/99 and NZ98/254 and similar against strains H44/76 and M10713.

In the 02_2_5 follow-on group, at 24-36 months after the completion of the vaccination course in V72_28 study, substantial proportions of subjects retained hSBA antibody titers ≥ 4 against strains 5/99 (79%) and H44/76 (52%). Against strain NZ98/254 the percentage of subjects with hSBA titers ≥ 4 was 29%. The percentages of subjects with persisting hSBA antibody titers ≥ 5 against strain M10713 was 34% (Table 2-7).

In the NAIVE_4A group at baseline, the percentages of subjects with hSBA antibody titers ≥ 4 were 27% against strain H44/76 and very low against strains 5/99 (4%) and NZ98/254 (7%). The

percentage of subjects with hSBA antibody titers ≥ 5 was comparable to follow-on subjects against strain M10713 (38%; Table 2-7).

Table 2-7 **Number (%) of Subjects (95% CI) With hSBA Titers ≥ 4 or ≥ 5 After 24-36 Months of Vaccination Course in V72_28 in Follow-on Subjects or Baseline in Vaccine-Naïve Subjects in V72_28E1 - FAS Persistence (4-7 and 8-12 Years of Age)**

	4-7 Years of Age		8-12 Years of Age	
	02_2_5	NAIVE_4A[a]	02_6_10	NAIVE_4B[a]
	N = 67	N = 55	N = 178	N = 50
H44/76 (fHbp)	35 (52%) (39.7%-64.6%)	15 (27%) (16.1%-41%)	103 (58%) (50.3%-65.2%)	10 (20%) (10%-33.7%)
	N = 67	N = 55	N = 179	N = 50
5/99 (NadA)	53 (79%) (67.4%-88.1%)	2 (4%) (0.44%-12.5%)	153 (85%) (79.4%-90.3%)	4 (8%) (2.2%-19.2%)
	N = 68	N = 55	N = 179	N = 50
NZ98/254 (PorA P1.4)	20 (29%) (19%-41.7%)	4 (7%) (2%-17.6%)	89 (50%) (42.2%-57.3%)	3 (6%) (1.3%-16.5%)
	N = 65	N = 53	N = 173	N = 49
M10713 (NHBA)	22 (34%) (22.6%-46.6%)	20 (38%) (24.8%-52.1%)	105 (61%) (53%-68%)	27 (55%) (40.2%-69.3%)

Source: Table 14.2.1.1.7; Table 14.2.1.1.1.

Abbreviations: CI, confidence interval; FAS, full analysis set; hSBA, human serum bactericidal assay.

[a]Baseline in V72_28E1 vaccine-naïve subjects: NAIVE_4A and NAIVE_4B.

Note: Immune response hSBA ≥ 4 was assessed only against strains H44/76, 5/99 and NZ98/254. For hSBA against strain M10713, the cut-off was ≥ 5.

8-12 years of age:

In 02_6_10 follow-on group, there was a decline in antibody titers against all strains at 24-36 months after the completion of the vaccination course in V72_28 study (visit 1 in V72_28E1) from the baseline in V72_28 and 1 month after last vaccination in V72_28 (Table 2-9).

Overall, at 24-36 months after the completion of the vaccination course in V72_28 study, hSBA antibody titers were higher in the 02_6_10 follow-on group than the NAIVE_4B group against strains H44/76, 5/99 and NZ98/254 and similar against strain M10713 (Table 2-7).

At 24-36 months after the completion of the vaccination course in V72_28 study, GMTs were higher in the 02_6_10 follow-on group than the NAIVE_4B group against strains H44/76, 5/99 and NZ98/254 and similar against strain M10713 (Table 2-9).

