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[redacted]
Risk & Policy Advisor
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Ref: H201806359

Dear [redacted]

Response to your request for official information

I refer to your request of 17 September 2018 under the Official Information Act 1982 (the Act) for:

> *"Can I please have copies of these documents:*
> *3.2.1 Bexsero (recombinant Meningococcal group B vaccine) RMP*
> *1. Risk Management Plan for Bexsero - version 4.0*
> *2. Medsafe clinical assessment report."*

I note that on 20 September we emailed to inform you that we would be responding to OIA request H201806398 for "*Can I have copies of any clinical assessments regarding effectiveness that Medsafe has?*" under this request, as this response will cover the one clinical assessment document held.

The information relating to this request is itemised below, with copies of documents attached. Some of the information you have requested will soon be in the public domain. Please see the table below for details.

Request	**Decision under OIA**
1. Risk Management Plan for Bexsero - version 4.0	This part of your request is refused under section 18(d) of the Act, as this document is publicly available at the following link: http://www.medsafe.govt.nz/committees/marc/reports/174-Bexsero%20(recombinant%20Meningococcal%20group%20B%20vaccine)%20RMP_Redacted.pdf. The redacted sections are withheld under section 9(2)(ba)(i) of the Act in order to protect information which is subject to an obligation of confidence. The making available of this information would likely prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied.
2. Medsafe clinical assessment report	Please see Attachment 1. This document is released in full.

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review my decision to withhold information under this request.

Please note this response (with your personal details removed) may be published on the Ministry of Health website.

Yours sincerely

[redacted]

Group Manager
Medsafe

ATTACHMENT 1

MEDICAL ADVISOR REPORT

TT50-10296

I.1 Type

NMA (abbreviated)

I.2 Medication

BEXSERO Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed) 0.5 mL suspension for injection.

In this evaluation, rMenB+OMV NZ (4-component MenB) as well as "4CMenB" are used as the name for the Bexsero vaccine.

I.2.1 Classification

If approved, Bexsero would, as are all meningococcal vaccines, be available through prescription, and through administration by an approved pharmacist (to a person 16 years of age or over). The primary aim of this classification was to reduce the incidence, morbidity, and mortality from meningococcal invasive disease, primarily in at-risk adolescents, by increasing access to the vaccine.

(An application for the reclassification of Meningococcal vaccine was considered at the 49th MCC meeting on 17 June 2013 and the 50th meeting on 12 and 13 November 2013, for the prevention of invasive meningococcal disease in people aged 16 years and older.)

Evaluator's comment

It is possible, that at times the Bexsero vaccine would be used for regional or national immunisation programmes targeted to adolescents. In those circumstances, the benefit risk balance of the vaccine would have been duly considered, and administration by approved pharmacist could be appropriate. In that circumstance, the need for (increased) access to the Bexsero vaccine would be similar to that for currently available meningococcal vaccines.

It could be argued that, when the vaccine is considered for use in an infant or toddler, or is intended for use sporadically and not part of an immunisation programme, pharmacist administration is less appropriate as there are multiple factors that have to be considered in deciding for meningococcal B vaccination.

- *The benefit risk is influenced by the changing epidemiology of meningococcal disease, with currently a high proportion of disease due to serotype B.*
- *For infants and toddlers, the likely limited duration of protection has to be taken into account, together with the risk of disease being highest in the very young.*
- *For infants and toddlers, the use of prophylactic paracetamol should be explained.*

The vaccine may in future be funded for groups at risk, and is currently recommended for consideration, for example for those about to go into student hostel accommodation.

- *The recommendation of vaccination may arise out of healthcare for a particular condition. For example, meningococcal C vaccines are currently funded for people aged 12 months to under 18 years when diagnosed with functional asplenia or pre-a or post-splenectomy.*
- *Although not funded, the Immunisation Handbook notes that meningococcal vaccination should be considered for adolescents and young adults living, or planning to live, in communal accommodation such as a hostel, student accommodation,*

boarding school, in military accommodation, in correctional facilities or in other long-term institutions are likely to be at higher risk of acquiring meningococcal infection.

