28 February 2019
EMA/203004/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bexsero

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

Procedure No. EMEA/H/C/002333/II/0073

Note

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

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Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CSR	Clinical study report
EC	European Commission
EU	European Union
EMA	European Medicines Agency
FAS	Full analysis set
fHbp	Factor H Binding Protein
GCP	Good Clinical Practice
GMT	Geometric mean titer
GMR	Geometric mean ratio
GSK Biologicals	GlaxoSmithKline Biologicals
hSBA	Serum bactericidal assay using human complement
ICH	International Conference on Harmonisation
moa	Months of age
NadA	Neisseria adhesin A
NHBA	Neisserial heparin binding antigen
OMV NZ	Outer membrane vesicle from Neisseria meningitidis serogroup B strain NZ98/254
PI	Product information
PorA	Porin A
PPS	Per protocol set
PT	Preferred term
rMenB+OMV NZ	Multicomponent meningococcal group B vaccine (recombinant, adsorbed)
SAE	Serious adverse event
SOC	System organ class
US	United States
Yoa	Years of age

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GSK Vaccines S.r.l submitted to the European Medicines Agency on 14 December 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.2 of the SmPC to recommend a 3rd (booster) dose in individuals at continued risk of exposure to meningococcal disease and section 5.1 of the SmPC to add data on antibody persistence and response to a booster dose in children, adolescents and adults. This submission is based on clinical studies V72_28E1 and V72_75 and constitutes follow-on to procedure EMEA/H/C/002333/P46/026.

Study V72_28E1 was a phase 3b, open label, multicentre extension study that evaluated the antibody persistence in children 4 through 12 years of age at 24 through 36 months after the last dose in follow-on subjects from the parent study V72_28.

Study V72_75 was a phase 3b, open label, controlled, multicentre study that assessed the long-term antibody persistence of bactericidal activity at 4 to 7.5 years after 2-dose primary series of vaccination and the booster response to a third dose in adolescents and young adults 15 through 24 years of age who previously participated in studies V72P10 and V72_41.

The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Bexsero (rMenB+OMV NZ) is a multicomponent meningococcal group B recombinant adsorbed vaccine, presented as a single-dose suspension for injection in a pre-filled syringe. The vaccine contains 3 purified recombinant proteins, Neisserial heparin binding antigen (NHBA) as fusion protein (also referred to as rp287-953), *Neisseria* adhesin A (NadA) as single protein (rp961c), factor H binding protein (fHbp) as fusion protein (rp936-741), and the outer membrane vesicles (OMV) from the New Zealand *Neisseria meningitidis* serogroup B strain NZ98/254 containing PorA P1.4 (the immunodominant antigen present in the OMV component), along with aluminium hydroxide as adjuvant adsorbent.

On 23 March 2018, in the framework of Article P46 procedure EMEA/H/C/002333/P46/026, the CHMP considered that a strong booster effect was observed after administration of the third dose and that no new safety concerns arose from the reported unsolicited adverse events. Furthermore, the CHMP concluded that the observations made with regards to the long persistence of antibodies and the effect of late booster vaccination should be reflected in the Product Information of Bexsero. To this end, the MAH submitted variation II-73, including a recommendation to consider a booster dose in individuals at continued risk of exposure to meningococcal disease, based on official recommendations (section 4.2 update) and updates on immunogenicity, persistence of antibodies and response to the booster dose (section 5.1 update).

Studies V72_28E1 and V72_75 describe the persistence of antibodies and the responses to a third (booster) dose in children 4 through 12 years of age and in adolescents and young adults who received a 2-dose primary series of rMenB+OMV NZ.

Immunogenicity data obtained at 24 to 36 months or at 4.5 to 7 years after completion of a 2-dose primary schedule of rMenB+OMV NZ in children and adolescents, respectively, showed a decrease in bactericidal antibody levels against all strains considered. The antibody titers were, nevertheless, higher among follow-on subjects compared with the baseline antibody levels in age-matched vaccine-naïve subjects.

The administration of a third (booster) dose of rMenB+OMV NZ in subjects previously primed with 2 doses of rMenB+OMV NZ vaccine induced an immune response, with higher increase of hSBA GMTs, compared with the response to a first dose of rMenB+OMV NZ vaccine in vaccine-naïve subjects of similar age. The anamnestic response to booster dose indicated that despite a decline of bactericidal antibodies over time, previous 2-dose vaccination with rMenB+OMV NZ resulted in effective priming.

The results indicated the benefits of an additional booster dose, with no change in the previously described safety profile in these age categories. Overall, the safety profile is considered in line with what was reported previously following a 2-dose primary series and no new clinical concerns have been raised.

Based on the available evidence, the CHMP was of the view that the proposed updates in sections 4.2 and 5.1 of the SmPC and the respective sections of the Package Leaflet are acceptable.

The benefit–risk profile of Bexsero remains unchanged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.2 of the SmPC to recommend a 3rd (booster) dose in individuals at continued risk of exposure to meningococcal disease and section 5.1 of the SmPC to add data on antibody persistence and response to a booster dose in children, adolescents and adults. This submission is based on clinical studies V72_28E1 and V72_75 and constitutes follow-on to procedure EMEA/H/C/002333/P46/026.

Study V72_28E1 was a phase 3b, open label, multicentre extension study that evaluated the antibody persistence in children 4 through 12 years of age at 24 through 36 months after the last dose in follow-on subjects from the parent study V72_28.

Study V72_75 was a phase 3b, open label, controlled, multicentre study that assessed the long-term antibody persistence of bactericidal activity at 4 to 7.5 years after 2-dose primary series of vaccination and the booster response to a third dose in adolescents and young adults 15 through 24 years of age who previously participated in studies V72P10 and V72_41.

The Package Leaflet is updated accordingly.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Bexsero-H-C-002333-II-73’ and to ‘Bexsero-H-C-002333-P46-26’.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Bexsero (rMenB+OMV NZ) is a multicomponent meningococcal group B recombinant adsorbed vaccine, presented as a single-dose suspension for injection in a pre-filled syringe. The vaccine contains 3 purified recombinant proteins, Neisserial heparin binding antigen (NHBA) as fusion protein (also referred to as rp287-953), *Neisseria* adhesin A (NadA) as single protein (rp961c), factor H binding protein (fHbp) as fusion protein (rp936-741), and the outer membrane vesicles (OMV) from the New Zealand *Neisseria meningitidis* serogroup B strain NZ98/254 containing PorA P1.4 (the immunodominant antigen present in the OMV component), along with aluminium hydroxide as adjuvant adsorbent.

The rMenB+OMV NZ vaccine was first registered in the European Union (EU) through the centralised procedure on January 14, 2013 and has received marketing authorization in 10 additional (non-EU) countries: Argentina, Australia, Brazil, Canada, Chile, Israel, New Zealand, Switzerland, the United States (US) and Uruguay. The vaccine is currently approved in 41 countries worldwide.

The vaccine is indicated for active immunization of individuals from 2 months of age and older against invasive meningococcal disease caused by *N. meningitidis* serogroup B. The indicated age range varies depending on the country, according to national recommendations.

The clinical development program for the rMenB+OMV NZ vaccine comprised studies in healthy adults, adolescents, children and infants. These studies have shown immune responses against the selected serogroup B reference or 'indicator' strains, measured by the serum bactericidal assay using human complement (hSBA) in all age cohorts studied.

The results of clinical study V72_28E1 in children 2 to 10 years of age were submitted to the European Medicines Agency (EMA) (EMEA/H/C/2333/II/059) to support the administration of a 2-dose primary series of rMenB+OMV NZ given in a 0, 1-month schedule. The study V72_28E1 also evaluated the antibody persistence at 24 to 36 months after a 2-dose primary series of rMenB+OMV NZ administered in the parent study V72_28 and the immune response to a third (booster) dose of rMenB+OMV NZ (Clinical Study Report [CSR] completed 28 October 2016).

The clinical study V72_75 in adolescents and young adults assessed the long-term antibody persistence and booster response of rMenB+OMV NZ vaccine administration in subjects that had previously received a 2-dose primary series of rMenB+OMV NZ as adolescents in studies V72_41 and V72P10 (CSR completed 13 September 2017). The results of clinical study V72_75 were submitted to the EMA on 30 October 2017 as required by Article 46 for pediatric studies (EMA/H/C/2333/P46/026). Following this submission, the CHMP requested to discuss to what extent the observations made with regard to long-term persistence and effect of late booster vaccination should be reflected in the Summary of Product Characteristics of the rMenB+OMV NZ vaccine.

As antibody persistence data are now available for different age brackets from various clinical studies, the MAH has evaluated the persistence of the immune response and booster recommendation for those age groups for which the need for a booster has not been established yet.

The immunogenicity and safety results from study V72_28E1 in children 4 through 12 years of age who received a 2-dose rMenB+OMV NZ primary vaccination at 2 through 10 years of age provides information on bactericidal antibody persistence and response to an additional third dose of rMenB+OMV NZ vaccine in children.

The V72_75 study immunogenicity and safety results in subjects 15 through 24 years of age who received a 2-dose rMenB+OMV NZ primary vaccination at 11 through 17 years of age provides

information on long- term bactericidal activity persistence and booster response to rMenB+OMV NZ vaccine in adolescents and young adults.