Table 2-9 **hSBA GMTs (95% CIs) After 24-36 Months of Vaccination Course in V72_28 in Follow-on Subjects or Baseline in Vaccine-Naïve Subjects in V72_28E1 - FAS Persistence (4-7 and 8-12 Years of Age)**

	4-7 Years of Age		8-12 Years of Age	
	02_2_5	NAIVE_4A[a]	02_6_10	NAIVE_4B[a]
H44/76 (fHbp)	N = 67	N = 55	N = 178	N = 50
	3.97 (2.99-5.28)	2.33 (1.77-3.07)	5.75 (4.78-6.91)	1.93 (1.39-2.68)
5/99 (NadA)	N = 67	N = 55	N = 179	N = 50
	21 (14-33)	1.20 (0.96-1.51)	21 (16-28)	1.38 (1.10-1.73)
NZ98/254 (PorA P1.4)	N = 68	N = 55	N = 179	N = 50
	2.81 (2.07-3.82)	1.37 (1.17-1.61)	4.57 (3.74-5.59)	1.22 (1.06-1.41)
M10713 (NHBA)	N = 65	N = 53	N = 173	N = 49
	3.53 (2.38-5.25)	4.26 (2.61-6.97)	7.82 (6.04-10)	6.95 (4.18-12)

Source: Table 14.2.1.3.1.

Abbreviations: CI, confidence interval; FAS, full analysis set; GMT, geometric mean titer; hSBA, human serum bactericidal assay.

[a]Baseline in V72_28E1 vaccine-naïve subjects: NAIVE_4A and NAIVE_4B.

In the 02_6_10 follow-on group, at 24-36 months after the completion of the vaccination course in V72_28 study, substantial proportions of subjects retained hSBA antibody titers ≥ 4 against strain 5/99 (85%). Against strains H44/76 and NZ98/254, 58% and 50% of subjects, respectively had hSBA antibody titers ≥ 4. The percentage of subjects with hSBA antibody titers ≥ 5 against strain M10713 was 61% (Table 2-7).

In the NAIVE_4B group at baseline, the percentages of subjects with hSBA antibody titers ≥ 4 were 20% against strain H44/76 and very low against strains 5/99 (8%) and NZ98/254 (6%). The percentage of subjects with hSBA antibody titers ≥ 5 was 55% against strain M10713 (Table 2-7).

Booster/first dose response in follow-on and vaccine-naïve subjects:

35-47 months of age:

Across vaccine follow-on groups (3-dose schedule: 2H3H511_V, 2-dose schedules: 3H5_11_V and 68_11_V) at 1 month after booster dose, 99% to 100% of subjects achieved hSBA antibody titers ≥ 4 against strains H44/76, 97% to 99% of subjects against 5/99 and 99% to 100% of subjects against strain NZ98/254. Against strain M10713, 70% to 97% of subjects had hSBA antibody titers ≥ 5.

At 1 month after first dose in NAIVE_123 group, the percentage of subjects with hSBA antibody titers ≥ 4 were 95% against strain H44/76; 88% against strain 5/99 and 78% against strain NZ98/254. The percentages of subjects with hSBA antibody titers ≥ 5 against strain M10713 were 47%.(Table 11.4.1-5a).

Table 11.4.1-5a **Number (%) of Subjects (95% CI) With hSBA Titers ≥ 4 or ≥ 5 at 1 Month After Booster Dose (After 24-36 Months of Vaccination Course in V72_28) in Follow-on Subjects or First Dose in Vaccine-Naïve Subjects in V72_28E1 – FAS Booster (35-47 Months of Age)**

	2H3H511_V	3H5_11_V	68_11_V	NAIVE_123
	N = 96	N = 86	N = 75	N = 96
H44/76 (fHbp)	95 (99%) (94.3%-99.97%)	86 (100%) (95.8%-100%)	75 (100%) (95.2%-100%)	91 (95%) (88.3%-98.3%)
	N = 96	N = 87	N = 76	N = 96
5/99 (NadA)	95 (99%) (94.3%-99.97%)	86 (99%) (93.8%-99.97%)	74 (97%) (90.8%-99.68%)	84 (88%) (79.2%-93.4%)
	N = 96	N = 86	N = 75	N = 96
NZ98/254 (PorA P1.4)	95 (99%) (94.3%-99.97%)	86 (100%) (95.8%-100%)	75 (100%) (95.2%-100%)	75 (78%) (68.5%-85.9%)
	N = 88	N = 79	N = 67	N = 88
M10713 (NHBA)	62 (70%) (59.8%-79.7%)	64 (81%) (70.6%-89.0%)	65 (97%) (89.6%-99.64%)	41 (47%) (35.9%-57.5%)

Source: Table 14.2.1.1.2; Table 14.2.1.1.8.