- *The relatively high reactogenicity, when given together with other vaccines, should be noted.*

I.3 Manufacturer

GSK

I.4 Background

BEXSERO has been approved in Australia (August 2013), Europe (January 2013), USA (January 2015), Canada (December 2013) and other countries worldwide.

The vaccine has been introduced to the UK schedule in September 2015.

During the EU assessment, three issues identified included the need to set clinically qualified specification limits for the in-vivo immunogenicity assay.

Characterisation of rMenB+OMV NZ vaccine

The current vaccine formulation (referred to as rMenB+OMV NZ, i.e., Novartis recombinant Meningococcal B vaccine with the OMV derived from New Zealand strain) is based on the following four proteins as antigens:

i) factor H binding protein (fHBP). To increase the potency of the immune response and to facilitate large-scale vaccine manufacturing, the fHBP protein has been combined with the accessory protein GNA2091 (936) to create a fusion protein.

ii) Neisserial adhesin A (NadA) and

iii) Neisserial Heparin Binding Antigen (NHBA)/ 287 combined with GNA1030 (953), to create the second fusion protein (referred to as NHBA)

iv) OMV NZ refers to the OMV derived from the New Zealand epidemic strain.

Vaccine Strain Coverage

To classify invasive N. meningitidis isolates according to the expression and variability of protein antigens that are contained in the rMenB+OMV NZ vaccine, Novartis has developed a new ELISA typing method called the Meningococcal Antigen Typing System (MATS).

MATS serves as a predictive model of vaccine strain coverage.

In Europe, Novartis has defined the potential effectiveness of the rMenB+OMV NZ vaccine using a representative subset of the meningococcal strains provided by five European reference laboratories, and agreed upon with the European Centre for Disease Prevention and Control (ECDC) and European regulators. The collection consists of 1052 invasive meningococcal disease strains isolated during the 2007-2008 epidemiologic year. Almost two-thirds of the total meningococcal serogroup B cases reported in European countries in 2006 occurred in these five countries (UK, Norway, Germany, France, and Italy).

Depending on the country of origin, between 73% and 87% of meningococcal serogroup B isolates had an appropriate MATS antigen type to be covered by the vaccine.

Strains in Australia

The application includes: Attachment 2.7.2 MATS Analysis of Australian MenB. Analysis of Australian data (provided by the Reference Laboratories of the different Australian States and

Territories) used MATS for MenB strains specimens isolated during the period January 2007-December 2011, for a total of 520 strains.

Of the 520 strains evaluated, 132 (25.4%) are not predicted to be covered. Importantly, of the 388 strains deemed covered by 4CMenB immune sera, roughly half (191) are covered by more than a single vaccine antigen.

MATS coverage was mostly associated with the presence of the following antigens above the MATS Positive Bactericidal Threshold (PBT): NHBA only (21.9%), fHbp and NHBA (17.1%), fHbp only (15.0%), or the combination PorA + fHbp + NHBA (13.1%), as presented in Table 1.

Table 1 Coverage by Antigen Combination (out of 520 strains total)

Antigen Combination	Number of Strains	Percentage
No Antigen	132	25.4%
fHbp	78	15.0%
NHBA	114	21.9%
PorA	5	1.0%
fHbp+NadA	2	0.4%
fHbp+NHBA	89	17.1%
PorA+fHbp	11	2.1%
PorA+ NHBA	21	4.0%
PorA+fHbp+NHBA	68	13.1%

Evaluator's comment

As noted in the application, the bulk of strain coverage was conferred primarily by the fHbp and NHBA vaccine antigens, either singly or in combination with other antigens.

Isolates with solely PorA strain identification was uncommon (1%), implying that for the about 75% of total strains expected to be covered, the issue of lack of persistence of protection to PorA, was not a major issue.

MATS uses positive bactericidal thresholds for minimum levels of the antigens (NHBA, fHbp, and PorA) to predict what the serum bactericidal assay would show. MATS uses pooled serum data. The Parikh article (see Appendix below) notes that there are uncertainties surrounding MATS for predicting killing of specific meningococcal group B strains. For example, some high NHba-expressing strains are resistant to anti-NHba antibodies elicited by Brexsero, but are included in MATS.