The purpose of this submission is to update the sections 'Clinical Pharmacology/Pharmacodynamic effects' and 'Posology' in the PI. The following information is proposed to be included:

1. Persistence of antibody responses following a 2-dose primary series in children and adolescents:

The current data in the PI supporting the indication in children includes immunogenicity responses at 1 month after the second dose of the 2-dose primary series administered at 2 through 10 years of age. The current data in the PI supporting the indication in adolescents and adults includes immunogenicity responses at 1 month after the second dose of the primary series. For adolescents, data describing persistence of antibody responses 18 to 23 months after the second dose is also present in the label.

The MAH proposes to include in section 5.1 Clinical Pharmacology/Pharmacodynamic effects" of the PI

a) the bactericidal antibody response data in children 4 through 12 years of age, 24 to 36 months after they received the 2-dose primary series of rMenB+OMV NZ;
b) bactericidal antibody response data from adolescents and young adults at 4 to 7.5 years after they had received a 2-dose primary series of rMenB+OMV NZ at 11 through 17 years of age, describing long-term antibody persistence.

2. Booster dose following a 2-dose primary series in children and adolescents:

No clinical data relevant to the need and time for a booster dose in children, adolescents and adults vaccinated with a 2-dose primary series are presented in the current PI. While this is still applicable, results of the studies V72_28E1 and V72_75, although showing a decline in antibody titers 24 to 36 months (V72_28E1) and 4 to 7.5 years (V72_75) after the primary series in children and adolescents respectively, also indicate an immunological memory when an additional third (booster) dose is administered.

The MAH considers that the data supports recommendation to consider the inclusion of a booster dose in individuals at continued risk of exposure to meningococcal disease in the posology section of the PI.

To inform prescribers that clinical data support the administration of an additional booster dose in children (2 years of age and above), adolescents and young adults, the MAH proposes to include a related statement in the posology section of the PI. The proposed wording specifies that the booster dose should be considered for individuals at continued risk of exposure to meningococcal disease. This category would include those with immunocompromising conditions (e.g. complement deficiencies, asplenia, human immunodeficiency virus [HIV] etc.), laboratory workers exposed to meningococci, individuals living in close quarters such as university students, military recruits etc. [Bruce 2001, CDC 2011, D'Amelio 2001, Figueroa 1993, Holdsworth 1991, Miller 2014, Tully 2006]. The need and timing of the booster dose as well as the definition of individuals at continued risk of meningococcal disease exposure depends on country- specific factors such as the timing of the primary vaccination schedule in children, country- and region-specific disease epidemiology, peak occurrence rates and risk factors in this age category and population [CDC 2016, ECDC 2016], country-specific vaccination policies for children and adolescents etc., and should therefore be based on official recommendations.

In addition, the MAH proposes minor corrections and/or non-substantive changes made for clarification purposes.

6. Clinical efficacy aspects

Clinical Studies

The proposed changes in the PI are supported by data from studies V72_28E1 and V72_75 (Table 1).

Table 1. Overview of clinical studies.

		Number of subjects			
Study ID: V72_28E1 Study countries: Hungary and Spain Study Design: Phase 3b, open label, multicenter extension study of study V72_28 Objectives Primary objectives Immunogenicity Antibody persistence at 24 to 36 months after the completion of the 2-dose vaccination course, in subjects aged 2- 10 years who participated in V72_28. Safety Safety and tolerability of an additional dose of rMenB+OMV NZ when administered 24 to 36 months after completion of the 2-dose vaccination course in subjects aged 2-10 years who participated in V72_28. Safety and tolerability of rMenB+OMV NZ when given as a 2-dose regimen (0, 1-month schedule) to vaccine-naïve subjects. Secondary objectives: Evaluate the immune response at 1 month after booster dose administered 24 to 36 months after completion of the vaccination course in the V72_28. Evaluate the immune response of 2 catch-up doses of rMenB+OMV NZ administered 1 month apart to vaccine- naïve children. Study groups and schedule of vaccination Population (Age) Follow-on: subjects Groups I–III: subjects 35 through 47 moa who had received 2 or 3 doses primary series as infants) (i.e. 24 through 36 months after study V72_28) Group IVa: subjects 4 through 7 yoa who had received 2 doses at 2 through 5 yoa (i.e. 24- 36 months after study V72_28). Group IVb: subjects approximately 8 through 12 yoa who received 2 doses at 6 through 10 yoa (i.e. 24–36 months after study V72_28)	Follow-on groups consisted of vaccinated and non-vaccinated subsets	Enrolled	Exposed	FAS Persistence	FAS Booster
	Group I (2H3H511)				
	Vaccinated	98	97	93	97
	Nonvaccinated	47	-	47	-
	Group II (3H5_11)				
	Vaccinated	89	89	89	87
	Nonvaccinated	43	-	42	-
	Group III (68_11)				
	Vaccinated	81	80	80	79
	Nonvaccinated	39	-	39	-
	Group IVa (02_2_5)				
	Vaccinated	32	32	32	32
	Nonvaccinated	36	-	36	-
	Group IVb (02_6_10))				
	Vaccinated	91	91	91	91
	Nonvaccinated	90	-	88	-
Vaccine-naïve subjects: NAÏVE_123: subjects 35 through 47 moa NAÏVE_4A: subjects 4 through 7 yoa NAÏVE_4B: subjects 8 through 12 yoa. All vaccine-naïve groups received 2 catch-up doses of rMenB+OMV NZ 1 month apart.	Naïve_123	100	100	100	96
	Naïve_4A	55	55	55	55
	Naïve_14B	50	50	50	50
Study ID: V72_75 Countries: Australia, Canada, Chile (2015/2016) Study design: Phase 3b, Open Label, Controlled, Multi-Center, Extension Study Objectives Primary immunogenicity objective: To assess serum bactericidal activity at approximately 4 to 7.5 years following a 2- dose primary series (persistence) compared to serum bactericidal activity at baseline in vaccine-naïve subjects. Primary safety objective: To assess and compare the safety and tolerability of a third dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2-dose primary series, with that of a 2dose primary series of rMenB+OMV NZ administered to vaccine-naïve subjects according to a 0, 1-month schedule. Secondary immunogenicity objectives: Adolescents and young adults (15-24 years of age) Study groups and schedule of vaccination Group 3B: Follow-on subjects from parent studies V72P10 and V72_41, third dose (booster) of rMenB+OMV NZ at month 0 or; Group B_0_1: Vaccine-naïve subjects, catch-up, i.e. 2 doses of rMenB OMV NZ at 0,1-month					
	Group A (3B)	276	275	275	269
	Group B (B1/B2 (B_0_1)	255	255	First dose 253	

V72_28E1 was a phase 3b, open label, multicenter extension of study V72_28, that evaluated the antibody persistence in children 4 through 12 years of age at 24 through 36 months after the last dose of rMenB+OMV NZ in follow-on subjects from the parent study V72_28. The extension study V72_28E1 also evaluated the safety and immunogenicity of an additional third (booster) dose of rMenB+OMV NZ at 24 to 36 months after the 2-dose primary vaccination. In addition, the safety and immunogenicity of a 2-dose catch-up schedule administered 1-month apart to age-matched vaccine-naïve children was also assessed.

V72_75 was a phase 3b, open label, controlled, multicenter study that assessed the long- term antibody persistence of bactericidal activity at 4 to 7.5 years after 2-dose primary series of rMenB+OMV NZ vaccine and the booster response to a third dose of rMenB+OMV NZ vaccine in adolescents and young adults 15 through 24 years of age who previously participated in studies V72P10 and V72_41.

Both parent studies were conducted in adolescents aged 11 through 17 years, with V72_41 enrolling subjects in Australia and Canada and V72P10 in Chile. In study V72P10, subjects were vaccinated with a 2-dose primary series of rMenB+OMV NZ administered at a 0, 1-month, or 0, 2-month, or 0, 6-month schedules while in V72_41, subjects received the primary series in a 0, 1-month schedule.

The clinical trials were approved by Ethics Committees, followed the International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, conformed to the Declaration of Helsinki and informed, written consent was obtained from all subjects or legal guardians as per GCP requirements.

6.1. Studies V72_28E1 and V72_75

6.2. Methods – analysis of data submitted

Study design

V72_28E1: Study V72_28E1 was a phase 3b, open label, multicenter extension study of V72_28. Follow-on subjects from study V72_28 (Groups I through IV), who had received various rMenB+OMV NZ vaccination schedules, were enrolled into the extension study to evaluate antibody persistence and the response to a further rMenB+OMV NZ dose.

To provide baseline descriptive comparison for antibody persistence and for the response to the further dose given to previously vaccinated follow-on subjects, age-matched vaccine-naïve subjects were enrolled into study V72_28E1 and received 2 doses of rMenB+OMV NZ administered 1 month apart.

Only persistence and booster data for follow-on subjects 4 through 7 and 8 through 12 years of age and data for corresponding age-matched vaccine-naive subjects are used in this submission to support the changes proposed in the PI. The following groups are in scope of the submission:

Follow-on subjects who received 2-doses of rMenB+OMV NZ vaccine 2 months apart (primary series) in study V72_28 were randomized in a 1:2 ratio to the non-vaccinated and vaccinated subsets, respectively.