Abbreviations: CI, confidence interval; FAS, full analysis set; hSBA, serum bactericidal activity using human complement.

Note: Immune response hSBA ≥ 4 was assessed only against strains H44/76, 5/99 and NZ98/254. For hSBA against strain M10713, the cut-off was ≥ 5.

Across follow-on groups versus NAIVE_123 group, GMRs visit 2/visit 1 were 41-fold to 46-fold versus 4.81-fold against strain H44/76, 41-fold to 75-fold versus 34-fold against strain 5/99, 27-fold to 29-fold versus 6.07-fold against strain NZ98/254 and 4.07-fold to 11-fold versus 1.38-fold against strain M10713, respectively.

Overall, at 1 month after booster/first dose in V72_28E1, the percentages of subjects with hSBA antibody titers across the 3 follow-on groups were higher than the NAIVE_123 group against strains NZ98/254 and M10713. The hSBA antibody titers against strain H44/76 were similar with the NAIVE_123 group. Against strain 5/99, values in the 68_11_V follow-on group are similar with the NAIVE_123 group (Table 11.4.1-5a).

At 1 month after booster/first dose, GMTs across the 3 follow-on groups were much higher than the NAIVE_123 group.

4-7 years of age:

At 1 month after booster dose in V72_28E1, 97% subjects in the 02_2_5_V follow-on group achieved hSBA antibody titers ≥ 4 against strains H44/76, 100% of subjects against strains 5/99 and NZ98/254. Against strain M10713, 93% of subjects had hSBA antibody titers ≥ 5.

At 1 month after first dose in the NAIVE_4A group, the percentage of subjects with hSBA antibody titers ≥ 4 were 91% against strain H44/76; 93% against strain 5/99 and 85% against strain NZ98/254. The percentages of subjects with hSBA antibody titers ≥ 5 against strain M10713 were 59%.

In the 02_2_5_V follow-on group versus NAIVE_4A group, GMRs (visit 2/visit 1) were 50-fold versus 7.08-fold against strain H44/76, 160-fold versus 22-fold against strain 5/99, 24-fold versus 9.58-fold against strain NZ98/254 and 13-fold versus 2.06-fold against strain M10713, respectively.

Overall, at 1 month after booster/first dose in V72_28E1, the percentages of subjects with hSBA antibody titers in the 02_2_5_V follow-on group were similar to the NAIVE_4A group against strains H44/76, 5/99 and NZ98/254 and higher against strain M10713.

At 1 month after booster/first dose, GMTs in the 02_2_5_V follow-on group were much higher than the NAIVE_4A group against all strains 44/76, 5/99, NZ98/254 and M10713.

8-12 years of age:

At 1 month after booster dose, 99% of subjects in the 02_6_10_V follow-on group achieved hSBA antibody titers ≥ 4 against strain H44/76, 100% of subjects against strains 5/99 and NZ98/254. Against strain M10713, 96% of subjects had hSBA antibody titers ≥ 5.

At 1 month after first dose in the NAIVE_4B group, the percentage of subjects with hSBA antibody titers ≥ 4 were 80% against strain H44/76; 80% against strain 5/99 and 70% against strain NZ98/254. The percentages of subjects with hSBA antibody titers ≥ 5 against strain M10713 were 60%, respectively.

In the 02_6_10_V follow-on group versus NAIVE_4B group, GMRs (visit 2/visit 1) were 42-fold versus 6.87-fold against strain H44/76, 135-fold versus 14-fold against strain 5/99, 18-fold versus 7.01-fold against strain NZ98/254 and 6.85-fold versus 1.55-fold against strain M10713, respectively.

Overall, at 1 month after booster/first dose in V72_28E1, the percentages of subjects with hSBA antibody titers in the 02_6_10_V follow-on group were higher than the NAIVE_4B group against all strains H44/76, 5/99, NZ98/254 and M10713.

At 1 month after booster/first dose, GMTs in the 02_6_10_V follow-on group were much higher than the NAIVE_4B group against all strains 44/76, 5/99, NZ98/254 and M10713.

2-dose catch-up series response in vaccine-naïve subjects:

At baseline, the percentage of subjects with hSBA antibody titers ≥ 4 or ≥ 5 across the vaccine-naïve groups (NAIVE_123, NAIVE_4A and NAIVE_4B) were lower against 5/99 and NZ98/254 strains and higher against H44/76 and M10713. At 1 month after first dose in V72_28E1, there was substantial increase in percentages of subjects achieving hSBA antibody titers against strains H44/76 (80% to 93%), 5/99 (71% to 85%) and NZ98/254 (82% to 95%), but not against strain M10713 (46% to 59%; Table 11.4.1-9).

At 1 month after second dose in V72_28E1, 98% to 100% of subjects achieved hSBA antibody titers ≥ 4 against strain H44/76 and all (100%) of subjects against strains 5/99 and NZ98/254 and 69% to 76% of subjects had achieved hSBA antibody titers ≥ 5 against strain M10713 across the vaccine-naïve groups (Table 11.4.1-9).

Table 11.4.1-9 Number (%) of Subjects (95% CI) With hSBA Titers ≥ 4 or ≥ 5 Following a 2-Dose Catch-up Series in Vaccine-Naïve Subjects – FAS Catch-up

	35-47 Months of Age	4-7 Years of Age	8-12 Years of Age
	NAIVE_123	NAIVE_4A	NAIVE_4B
H44/76 (fHbp)	**N = 98**	**N = 54**	**N = 49**
Baseline (Visit 1 in V72_28E1)	37 (38%) (28.2%-48.1%)	14 (26%) (15%-39.7%)	10 (20%) (10.2%-34.3%)
1 Month After First Dose (Visit 2 in V72_28E1)	90 (95%) (88.1%-98.3%) N = 95	49 (91%) (79.7%-96.9%)	40 (82%) (68%-91.2%)
1 Month After Second Dose (Visit 3 in V72_28E1)	98 (100%) (96.3%-100%)	53 (98%) (90.1%-99.95%)	49 (100%) (92.7%-100%)
5/99 (NadA)	**N = 98**	**N = 54**	**N = 49**
Baseline (Visit 1 in V72_28E1)	3 (3%) (0.6%-8.7%)	2 (4%) (0.45%-12.7%)	3 (6%) (1.3%-16.9%)
1 Month After First Dose (Visit 2 in V72_28E1)	83 (87%) (79%-93.3%) N = 95	50 (93%) (82.1%-97.9%)	39 (80%) (65.7%-89.8%)
1 Month After Second Dose (Visit 3 in V72_28E1)	98 (100%) (96.3%-100%)	54 (100%) (93.4%-100%)	49 (100%) (92.7%-100%)
NZ98/254 (PorA P1.4)	**N = 98**	**N = 54**	**N = 48**
Baseline (Visit 1 in V72_28E1)	2 (2%) (0.25%-7.2%)	4 (7%) (2.1%-17.9%)	3 (6%) (1.3%-17.2%)
1 Month After First Dose (Visit 2 in V72_28E1)	74 (78%) (68.2%-85.8%) N = 95	45 (85%) (72.4%-93.3%) N = 53	34 (71%) (55.9%-83%)
1 Month After Second Dose (Visit 3 in V72_28E1)	98 (100%) (96.3%-100%)	54 (100%) (93.4%-100%)	48 (100%) (92.6%-100%)
M10713 (NHBA)	**N = 91**	**N = 52**	**N = 49**
Baseline (Visit 1 in V72_28E1)	30 (34%) (24.6%-45.4%) N = 87	20 (40%) (26.4%-54.8%) N = 50	27 (55%) (40.2%-69.3%)
1 Month After First Dose (Visit 2 in V72_28E1)	37 (46%) (34.6%-57.1%) N = 81	28 (57%) (42.2%-71.2%) N = 49	27 (59%) (43.2%-73%) N = 46
1 Month After Second Dose (Visit 3 in V72_28E1)	68 (75%) (64.5%-83.3%)	36 (69%) (54.9%-81.3%)	37 (76%) (61.1%-86.7%)

Source: Table 14.2.1.1.3; Table 14.2.1.1.9.
Abbreviations: CI, confidence interval; FAS, full analysis set; hSBA, serum bactericidal activity using human complement.