- Group G vaccinated, Group H non-vaccinated: both 4 through 7 years of age, collectively referred to as Group 02_2_5 throughout this document
- Group I vaccinated, Group J non-vaccinated: both 8 through 12 years of age, collectively referred to as Group 2_6_10 throughout this document.

Vaccine-naïve subjects of similar age who receive 2 doses of rMenB+OMV NZ in the extension study:

- NAÏVE_4A: 4 through 7 years of age;
- NAÏVE_4B: 8 through 12 years of age.

Please refer to Table 1 for the details of the other vaccination groups in Study V72_28E1. This submission presents results for the evaluation of the following study objectives:

- Primary immunogenicity objective: evaluate the antibody persistence 24 to 36 months after the completion of the vaccination course, in subjects who participated in the parent study V72_28.
- Primary safety objective: 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 subjects who participated in the study V72_28, 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.
- Secondary immunogenicity objectives: 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.

V72_75: Study V72_75 was a phase 3b, open label, controlled, multicenter, extension study. The study evaluated bactericidal antibody persistence 4 years after the 2-dose primary series in study V72_41 (Canada and Australia) and 7.5 years after the primary series in study V72P10 (Chile). The study also assessed responses to a booster dose in the follow-on subjects in addition to responses in the vaccine-naïve subjects receiving their primary schedule. Vaccine-naïve subjects served primarily as a descriptive comparator for safety, persistence, booster response and antibody kinetics of primary immunization with rMenB+OMV NZ according to a 0, 1-month schedule. Subjects were enrolled in the following groups:

- Follow-on subjects (Group 3B): included 276 subjects who had received 2 doses of rMenB+OMV NZ vaccine in the parent studies (V72_41 and V72P10), received no subsequent meningococcal group B vaccines, and who were to receive a booster dose of rMenB+OMV NZ vaccine in the current study. All subjects from the parent study V72P10, irrespective of the rMenB+OMV NZ schedule (0, 1-, 0, 2-, or 0, 6-month) of the 2-dose primary series, were eligible to be enrolled in this group.
- Vaccine-naïve subjects (Group B_0_1): included approximately 250 healthy vaccine-naïve subjects similar in age to subjects in the follow-on groups (15 through 24 years), and who were to receive 2 doses of rMenB+OMV NZ vaccine as a primary series 1 month apart, in the current study. On day 1, subjects were to be randomized into 2 different blood draw schedules according to a 1:1 ratio. Results of Groups B1 and B2 were also analysed together as Group B_0_1.

For the purpose of this variation only antibody persistence and booster response data after rMenB+OMV NZ 2-dose primary series from follow-on subjects is considered. Safety and immunogenicity data at corresponding time-points from the vaccine-naïve subjects is also included to enable a descriptive comparison.

This submission presents results for the evaluation of the following study objectives:

- Primary safety objective: the safety and tolerability of a single dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2-dose primary series in parent studies V72_41 and V72P10, assessed and compared with that of 2 doses of rMenB+OMV NZ administered to vaccine-naïve subjects according to a 0, 1-month schedule.
- Primary immunogenicity objective: the persistence of bactericidal activity at 4 to 7.5 years after a 2-dose primary series of rMenB+OMV NZ (0, 1-; 0, 2-; 0, 6-month schedule) and the response to a third dose in adolescents and young adult subjects who previously participated in parent studies V72_41 and V72P10, compared to vaccine-naïve healthy controls of similar age.
- Secondary immunogenicity objective: the immune response at 1 month after a third dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series compared to the immune response at 1 month after the first dose of rMenB+OMV NZ administered to vaccine-naïve subjects according to a 0, 1-month schedule.

Methods used to evaluate immunogenicity

The immunogenicity of the rMenB+OMV NZ vaccine was assessed in this study by measuring the hSBA which is a functional measure of the ability of antibodies, in conjunction with complement, to kill meningococci, and is widely accepted and generally recognized as the serological correlate of protection. Serum bactericidal antibody titers ≥4 are considered an appropriate correlate of protection, based on the work by Goldschneider et al. (1969) and also agreed upon with the CHMP [EMEA/H/SA/834/1/2006/III]. While this was the cut-off used in early studies in the clinical development program of rMenB+OMV NZ, in recent clinical studies the threshold was set to ≥1:5 if the hSBA assay was performed internally at GSK (Clinical Serology Laboratory, Marburg, Germany). This is to ensure with 95 % confidence that subjects with a titer of 5 or greater will have achieved a titer of at least 4. However, the 1:4 cut-off continued to be used in recent studies if the hSBA assay was performed by an external laboratory for all or some strains.

Serum bactericidal activity against rMenB+OMV NZ was determined by performing serum bactericidal assays using human plasma as source of exogenous complement against a standard panel consisting of 4 meningococcal B indicator strains: H44/76, 5/99, NZ98/254 and M10713. Each of these strains measures bactericidal activity primarily directed against one of the major bactericidal antigens included in the vaccine: strain H44/76 against the 741 part of the 936-741 antigen, also known as fHbp variant 1.1; strain 5/99 against antigen 961c, also known as NadA; strain NZ98/254 against PorA P1.4, the immunodominant antigen in the OMV NZ vaccine component (Giuliani 2010); and strain M10713 against the 287 part of the 287-953 antigen, also known as NHBA (Snape 2013).

Children – study V72_28E1

Testing for the V72_28E1 study was conducted for strain M10713 at GSK's Clinical Laboratory Sciences in Marburg, Germany with a cut-off of 1:5, and for strains H44/76, 5/99 and NZ98/254 at the designated laboratory (Public Health England, UK), with a cut-off of 1:4. The immunogenicity results presented in the CSR for the different strains reflect the dilutions used in the corresponding labs at which they were tested. In addition, the CSR also provides immunogenicity results for all the strains analysed using both thresholds (i.e., subjects that achieved a cut-off of ≥1:4 and ≥1:5). This difference in cut-offs was shown to have no clinical impact, as seen from the results presented in CSR V72_28E1. For the purpose of this submission, immunogenicity results from this study are presented using the cut-offs used in the lab, in order to ensure comparability with data already present in the PI for the parent study V72_28.

Adolescents – study V72_75

Testing in study V72_75 was conducted for strains H44/76 and M10713 at GSK's Clinical Laboratory Sciences in Marburg, Germany with a cut-off of 1:5, and for strains 5/99 and NZ98/254 at the designated laboratory (Charles River, Edinburgh, Scotland), with a cut-off of 1:4. The immunogenicity results presented in the V72_75 CSR for the different strains reflect the dilutions used in the corresponding labs at which they were tested. The CSR also provides immunogenicity results for all the strains analysed using both thresholds (i.e., subjects that achieved a cut-off of ≥1:4 and ≥1:5). The calculation of the percentage of subjects with titer ≥4 in the CSR included all subjects for which a hSBA titer of ≥4 was measured, while calculations for the percentages of subjects with titer ≥5 included all those subjects that achieved an hSBA titer of ≥5. This difference in cut-offs was shown to have no clinical impact, as seen from the results presented in CSR V72_75.

Therefore, for the purpose of this submission, immunogenicity results of follow-on subjects in V72_75 enrolled from parent study V72P10 and the corresponding vaccine- naïve subjects of similar age enrolled in V72_75 study are presented using a cut-off of 1:4, in order to ensure comparability with data already present in the PI and the parent study. Using a similar approach, results from subjects enrolled from

V72_41 (and corresponding vaccine-naïve subjects) are presented here with the threshold used in the V72_41 parent study (1:5), although data from parent study V72_41 are not currently included in the PI.

Blood samples to obtain serum for hSBA assays were collected at the time points specified in the CSR. Blood samples collected at baseline (prior to booster or first dose) and 30 days after booster dose/first dose were analysed for the objectives evaluated in this submission.

Statistical methods

The study endpoints evaluated for immunogenicity in this submission are described below.

Children – study V72_28E1

Primary endpoint: persistence of bactericidal activity measured against the

N. meningitidis serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713 prior to booster vaccination (visit 1 in V72_28E1 study) in follow-on subjects was evaluated as follows:

- percentage of subjects with hSBA titers ≥ 4 and ≥ 5
- hSBA geometric mean titers (GMTs).
- hSBA geometric mean ratios (GMRs) of GMTs at 24 through 36 months after the completion of the vaccination course in the parent study (visit 1 of V72_28E1) over GMT at:
    - 1 month after the completion of the 2-dose vaccination course in the parent study V72_28.
    - Pre-primary vaccination in the parent study V72_28.

Secondary endpoint: Immune response at 1 month after a booster dose administration of rMenB+OMV NZ vaccine in follow-on subjects in the vaccination subset against serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713 was evaluated as follows:

At pre-vaccination (visit 1) and 1 month after the booster/first-dose administration (visit 2) (unless indicated otherwise) in V72_28E1 in follow-on (vaccination subset) and vaccine-naïve subjects:

- percentage of subjects with hSBA titers ≥ 4, ≥ 5, and ≥ 8
- hSBA GMTs at visit 1 and visit 2
- percentage of subjects with 4-fold rise in hSBA titers from visit 1 to visit 2, from post-primary visit to visit 2, and for follow-on subjects in the vaccination subset, from preprimary vaccination to visit 2
- hSBA GMRs of GMTs: visit 2 over visit 1, visit 2 over post-primary vaccination visit, and for follow-on subjects visit 2 over pre-primary vaccination visit (baseline of parent V72_28 study).

The analysis of immunogenicity was descriptive and was performed on the full analysis set (FAS).

Adolescents – study V72_75

Primary immunogenicity endpoints:

The persistence of bactericidal activity was measured against the 4 N. meningitidis serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713. Data were to be summarized by calculating:

Percentages of subjects with hSBA ≥1:4 and ≥1:5 at day 1 in study V72_75 (i.e. 4 or 7.5 years after last dose in studies V72P10 and V72_41, respectively);

hSBA GMTs and GMRs of GMTs prevaccination versus GMTs at 1 month after the last dose of rMenB+OMV NZ in the V72_41 and V72P10 studies, to each of the 4 indicator strains.

Prevaccination data in vaccine-naïve subjects served as a comparator to evaluate bactericidal activity 4 to 7.5 years post-second dose in follow-on subjects.

Secondary immunogenicity endpoints:

- The immune response was measured against the 4 N. meningitidis serogroup B indicator strains. Data were summarized by calculating the percentage of subjects with hSBA ≥1:4 and ≥1:5; hSBA GMTs, GMRs of GMTs at 1 month post-vaccination of a booster dose versus pre-booster dose (follow-on subjects) or first dose of rMenB+OMV NZ versus pre-first dose (vaccine-naïve subjects), to each of the 4 indicator strains.
- Post-first dose data in vaccine-naïve subjects served as a comparator to evaluate response to a booster dose in follow-on subjects. Additionally, data were summarized by calculating the percentages of subjects with a 4-fold rise at 1 month post-vaccination with a booster dose (follow-on subjects) or first dose (vaccine-naïve subjects) of rMenB+OMV NZ versus pre-vaccination, for each indicator strain.

There were no statistical hypotheses associated with the immunogenicity or safety objectives.

The primary population for each of the immunogenicity-associated analyses described in this submission was the FAS.

In analyses where the vaccine-naïve group (Group B1 and B2) served as a control to the follow-on subjects, adjusted GMTs were computed from a 2-way analysis of variance (ANOVA) with factors for vaccine group, country and the ratios of GMTs between vaccinated group and vaccine-naïve group were computed by exponentiating (base 10) the corresponding log-transformed difference of least square means from the above described model.

For all primary and secondary immunogenicity objectives:

- Analyses were performed on V72_41 and V72P10 follow-on subjects both separately and combined. Vaccine-naïve subjects enrolled in Canada and Australia were to serve as a control for the V72_41 analyses and vaccine-naïve subjects enrolled in Chile were to serve as a control for the V72P10 analyses.
- In the combined ANOVA models where subjects from V72P10 and V72_41 were pooled, and in the ANOVA model for follow-on subjects from V72_41, country was also included as an effect. Vaccine group was included as an effect in the analyses on V72_41 and V72P10 both separately and combined.

Population evaluated

Children – study V72_28E1

Follow-on subjects were included if they were healthy and had completed vaccination with rMenB+OMV NZ vaccine 2-dose schedule in study V72_28 and for whom a parent/legal guardian had given written informed consent to participate in the study.

Vaccine-naïve subjects were included if they were healthy, had not a had history of any meningococcal B vaccine administration and were aged 4 through 7 and 8 through 12 years of age and for whom a parent/legal guardian had given written informed consent to participate in the study.

Detailed inclusion and exclusion criteria are described in CSR V72_28E1 Section 9.3.

Adolescents – study V72_75

Follow-on subjects were included if they had completed vaccination with rMenB+OMV NZ vaccine in a 2-dose schedule in study V72_41 or V72P10.

Vaccine-naïve subjects were included if they were:

– 15 through 21 years of age on the day of informed consent and assent, as applicable (according to the subject's age and European Commission [EC] requirements), enrolled at sites that participated in study V72_41.
– 17 through 24 years of age on the day of informed consent and assent, as applicable (according to the subject's age and EC requirements), enrolled at sites that participated in study V72P10.

Subjects were excluded if:

– Follow-on subjects: they received a third dose of a meningococcal group B vaccine prior to enrolment in this study.
– Vaccine-naïve subjects: they received any other meningococcal group B vaccines prior to enrolment in this study.

6.3. Results

Efficacy results

Demographic characteristics and study completion

Children – study V72_28E1

All demographic and baseline characteristics were balanced across the follow-on and vaccine-naïve subjects. The mean age of the subjects 4 through 7 years enrolled into the study was 6.6 ± 1.15 years for the follow-on subjects and 5.8 ± 1.12 years for the vaccine-naïve group. The mean age of the subjects 8 through 12 years enrolled into the study was 10.4 ± 1.43 years for the follow-on subjects and 9.7 ± 1.38 years for the vaccine-naïve group.

All follow-on subjects were randomized to receive the booster and all age-matched vaccine-naïve subjects completed the study. All were included in the FAS datasets for persistence and booster: 32 follow-on and 55 vaccine-naïve subjects for the 4 through 7 years of age group, and 91 follow-on and 50 vaccine-naive subjects for the 8 through 12 years of age group.

Adolescents – study V72_75

All demographic and baseline characteristics were balanced across the groups of follow-on (Group 3B) and vaccine-naïve (Group B_0_1) subjects. The mean age of the subjects enrolled from study V72_41 (Canada, Australia) was 18 ± 1.88 years for the follow-on subjects and 17.5 ± 1.85 years for the vaccine-naïve group; for study V72P10 (Chile), the mean age was 21.2 ± 1.73 years for the follow-on subjects and 21.7 ± 1.56 years for the vaccine-naïve group, in the respective groups.

Across study groups 98 % to 99 % of subjects completed the study. Overall, 98 % to 100 % of enrolled subjects were included in the FAS datasets for persistence and booster.

Immunogenicity results

Antibody persistence

Antibody persistence approximately 24 to 36 months following a 2-dose primary series in children (V72_28E1)

As this submission is focusing on the persistence and booster data of follow-on subjects who received a 2-dose primary series of rMenB+OMV NZ in the parent study V72_28, immunogenicity results presented here also include the results from the parent study.

Although there was a decline in bactericidal antibody titers approximately 24 to 36 months after a 2-dose primary series given to children 2 through 10 years of age (in the parent study V72_28), persistence of the immune response was observed in the follow-on subjects (Table 2).

Percentage of subjects with hSBA titer ≥4 for strains H44/76, 5/99, NZ98/254 and titer ≥5 for strain M10713

At approximately 24 to 36 months after a 2-dose primary series, the percentages of subjects with hSBA titer ≥4 (against strains H44/76, 5/99, NZ98/254) or hSBA titer ≥5 (against strain M10713) in follow-on subjects were 52 % for strain H44/76, 79 % for 5/99, 29 % for NZ98/254, and 34 % for M10713 in children 4 through 7 years of age, and 58 % for strain H44/76, 85 % for 5/99 (NadA), 50 % for NZ98/254, and 61 % for M10713 in children 8 through 12 years of age (Table 2).

Table 2. Antibody Responses in Parent Study V72_28 in Subjects receiving a 2-dose Primary Series and Persistence at 24 to 36 Months in Follow-on Subjects in Study V72_28E1 – FAS Persistence – Study V72_28E1.

Strains (antigens)	Number (%) of Subjects (95% CI) with hSBA titers ≥predefined cut-off[a]	
	4-7 Years of Age	8-12 Years of Age
	Group 02_2_5	Group 02_6_10
H44/76 (fHbp)	**N = 67**	**N = 178**
Baseline in V72_28	11 (16%) (8.5%-27.5%)	28 (16%) (10.8%-22%) N = 177
1 Month After Last Vaccination in V72_28	67 (100%) (94.6%-100%)	171 (99%) (95.9%-99.86%) N = 173
Persistence After 24-36 Months (Visit 1 in V72_28E1)	35 (52%) (39.7%-64.6%)	103 (58%) (50.3%-65.2%)
5/99 (NadA)	**N = 67**	**N = 179**
Baseline in V72_28	1 (1%) (0.04%-8%)	15 (8%) (4.8%-13.6%) N = 177
1 Month After Last Vaccination in V72_28	65 (98%) (91.8%-99.96%) N = 66	175 (99%) (96.9%-99.99%) N = 176
Persistence After 24-36 Months (Visit 1 in V72_28E1)	53 (79%) (67.4%-88.1%)	153 (85%) (79.4%-90.3%)
NZ98/254 (PorA P1.4)	**N = 68**	**N = 179**
Baseline in V72_28	1 (1%) (0.04%-8%) N = 67	13 (7%) (4%-12.2%) N = 177
1 Month After Last Vaccination in V72_28	67 (99%) (92.1%-99.96%)	173 (99%) (96.8%-99.99%) N = 174
Persistence After 24-36 Months (Visit 1 in V72_28E1)	20 (29%) (19%-41.7%)	89 (50%) (42.2%-57.3%)
M10713 (NHBA)	**N = 65**	**N = 173**
Baseline in V72_28	25 (45%) (31.3%-58.5%) N = 56	97 (60%) (51.6%-67.1%) N = 163
1 Month After Last Vaccination in V72_28	55 (90%) (79.8%-96.3%) N = 61	153 (96%) (91.2%-98.2%) N = 160
Persistence After 24-36 Months (Visit 1 in V72_28E1)	22 (34%) (22.6%-46.6%)	105 (61%) (53%-68%)

Source: CSR V72_28E1 Table 11.4.1-2b.
Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; NadA, *Neisseria* adhesin A; NHBA, Neisserial heparin binding antigen; PorA, Porin A.
Note: The N's indicate the number of subjects with evaluable serum for that strain and timepoint.
[a] Immune response hSBA ≥ 4 was assessed against strains H44/76, 5/99 and NZ98/254, while the hSBA cut-off against strain M10713 was ≥ 5.