Overall, hSBA antibody titers across the 3 vaccine-naïve groups (NAIVE_123, NAIVE_4A and NAIVE_4B) were similar against each given strain (Table 11.4.1-9). At baseline (visit 1 in V72_28E1) the GMTs were low across vaccine-naïve subjects against all strains. The 1 month after first dose/baseline GMRs were 5.35-fold to 8.15-fold against strain H44/76, 14-fold to 35-fold against strain H44/76, 5.72-fold to 7.28-fold against strain NZ98/254 and 1.40-fold to 1.68-fold against strain M10713.

Across all vaccine-naive groups, the 1 month of second dose/baseline GMRs were 34-fold to 46-fold against strain H44/76; 242-fold to 558-fold against strain H44/76; 27-fold to 30-fold against strain NZ98/254 and 2.20-fold to 3.86-fold against strain M10713.

Against all strains, at 1 month after first dose (visit 2 in V72_28E1) there was an increase in the titers with some variability depending on the strains. A more robust increase in the titers was observed at 1 month after the second dose (visit 3 in V72_28E1) especially against strain 5/99 (Table 11.4.1-10).

CHMP comment:

Booster dosing:
For both young and older children 4 to 7 years and 8 to 12 years booster dosing resulted in substantial increase in AB titers for the majority of strains with lowest outcome for M10713.

2-dose catch-up series response in vaccine-naïve subjects:
Catch-up dosing resulted in a substantial increase of subjects developing hSBA antibody titers especially against H44/76, 5/99 and NZ98/254 with low outcome for M10713

Safety results

All subjects enrolled in vaccination subset were included in the safety set for solicited and unsolicited AEs across vaccine groups except for 5 subjects across vaccine groups 2H3H511_V, 68_11_V and NAIVE_123 (Table 12.1-1).

Solicited AEs

Follow-on subjects:

35-47 months of age:

Across vaccine follow-on groups (2H3H511_V, 3H5_11_V, 68_11_V), 91% to 94% of subjects reported at least one solicited local AE from 6 hours through day 7 after the booster dose (Table 2-10a). The most frequently reported solicited local AE was tenderness, reported by 88% to 91% of subjects (severe in 14% to 21% of subjects).

At least one systemic AE was reported by 69% to 71% of subjects across vaccine follow-on groups from 6 hours through day 7 after the booster dose. The most frequently reported solicited systemic AE was irritability reported by 56% to 59% of subjects.

4-7 years of age:

In the 02_2_5_V group, 97% of subjects in 02_2_5_V group reported at least one solicited local AE from 6 hours through day 7 after the booster dose. The most frequently reported by solicited local AE was tenderness reported by 97% of subjects (severe in 9% subjects)

At least one systemic AE was reported by 56% of subjects from 6 hours through day 7 after the booster dose. The most frequently reported solicited system AE was irritability reported by 28% of subjects.

8-12 years of age:

In the 02_6_10_V group, 93% of subjects reported at least one solicited local AE from 6 hours through day 7 after the booster dose (Table 2-10b). The most frequently reported solicited local AE was injection site pain reported by 93% of subjects (severe in 13% of subjects).

At least one systemic AE was reported by 63% of subjects in 02_6_10_V group from6 hours through day 7 after the booster dose (Table 2-10b). The most frequently reported solicited system AE were malaise by 39% of subjects and headache reported by 30% of subjects.

Vaccine-naïve subjects:

35-47 months of age:

In the NAIVE_123 group after the first and the second vaccination, at least one solicited local AE was reported by 88% and 80% of subjects, respectively. The most frequently reported solicited local AE was tenderness reported by 87% and 78% of subjects, respectively. Severe tenderness was reported by 21% and 10% of subjects, respectively.

At least one solicited systemic AE after the first and the second vaccination was reported by 64% and 46% of subjects from 6 hours through day 7, respectively. After the first and the second vaccination, the most frequently reported solicited systemic AE was irritability: 40% and 25% of subjects, respectively. Severe irritability was reported by 3% and 2% of subjects, respectively.

4-7 years of age:

In the NAIVE_4A group after the first and the second vaccination, all (100%) subjects and 93% of subjects reported at least one solicited local AE from 6 hours through day 7 after any vaccination, respectively.

After the first and the second vaccination, the most frequently reported solicited local AE was tenderness reported by all (100%) subjects and 93% of subjects, respectively. Severe tenderness reported by 18% and 5% of subjects, respectively.