For all strains except M10713 these percentages were higher in follow-on subjects than values observed at baseline in vaccine-naïve subjects of similar age (H44/76: 27 %, 5/99: 4 %, NZ98/254: 7 %, M10713:

38 % in children 4 through 7 years of age, and H44/76: 20 %, 5/99: 8 %, NZ98/254: 6 %, M10713: 55 %) in children 8 through 12 years of age.

hSBA GMTs

At approximately 24 to 36 months after a 2-dose primary series, hSBA GMTs in follow-on subjects were 3.97 for strain H44/76, 21 for 5/99, 2.81 for NZ98/254 and 3.53 for M10713 in children 4 through 7 years of age, and 5.75 for strain H44/76, 21 for 5/99, 4.57 for NZ98/254, and 7.82 for M10713 in children 8 through 12 years of age.

For all strains except M10713, hSBA GMTs were higher in follow-on subjects than at baseline in vaccine-naïve subjects of similar age (H44/76: 2.33, 5/99: 1.20, NZ98/254:1.37, M10713: 4.26 in children 4 through 7 years of age, and H44/76: 1.93, 5/99: 1.38, NZ98/254: 1.22, M10713: 6.95) in children 8 through 12 years of age.

Antibody persistence approximately 4 to 7.5 years following a 2-dose primary series as adolescents (study V72_75)

Although there was a reduction in the antibody titers approximately 4 or 7.5 years after a 2-dose primary series, persistence of the immune response was observed in the follow-on subjects from studies V72_41 and V72P10 (Table 3).

Percentages of subjects with hSBA titer of at least 4/of at least 5

At approximately 4 years after a 2-dose primary series, the percentages of subjects with hSBA titer of at least 5 in follow-on subjects in Group 3B (V72_41) were: 26 % for strain H44/76, 84 % for strain 5/99, 9 % for strain NZ98/254 and 71 % for strain M10713.

At approximately 7.5 years after a 2-dose primary series, the percentages of subjects with hSBA titer of at least 4 in follow-on subjects in Group 3B (V72P10) were: 44 % for strain H44/76, 84 % for strain 5/99, 29 % for strain NZ98/254 and 81 % for strain M10713.

The percentage of subjects with hSBA titer of at least 4/at least 5 in follow-on subjects at approximately 4 or 7.5 years after a 2-dose primary series was higher than at baseline for vaccine-naïve subjects of similar age for all indicator strains, except for strain M10713. This is also indicated by the vaccine group difference and respective lower-limit of the 95 % confidence interval (CI) (Table 3).

Table 3. Persistence of Antibody Responses at 1 Month and 4 or 7.5 Years after the Last Dose of rMenB+OMV NZ in Subjects receiving a 2-dose Primary Series and at the Baseline for Vaccine-Naïve Subjects – FAS Persistence – Study V72_75.

Strain (Antigen)		Number (%) of Subjects (95% CI)					
		V72_41 Follow-on and corresponding vaccine-naïve subjects (hSBA titers ≥5)		Vaccine group difference	V72_P10 Follow-on and corresponding vaccine-naïve subjects (hSBA titers ≥4)		Vaccine group difference
		Group 3B (V72_41) (N = 144)	Group B_0_1 (V72_41) (N = 105)	Group 3B minus. Group B_0_1 (V72_41)	Group 3B (V72P10) (N = 131)	Group B_0_1 (V72P10) (N = 150)	Group 3B minus Group B_0_1 (V72P10)
H44/76 (fHbp)	1 month after the last dose in parent study	142 (99%) (95.1%-99.83%)	NA	NA	131 (100%) (97.2%-100%)	NA	NA
	Day 1 (V72_75)	38 (26%) (19.4%-34.4%)	5 (5%) (1.6%-10.8%)	22% (13.2%-30.1%)	58 (44%) (35.6%-53.2%)	19 (13%) (7.8%-19.1%)	32% (21.4%-41.5%)
5/99 (NadA)	1 month after the last dose in parent study	134 (100%) (97.3%-100%) N = 134	NA	NA	120 (100%) (97%-100%) N=120	NA	NA
	Day 1 (V72_75)	112 (84%) (76.2%-89.4%) N = 134	5 (5%) (1.6%-11.3%) N = 100	79% (69.7%-85%)	101 (84%) (76.4%-90.2%) N = 120	33 (24%) (16.9%-31.7%) N = 139	60% (49.9%-69.2%)
NZ98/254 (PorA P1.4)	1 month after the last dose in parent study	111 (77%) (69.3%-83.7%)	NA	NA	128 (99%) (95.8%-99.98%) N = 129	NA	NA
	Day 1 (V72_75)	13 (9%) (4.9%-14.9%)	0 (0%) (0%-3.5%)	9% (5.3%-14.8%)	37 (29%) (21.1%-37.3%) N = 129	21 (14%) (9%-20.9%) N = 148	14% (4.9%-24.2%)
M10713 (NHBA)	1 month after the last dose in parent study	95 (68%) (59.4%-75.5%) N = 140	NA	NA	129 (98%) (94.6%-99.81%)	NA	NA
	Day 1 (V72_75)	102 (71%) (63.2%-78.6%) N = 143	62 (59%) (49%-68.5%)	12% (0.33%-24.2%)	106 (81%) (73.1%-87.3%)	119 (79%) (72%-85.5%)	2% (-8%-10.9%)

hSBA GMTs

At approximately 4 years after a 2-dose primary series, the hSBA GMTs in follow-on subjects in Group 3B (V72_41) were: 2.43 for strain H44/76, 24 for strain 5/99, 1.31 for strain NZ98/254, and 13 for strain M10713.

At approximately 7.5 years after a 2-dose primary series, the hSBA GMTs in follow-on subjects in Group 3B (V72_P10) were: 4.51 for strain H44/76, 31 for strain 5/99, 2.56 for strain NZ98/254, 22 for strain M10713.

At approximately 4 to 7.5 years following a 2-dose primary series, hSBA GMTs for all strains, except for strain M10713, in follow-on subjects were higher than at baseline in the vaccine-naïve groups.

Immune response of a booster vaccination

Immune response of a booster vaccination approximately 24 to 36 months after a 2- dose primary series in children (study V72_28E1)

The immune response to a booster dose of rMenB+OMV NZ in follow-on subjects (vaccinated subset) administered at approximately 24 to 36 months after a 2-dose primary series given at 2 through 10 years of age was higher than the response to 1 dose of rMenB+OMV NZ vaccine in vaccine-naïve subjects of similar age.

Percentage of subjects with hSBA titer ≥4 for strains H44/76, 5/99, NZ98/254 and titer ≥5 for strain M10713:

At 1 month after a booster dose at approximately 24 to 36 months after a 2-dose primary series, the percentages of subjects with hSBA titer ≥4 (against strains H44/76, 5/99, NZ98/254) and hSBA titer ≥5 (against M10713 strain) in follow-on subjects were high across the strains, ranging from 93 % to 100 % in children 4 through 7 years of age, and 96 % to 100 % in children 8 through 12 years of age (Table 4).

For all 4 strains, the percentages in follow-on subjects after the third (booster) dose were generally higher than for vaccine-naïve subjects after the first dose, ranging across strains from 59 % to 93 % in children 4 through 7 years of age, and from 60 % to 80 % in children 8 through 12 years of age.

hSBA GMTs and GMRs

An increase in hSBA GMTs was observed in follow-on subjects at 1 month after a third dose (booster) of rMenB+OMV NZ administered approximately 24 to 36 months after a 2 dose primary series.

In follow-on subjects, hSBA GMT increases compared to pre-booster levels were 50-fold for strain H44/76, 160-fold for strain 5/99, 24-fold for strain NZ98/254 and 13-fold for strain M10713 in children 4 through 7 years of age. In children 8 through 12 years of age, increase in hSBA GMTs compared to pre-booster values were 42-fold for strain H44/76, 135-fold for strain 5/99, 18-fold for strain NZ98/254 and 6.85-fold for strain M10713.

For all 4 strains, the hSBA GMTs achieved after booster in follow-on subjects were higher than after a single vaccine dose in vaccine-naïve subjects. In vaccine-naïve subjects, hSBA GMT increases compared to pre-vaccination titers were 7.08-fold for strain H44/76, 22-fold for strain 5/99, 9.58-fold for strain NZ98/254 and 2.06-fold for strain M10713 in children 4 through 7 years of age, and 6.87-fold for strain H44/76, 14- fold for strain 5/99, 7.01-fold for strain NZ98/254 and 1.55-fold for strain M10713 in children 8 through 12 years of age.

Table 4. Antibody Responses in Parent Study V72_28 in Subjects receiving a 2-dose Primary Series, Persistence at 24 to 36 Months and Booster Response in Follow-on Subjects in Study V72_28E1 – FAS Booster – Study V72_28E1.

Strains (antigens)	Number (%) of Subjects (95% CI) with hSBA titers ≥predefined cut-off[a]	
	4-7 Years of Age	8-12 Years of Age
	02_2_5_V	02_6_10_V
H44/76 (fHbp)	**N = 32**	**N = 91**
Baseline in V72_28	8 (25%) (11.5%-43.4%)	11 (12%) (6.2%-20.6%)
1 Month after Last Vaccination in V72_28	32 (100%) (89.1%-100%)	88 (100%) (95.9%-100%) N = 88
Persistence at 24-36 Months (Visit 1 in V72_28E1)	12 (39%) (21.8%-57.8%) N = 31	54 (59%) (48.5%-69.5%)
1 Month After Booster Dose (Visit 2 in V72_28E1)	31 (97%) (83.8%-99.92%)	90 (99%) (94%-99.97%)
5/99 (NadA)	**N = 32**	**N = 91**
Baseline in V72_28	1 (3%) (0.08%-16.2%)	7 (8%) (3.2%-15.4%) N = 90
1 Month after Last Vaccination in V72_28	32 (100%) (89.1%-100%)	89 (100%) (95.9%-100%) N = 89
Persistence at 24-36 Months (Visit 1 in V72_28E1)	23 (74%) (55.4%-88.1%) N = 31	78 (86%) (76.8%-92.2%)
1 Month After Booster Dose (Visit 2 in V72_28E1)	32 (100%) (89.1%-100%)	91 (100%) (96%-100%)
NZ98/254 (PorA P1.4)	**N = 32**	**N = 91**
Baseline in V72_28	1 (3%) (0.08%-16.7%) N = 31	6 (7%) (2.5%-13.9%) N = 90
1 Month after Last Vaccination in V72_28	31 (97%) (83.8%-99.92%)	88 (100%) (95.9%-100%) N = 88
Persistence at 24-36 Months (Visit 1 in V72_28E1)	8 (25%) (11.5%-43.4%)	43 (47%) (36.7%-58%)
1 Month After Booster Dose (Visit 2 in V72_28E1)	32 (100%) (89.1%-100%)	91 (100%) (96%-100%)
M10713 (NHBA)	**N = 30**	**N = 89**
Baseline in V72_28	10 (37%) (19.4%-57.6%) N = 27	48 (59%) (47.1%-69.3%) N = 82
1 Month after Last Vaccination in V72_28	26 (90%) (72.6%-97.8%) N = 29	79 (98%) (91.4%-99.70%) N = 81
Persistence at 24-36 Months (Visit 1 in V72_28E1)	6 (21%) (8%-39.7%) N = 29	55 (63%) (52.2%-73.3%) N = 87
1 Month After Booster Dose (Visit 2 in V72_28E1)	28 (93%) (77.9%-99.2%)	85 (96%) (88.9%-98.8%)

Immune response of a booster vaccination approximately 4 to 7.5 years after a 2 dose primary series as adolescents (study V72_75)

The immune response to a booster dose of rMenB+OMV NZ in follow-on subjects administered at approximately 4 or 7.5 years after a 2-dose primary series as adolescents was higher than the response to 1 dose of vaccine in vaccine-naïve subjects of similar age (Table 5).

Percentages of subjects with hSBA titer of at least 4/of at least 5

At 1 month after a booster dose at approximately 4 or 7.5 years following a 2-dose primary series, the percentages of subjects with hSBA titer of at least 4 in follow-on subjects were high across the strains, ranging from 92 % to 100 % in Group 3B (V72_41) and 93 % to 100 % in Group 3B (V72P10) (Table 5).

The percentages in follow-on subjects after the booster dose were higher than for vaccine-naïve subjects after the first dose for all 4 indicator strains, as also indicated by the vaccine group difference and respective lower-limit of the 95 % CI (Table 5).

hSBA GMTs and GMRs

In follow-on subjects, a high hSBA GMT increase was observed at 1 month after a third dose (booster) of rMenB+OMV NZ administered approximately 4 or 7.5 years after a 2-dose primary series.

In Group 3B (V72_41), GMT increases compared to pre-booster titers were 65-fold for strain H44/76, 100-fold for strain 5/99, 23-fold for strain NZ98/254 and 4.69-fold for strain M10713. In Group 3B (V72P10), GMT increases compared to pre-booster titers were 58-fold for strain H44/76, 64-fold for strain 5/99, 16-fold for strain NZ98/254 and 5.16-fold for strain M10713.

The hSBA GMT achieved after booster in follow-on subjects were higher than after a single vaccine dose in vaccine-naïve subjects for all 4 indicator strains, as also indicated by the between vaccine group ratio for GMTs post-booster dose of follow-on subjects versus post-first rMenB+OMV NZ dose of vaccine-naïve subjects and the respective lower limit of the 95 % CI.

Table 5. Antibody Responses at 1 Month after Booster Dose / First Dose of rMenB+OMV NZ – FAS Booster Study – Study V72_75.

	Number (%) of Subjects (95% CI)					
	V72_41 Follow-on and corresponding vaccine-naïve subjects (hSBA titers ≥5)		Vaccine group difference	V72_P10 Follow-on and corresponding vaccine-naïve subjects (hSBA titers ≥4)		Vaccine group difference
Strain (Antigen)	Group 3B (V72_41) (N = 142)	Group B_0_1 (V72_41) (N = 104)	Group 3B minus Group B_0_1 (V72_41)	Group 3B (V72P10) (N = 127)	Group B_0_1 (V72P10) (N = 149)	Group 3B minus Group B_0_1 (V72P10)
H44/76 (fHbp)	138 (98%) (93.9%-99.56%) N = 141	83 (80%) (70.8%-87%)	18% (10.7%-27%)	127 (100%) (97.1%-100%)	120 (81%) (73.3%-86.6%)	19% (13.9%-26.6%)
5/99 (NadA)	124 (100%) (97.1%-100%) N = 124	83 (86%) (77.0%-91.9%) N = 97	14% (8.8%-22.8%)	102 (100%) (96.4%-100%) N = 102	115 (84%) (76.7%-89.7%) N = 137	16% (10.8%-23.1%)
NZ98/254 (PorA P1.4)	131 (92%) (86.6%-96.1%)	41 (40%) (30.3%-49.9%) N = 103	52% (41.6%-62.3%)	112 (93%) (87.3%-97.1%) N = 120	92 (62%) (53.8%-70%) N = 148	31% (22%-40.1%)
M10713 (NHBA)	140 (99%) (96.1%-99.98%) N = 141	82 (80%) (70.5%-86.9%) N = 103	20% (12.8%-28.6%)	126 (99%) (95.7%-99.98%)	138 (93%) (87.2%-96.3%)	7% (2.2%-12.1%)

Percentages of subjects with at least 4-fold increases in hSBA titers:

The percentage of subjects achieving at least a 4-fold increase in hSBA titers after booster in the follow-on subjects were higher than after a first dose in vaccine-naïve subjects for all 4 indicator strains, as also indicated by the vaccine group difference and respective lower limit of the 95 % CI which were all above 0.

At 1 month after a booster dose at approximately 4 or 7.5 years after a 2-dose primary series, a 4-fold increase in hSBA titers was seen in the majority of follow-on subjects from both parent studies against strains H44/76, 5/99 and NZ98/254 (≥77 %) and in 49 % against strain M10713. At 1 month after the first dose of rMenB+OMV NZ in vaccine-naïve subjects of similar age, at least a 4-fold increase in hSBA titers was observed in smaller percentages against all 4 strains.

Discussion by the MAH

Children:

Antibody titers had declined by 24 to 36 months after a 2-dose primary series of rMenB+OMV NZ administered in children 2 through 10 years of age, but persistence of the immune response was observed in the follow-on subjects, as indicated by:

- In children 4 through 12 years of age administered the primary series at 2 through 10 years of age, hSBA GMTs at 24 to 36 months after vaccination in follow-on subjects declined compared with those at 1 month after the primary series, but still higher than baseline values for vaccine-naïve subjects of similar age (except against strain M10713).
- For both age groups, at 24 to 36 months after a 2-dose primary series, for all 4 indicator strains the percentage of subjects with hSBA titer of at least 4 in follow-on subjects was higher (except for strain M10713) than baseline titers in vaccine-naïve subjects of similar age.

A single booster dose of rMenB+OMV NZ vaccine in follow-on subjects at 4 through 12 years of age approximately 24 to 36 months after a 2-dose primary series as children induced an immune response against all indicator strains, as indicated by:

- The majority of subjects (≥93 %) achieved post-vaccination titers ≥4 (for strains H44/76, 5/99, NZ98/254) and ≥5 (for strain M10713), and a strong increase in GMTs after the booster dose.
- The percentages of subjects with titers ≥4 (for strains H44/76, 5/99, NZ98/254) and ≥5 (for strain M10713) after the booster dose compared to values for age-matched vaccine-naïve subjects after the first dose were generally higher against all 4 strains.
- The hSBA GMTs achieved after booster in follow-on subjects were higher than after a single vaccine dose in vaccine-naïve subjects for all 4 indicator strains.

Adolescents:

Although there was a reduction in the antibody titers approximately 4 or 7.5 years after a 2-dose primary series of rMenB+OMV NZ, persistence of the immune response was observed in the follow-on subjects, as indicated by:

- hSBA GMTs in follow-on subjects declined compared to those at 1 month after the primary series (except for strain M10713 in V72_41 subjects), although still higher than baseline values for vaccine-naïve subjects of similar age.
- for all 4 indicator strains the percentage of subjects with hSBA titer of at least 4 in follow-on subjects was higher (except for strain M10713 in V72P10 subjects) than for vaccine-naïve subjects of similar age.