At least one solicited systemic AE after the first and the second vaccination was reported by 44% and 33% of subjects from 6 hours through day 7, respectively.

After the first and the second vaccination, the most frequently reported solicited system AE was irritability was reported by 29% and 20% of subjects, respectively.

8-12 years of age:

In the NAIVE_4B group after the first and the second vaccination, 98% and 86% of subjects reported at least one solicited local AE from 6 hours through day 7, respectively.

After the first and the second vaccination, the most frequently reported solicited local AE was injection site pain reported by 96% and 82% of subjects, respectively. Severe injection site pain was reported by 14% and 6% of subjects, respectively.

At least one systemic AE after the first and the second vaccination was reported by 48% and 50% of subjects from 6 hours through day 7, respectively.

After the first and the second vaccination, the most frequently reported solicited systemic AE was headache was reported by 31% and 20% of subjects, respectively. Severe headache was reported by 2% of subjects after first vaccination.

Unsolicited AEs

Follow-on subjects:

35-47 months of age:

Across vaccine follow-on groups (2H3H511_V, 3H5_11_V, 68_11_V), 21% to 33% of subjects reported unsolicited AEs. Out of these, 8% to 13% were at least possibly or probably related unsolicited AEs as per the investigator (Table 2-12a). Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination. There were no SAEs reported in this study.

4-7 years of age:

In the 02_2_5_V group, 28% of subjects reported unsolicited AE after any vaccination. Out of these, 19% of subjects were at least possibly or probably related unsolicited AEs as per the investigator. Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination. There were no SAEs or AEs leading to withdrawal reported in this study.

8-12 years of age:

In the 02_6_10_V group, 15% of subjects reported unsolicited AE after any vaccination. Out of these, 12% of subjects were at least possibly or probably related unsolicited AEs as per the investigator. Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination.

There were no SAEs or AEs leading to withdrawal reported in this study.

Vaccine-naïve subjects:

35-47 months of age:

In the NAIVE_123 group after first and second vaccination, 15% and 12% of subjects reported unsolicited AE, respectively. Out of these, 5% and 8% of subjects were at least possibly or probably related unsolicited AEs as per the investigator. Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination.

There were no SAEs reported in this study. One subject (subject ID: V72_28E1-106009) in the NAIVE_123 group reported abdominal pain leading to withdrawal.

4-7 years of age:

In the NAIVE_4A group after first and second vaccination, 13% of subjects each reported unsolicited AE, respectively. Out of these, 11% and 9% of subjects were at least possibly or probably related unsolicited AEs as per the investigator (Table 2-13). Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination.

There were no SAEs or AEs leading to withdrawal reported in this study.

8-12 years of age:

In the NAIVE_4B group after first and second vaccination, 12% and 8% of subjects reported unsolicited AE, respectively. Out of these, 10% and 6% of subjects were at least possibly or probably related unsolicited AEs as per the investigator. Most of them were solicited local and systemic AEs persisting beyond day 7 after vaccination

There were no SAEs or AEs leading to withdrawal reported in this study.

CHMP comment:

No SAEs were reported in the study.
No unexpected safety signal was generated during the study

2.3.3. Discussion on clinical aspects

24-36 months after the completion of the vaccination course in V72_28, the antibody levels declined against all strains across all follow-on vaccine groups with in general higher GMTs and AB titters in follow-on subjects compared to vaccine-naïve subjects.

The immunogenicity outcome for M10713 was in general low across the groups investigated. This is not unexpected, as the responses to this strain were seen as problematic in previous studies as well.

The administration of a booster dose of rMenB+OMV NZ vaccine in previously primed subjects (follow-on groups) or two catch-up doses of rMenB+OMV NZ administered 1 month apart to vaccine-naïve subjects induced strong hSBA titers with lowest results for M10713. The results were hereby comparable for booster vaccinations in infants who initially received either 2 or 3 doses.

No unexpected safety signal was generated. No SAEs were reported in this study.

The MAH is planning to submit a type II variation to update the SPC with data from the current study. This is endorsed.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

This article 46 submission is considered satisfactory and no further regulatory action regarding Bexsero is required.

Recommendation

☒ **Fulfilled**