Across the 4 serogroup B indicator strains, the highest persistence was observed for strain 5/99, followed by strain M10713, H44/76, and NZ98/254.

The immune response to a booster dose of rMenB+OMV NZ in follow-on subjects at approximately 4 or 7.5 years after a 2-dose primary series as adolescents was higher than the response to 1 dose of rMenB+OMV NZ vaccine in vaccine-naïve subjects of similar age as indicated by:

- The percentages in follow-on subjects after the booster dose were higher than for vaccine-naïve subjects after the first dose for all 4 indicator strains, as also indicated by the vaccine group differences.

- The hSBA GMT achieved after booster in follow-on subjects were higher than after a single vaccine dose in vaccine-naïve subjects for all 4 indicator strains, as also indicated by the between vaccine group ratio for GMTs post-booster dose of follow- on subjects versus post-first rMenB+OMV NZ dose in vaccine-naïve subjects.
- Similarly, the percentage of subjects achieving at least a 4-fold increase in hSBA titers after booster in the follow-on subjects were higher than after a first dose in vaccine-naïve subjects for all 4 indicator strains.
- The booster response was similar in both V72_41 and V72P10 follow-on subjects, irrespective of the persistence period of 4 years or 7.5 years after the last vaccination in the parent studies.

These data suggest that although bactericidal antibody titers decline over time, a 2-dose primary vaccination with rMenB+OMV NZ in children and adolescents results in adequate priming of the immune system of vaccine recipients and induces immunological memory. The data also support the proposal that the rMenB+OMV NZ vaccine may be considered as booster vaccination in subjects who previously received 2-doses primary series of rMenB+OMV NZ as children (2 through 10 years of age) or adolescents.

6.4. Discussion

Of note, the submitted studies have been assessed in previous submissions (see Chapter 2).

Immunogenicity data obtained at 24 to 36 months or at 4.5 to 7 years after completion of a 2-dose primary schedule of rMenB+OMV NZ in children and adolescents, respectively, show a decrease in bactericidal antibody levels against all strains considered. The antibody titers were, nevertheless, higher among follow-on subjects compared with the baseline antibody levels in age-matched vaccine-naïve subjects.

The administration of a third (booster) dose of rMenB+OMV NZ in subjects previously primed with 2 doses of rMenB+OMV NZ vaccine induced an immune response, with higher increase of hSBA GMTs, compared with the response to a first dose of rMenB+OMV NZ vaccine in vaccine-naïve subjects of similar age. The anamnestic response to booster dose indicates that despite a decline of bactericidal antibodies over time, previous 2-dose vaccination with rMenB+OMV NZ results in effective priming.

The data is considered to adequately support the proposed changes in PI.

7. Clinical safety aspects

7.1. Methods – analysis of data submitted

Children – study V82_28E1

For follow-on subjects in the vaccinated subset and vaccine-naïve subjects, solicited local, systemic adverse events (AE) and all unsolicited AEs were collected for 7 consecutive days after each vaccination by the subjects' parent/legal guardian. Data were collected after the first (day 1, all subjects) and second (day 31, for vaccine-naïve subjects only) vaccination. The serious adverse events (SAE) and medically attended AEs (AEs that required a medical visit to or from medical personnel), and/or AEs that resulted in premature withdrawal from the study were collected throughout the study, with a maximum duration of 2 months for the vaccine-naïve groups.

All unsolicited AEs and related concomitant medications were collected for the entire study period in subjects in the nonvaccinated subset.

Adolescents – study V72_75

Primary safety endpoints:

- The frequencies and percentages of subjects with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [temperature ≥ 38.0 °C], high fever [temperature ≥39.5°C], nausea, fatigue, myalgia, arthralgia, headache) AEs were assessed for 7 days (including the day of vaccination) after each vaccination;
- The frequencies and percentages of subjects with any unsolicited AEs for the 30 days (including the day of vaccination) after each vaccination.
- The frequencies and percentages of subjects with any SAEs, AEs leading to withdrawal, and medically attended AEs throughout the entire study.

The solicited AEs were collected by the subject and/or parent(s)/legal guardian(s) for 7 consecutive days following a vaccination, using a predefined subject diary. Data were collected after the first (visit 1, all subjects) and second (visit 3, for vaccine-naïve subjects only) vaccination. Any unsolicited AEs were collected during the first 30 days after vaccination, at visit 1 (all subjects) and at visit 3 (vaccine-naïve subjects only).

Unsolicited AEs leading to withdrawal, medically attended AEs, and SAEs were collected starting from signature of informed consent until study termination (day 31 for follow-on subjects and day 61 for vaccine-naïve subjects).

Follow-on subjects from V72_41 and V72P10 were combined for the analysis of safety data.

Data sets analysed

In both studies V72_28E1 and V72_75, the following data sets were used for the analyses of safety:

- Overall safety set: all subjects who were in the solicited safety set and/or in the unsolicited safety set.
- Solicited safety set: all subjects in the 'all exposed set' who provided post-vaccination solicited AEs data.
- Unsolicited safety set: all subjects in the 'all exposed set' who provided post-vaccination unsolicited AE data.

There was no statistical hypothesis associated with the safety objectives.

7.2. Results

Children – study V72_28E1

All subjects enrolled in the vaccination subsets were exposed to the vaccine and included in the safety set for solicited and unsolicited AEs. This represented a total of 32 and 91 subjects in the follow-on and a total of 55 and 50 subjects in the vaccine-naïve group for the 4 through 7 and 8 through 12 years of age groups, respectively.

Adolescents – study V72_75

In Group 3B follow-on subjects, of the 276 enrolled subjects, 275 (>99 %) received at least 1 dose of the study vaccine and were included in the overall and unsolicited safety set; 266 (96 %) were included in the solicited safety set.

In Group B_0_1 vaccine-naïve subjects, all the 255 enrolled subjects received at least 1 dose of the study vaccine and were included in the overall and unsolicited safety set; 254 (>99 %) were included in the solicited safety set. A total of 250 subjects (98 %) received a second dose of study vaccine.

Solicited adverse events

Children – study V72_28E1

In subjects 4 through 7 years of age, the most common solicited local AE during the 7- day follow-up period after vaccination was tenderness, reported by 97 % of follow-on subjects after the booster dose and by 100 % and 93 % of vaccine-naïve-subjects after the first and second dose, respectively. Severe tenderness was reported by 9 %, 18 % and 5 % of subjects, respectively.

In subjects 8 through 12 years of age, the most common solicited local AE during the 7- day follow-up period after vaccination was injection site pain, reported by 93 % of follow-on subjects after the booster dose and by 96 % and 82 % of vaccine-naïve subjects after the first and second dose, respectively. Severe pain was reported by 13 %, 14 % and 6 % of subjects, respectively.

Most of the solicited local AEs had their onset on day 1 through day 3 and in the majority of subjects they resolved within 7 days of vaccination.

In subjects 4 through 7 years of age, the most common solicited systemic AE during the 7-day follow-up period after vaccination was irritability, reported by 28 % of follow-on subjects after the booster dose and by 29 % and 20 % of vaccine-naïve subjects after the first and second dose, respectively. Reactions of severe intensity, if they occurred, were reported by a maximum of 3 % of subjects. Fever was reported by 6 % of follow-on subjects after the booster dose and by 4 % and 5 % of vaccine-naïve subjects after the first and second dose, respectively. No subject 4 through 7 years of age reported body temperature equal or above 40 °C after vaccination.

In subjects 8 through 12 years of age, the most common solicited systemic AE during the 7-day follow-up period after vaccination were malaise and headache, reported by 39 % and 30 % of follow-on subjects after the booster dose and by 14 % and 26 % (malaise) and 31 % and 20 % (headache) of vaccine-naïve subjects after the first and second dose, respectively. Reactions of severe intensity, if they occurred, were reported by a maximum of 4 % of subjects. Fever was reported by 11 % of follow-on subjects after the booster

dose and by 6 % and 2 % of vaccine-naïve subjects after the first and second dose, respectively. No subject 8 through 12 years of age reported body temperature equal or above 40°C after vaccination.

Adolescents – study V72_75

The most common solicited local AE during the 7-day follow-up period after vaccination was pain, reported by 98 % of follow-on subjects after booster dose, 98 % of vaccine-naïve subjects after the first dose, and 91 % of vaccine-naïve subjects after the second dose. Severe pain was reported by 27 % of follow-on subjects and in 19 % and 13 % of vaccine-naive subjects after the first and second dose, respectively.

Most of the reported solicited local AEs after either dose of vaccine were mild to moderate in intensity with onset 6 hours to day 3 after vaccination. In the follow-on subjects most of the solicited local AEs resolved within 7 days. In the vaccine-naïve subjects, pain (after the first dose), induration (after the second dose), and swelling (after each dose) continued past 7 days of the dose in majority (>50 %) of the subjects.

The most common solicited systemic AE was fatigue, reported by 58 % of follow-on subjects after the booster dose, 44 % of vaccine-naïve subjects after the first dose, and 37 % vaccine-naïve subjects after the second dose. This was followed by headache, reported by 55 % of follow-on subjects after the booster dose and 37 % and 34 % of vaccine-naïve subjects after the first and second dose, respectively. Severe fatigue was reported by 10 % of follow-on subjects and in 5 % (first dose) and 6 % (second dose) of

vaccine-naïve subjects, while severe headache was reported by 7 % of follow-on subjects and 4 % and 5 % vaccine-naïve subjects after the first and second dose, respectively.

Unsolicited adverse events

Children (V72_28E1):

In subjects 4 through 7 years of age, the percentages of subjects reporting unsolicited AEs within 30 days of vaccination were 28 % for follow-on subjects after booster dose and 25 % after both first and second vaccination for vaccine-naïve subjects.

The most commonly affected system organ classes (SOCs) were 'general disorders and administration site conditions' and 'infections and infestations' both in follow-on subjects after the booster dose (both 9 %) and in vaccine-naïve subjects after the first (11 % and 13 %) and second (9 % and 15 %) vaccinations.

The number of subjects with at least possibly related unsolicited AEs were 19 % in follow-on subjects after the booster and 11 % and 9 % in vaccine-naive subjects after the first and second vaccination, respectively. The most common possibly or probably related unsolicited AE by preferred term (PT) were injection site induration and injection site swelling (i.e., local reactions persisting beyond day 7), which were reported in 6 % and 3 % of follow-on subjects after booster, respectively, and in 4 % and 5 % of vaccine-naïve-subjects after the first and second vaccinations, respectively.

In subjects 8 through 12 years of age, the percentages of subjects reporting unsolicited AEs within 30 days of vaccination were similar between the groups of follow-on subjects receiving the booster dose (15 %) and vaccine-naïve subjects (16 % and 14 % after the first and second vaccination, respectively). The most commonly affected SOC was 'general disorders and administration site conditions' in both follow-on subjects after the booster dose (12 %) and in vaccine-naïve subjects after the first (12 %) and second (6 %) vaccinations, respectively. The SOC 'infections and infestations' was also reported in 6 % of subjects after the second vaccination in vaccine- naïve subjects.

The number of subjects with at least possibly related unsolicited AEs were 12 % in follow-on subjects after the booster dose and 10 % and 6 % in vaccine-naïve subjects after the first and second vaccination, respectively. The most common possibly or probably related unsolicited AEs by PT were injection site induration and injection site swelling (i.e., solicited local reactions persisting beyond day 7) reported in 7 % and 8 % of follow-on subjects after booster, respectively, and in 6 % (both) of vaccine-naïve subjects after the first vaccination and 4 % and 2 % of vaccine-naïve subjects after the second vaccination, respectively.

Most of the unsolicited AEs, regardless of vaccine relatedness and those assessed by the investigator as possibly or probably related, were mild to moderate in intensity.

Adolescents (V72_75):

Within comparable reporting periods (30 days after a single dose), the percentages of subjects reporting unsolicited AEs were similar between the groups (32 % of follow-on and 38 % of vaccine-naïve subjects). In the group of vaccine- naïve subjects, 29 % of vaccine-naïve subjects reported unsolicited AEs after the second dose. The most commonly affected SOCs were 'general disorders and administration site conditions' and 'infections and infestations' while the most common unsolicited AE by PT were injection site pain and viral upper respiratory tract infection. Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Within comparable reporting periods (30 days after a single dose), the percentages of subjects with at least possibly related unsolicited AEs were 16 % and 23 % in the follow- on and vaccine-naïve groups, respectively. In the group of vaccine-naïve subjects, 17 % reported at least possibly related unsolicited

AEs after the second dose. The most commonly affected SOC was ‘general disorders and administration site conditions’. The most common at least possibly related AE reported throughout the study after any dose, by PT, was injection site pain. This was mainly owing to solicited AEs that had persisted beyond the 7-day reporting period.

Deaths and other serious adverse events

Children (V72_28E1): No deaths and no SAEs were reported in study V72_28E1. No AEs leading to withdrawal from the study were reported in the children study.

Adolescents (V72_75): No death was reported in the study. One vaccine-naïve subject had an SAE (severe appendicitis) after the first dose that was considered unrelated to the study vaccine by the investigator with the outcome recovered/resolved at the end of the study. No SAEs were reported in the follow-on subjects.

Other significant adverse events

One vaccine-naïve subject in study V72_75, after the first dose had AEs (lymphadenopathy and herpangina) leading to premature withdrawal from the study. Lymphadenopathy was considered by the investigator as possibly related while herpangina was considered unrelated to the study vaccine. The outcome of both AEs of lymphadenopathy and herpangina were reported as recovered/resolved at the end of the study.

Discussion by the MAH

The vaccine formulation was generally well-tolerated following the booster dose in both age categories although, as expected, the reactogenicity was common with solicited AEs reported in the majority of both follow-on and vaccine-naïve subjects.

Children (V72_28E1): In subjects receiving the booster at 4 through 7 years of age, tenderness was the most commonly reported solicited local AE and irritability was the most common systemic solicited AEs. In subjects receiving the booster at 8 through 12 years of age, injection site pain was the most commonly reported solicited local AE, while malaise and headache were the most common systemic solicited AEs. Most of the reported solicited local AEs were mild to moderate in intensity, with onset day 1 through day 3 after vaccination and resolving within 7 days.

The incidence of unsolicited AEs reported was similar between the follow-on and vaccine-naïve subjects after each vaccination. The most commonly affected SOCs were ‘general disorders and administration site conditions’ and ‘infections and infestations’. Injection site induration and swelling were the most commonly occurring AE considered related to the vaccination. Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Adolescents (V72_75): In both follow-on and vaccine-naïve subjects that received the booster, pain was the most common solicited local AE reported, and fatigue and headache were the most common systemic AEs. Most of the reported solicited local AEs were mild to moderate in intensity, with onset 6 hours to day 3 after vaccination and resolving within 7 days.

The incidence of unsolicited AEs reported was similar between the follow-on and vaccine-naïve subjects. The most commonly affected SOCs were ‘general disorders and administration site conditions’ and ‘infections and infestations’ while the most common unsolicited AE by PT were injection site pain and viral upper respiratory tract infection. Injection site pain was the most commonly occurring AE considered at least possibly related to the vaccination. Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Overall, the safety profile following a third/booster dose in both V72_28E1 and V72_75 studies was comparable with that of a 2-dose primary series in age-matched vaccine-naïve children and adolescents, aligned with what has been reported previously for subjects in these age categories and already described in the current PI. No new clinical concerns were raised with respect to the safety data available in these 2 studies.

The current Periodic Benefit Risk Evaluation Report (PBRER, dated 14 March 2018) documents safety information of rMenB+OMV NZ collected through post-marketing surveillance from launch up to the data lock-point of 13 January 2018. A total of 21.071.640 doses of rMenB+OMV NZ have been distributed worldwide since launch. As the vaccination schedule vary between 2 and 4 doses per subject in accordance with local recommendations, subject exposure can be estimated to be between 5.267.910 and 10.535.820. Since market launch, no actions were taken for safety reasons concerning withdrawal, rejection, suspension or failure to obtain a renewal of a Marketing Authorisation.

7.3. Discussion

Of note, the submitted studies have been assessed in previous submission (see Chapter 2.). The safety profile is aligned with what has been reported previously for subjects in these age categories following a 2-dose primary series. Overall, no new clinical concerns were raised with respect to the available safety data.

7.4. Conclusion

In conclusion, studies V72_28E1 and V72_75 describe the persistence of antibodies and the responses to a third (booster) dose in children 4 through 12 years of age and in adolescents and young adults who received a 2-dose primary series of rMenB+OMV NZ.

Immunogenicity data obtained at 24 to 36 months or at 4.5 to 7 years after completion of a 2-dose primary schedule of rMenB+OMV NZ in children and adolescents, respectively, show a decrease in bactericidal antibody levels against all strains considered. The antibody titers were, nevertheless, higher among follow-on subjects compared with the baseline antibody levels in age-matched vaccine-naïve subjects.

The administration of a third (booster) dose of rMenB+OMV NZ in subjects previously primed with 2 doses of rMenB+OMV NZ vaccine induced an immune response, with higher increase of hSBA GMTs, compared with the response to a first dose of rMenB+OMV NZ vaccine in vaccine-naïve subjects of similar age. The anamnestic response to booster dose indicates that despite a decline of bactericidal antibodies over time, previous 2-dose vaccination with rMenB+OMV NZ resulted in effective priming.

The results demonstrate the benefits of an additional booster dose, with no change in the previously described safety profile in these age categories.

The MAH proposes that the assessment of the need and timing of the booster dose in children, adolescents and young adults at continued risk of exposure to meningococcal disease should be based on national health authority recommendations.

The safety profile is aligned with what has been reported previously following a 2-dose primary series. Overall, no new clinical concerns have been raised.

It can be concluded that the data adequately supports the proposed changes, which are acceptable. The benefit–risk profile for rMenB+OMV NZ remains favorable following the review of the available data.

8. Changes to the Product Information

As a result of this variation, Sections 4.2 and 5.1 of the SmPC are being updated to:

- include a recommendation to consider a booster dose in individuals at continued risk of exposure to meningococcal disease, based on official recommendations, and
- include updates on immunogenicity and persistence of antibodies and in particular the response to a booster dose.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.