When the 319 MenB strains for which subject ages were available were stratified into five age groups, a comparison of point estimates did not identify any significant difference among the age groups when either coverage by at least one or at least two antigens was considered.

I.5 Indication

From datasheet:

> BEXSERO is indicated for active immunisation against invasive disease caused by N. meningitidis group B strains. See section 5.1 for information on protection against specific group B strains.
>
> BEXSERO is indicated for vaccination of individuals from 2 months of age and older.

The use of BEXSERO should be in accordance with official recommendations.

Evaluator's comment

The proposed datasheet refers to the Pharmacodynamic properties section regarding protection against specific strains, but does not highlight the need to consider epidemiology.

In addition to the proposed NZ indication, the EU SPC includes under Therapeutic Indications:

> The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating. See section 5.1 for information on protection against specific group B strains.

The US package insert has under indications that:

> Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States.

The evaluator had (initially) considered asking the Sponsor for a revised datasheet that should include in the indications section, text similar to that, for example, given below. However, although it reflects information provided by some regulators, the evaluator considered that this information was not the highest priority to add to the draft New Zealand datasheet. Although the proposed first paragraph refers to epidemiology of the various group B strains, this information does not currently appear to be available for New Zealand. The second paragraph could suggest that the vaccine strains are based on out-dated data, whereas the slow evolution of meningococcal strains suggests that the international information regarding prevalent strains is relevant to New Zealand.

> The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating.
>
> Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent MenB strains specimens isolated in Australia (during the period January 2007- December 2011), England and the US.

The datasheet explains that the vaccine is given by deep intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older subjects.

The **dosage section** specifies that for infants 2 months to 5 months of age at time of first dose, three doses, with not less than 1 month between doses. A booster [that is, a fourth] dose (at least 6 months after primary course) is recommended in the second year of life.

Infants 6 months to 11 months of age at the time of the first dose, two doses not less than 2 months apart. A booster dose (at least 2 months after primary course) is recommended in the second year of life.

For children from 12 months, two doses at least 2 months apart. Need for booster not established. For adolescents and adults from 11 years of age at the time of the first dose. Two doses at least 1 month apart.

Evaluator's comment

The indication does not specify strain details, but refers to section 5.1 for this information.

The **5.1 Pharmacodynamic properties** section includes, among other information, that:

> Immunisation with BEXSERO is intended to stimulate the production of bactericidal antibodies against the vaccine antigens (NHBA, NadA, fHBP, and PorA P1.4 (the immunodominant antigen present in the OMV component).
>
> The efficacy of BEXSERO has been inferred by measuring bactericidal antibody responses to each of the vaccine antigens NadA, fHBP, NHBA and PorA P1.4, using a set of four meningococcal group B reference strains (5/99, H44/76, M10713 and NZ98/254).

Evaluator's comment

A more limited indication is approved in the US:

> BEXSERO® is a vaccine indicated for active immunization to prevent invasive disease caused 3 by Neisseria meningitidis serogroup B. BEXSERO is approved for use in individuals 10 4 through 25 years of age.

The dose schedule is as follows:

> Administer two doses (0.5 mL each) of BEXSERO at least 1 month apart.

In the EU; from 2 months of age and older. In Canada; from 2 months through 17 years old. In Australia; from 2 months of age and older.

Evaluator's comment – PI information on persistence of protection

The Australian PI, upon which the draft New Zealand datasheet is based, variously notes the need for a booster dose although for some age groups it is noted that: "The need for a booster dose after this vaccination schedule has not been established." It could be argued that guidance about relative need for additional boosters is lacking, in light of datasheet information about persistence of antibodies against at least some of the antigens.

However, the PI does include Table 2 with persistence of bactericidal antibody one year after the booster (Study V72P13E2), showing 17% for PorA P1.4, and 36% for NHBA. These data apply to subjects who as infants received the 2, 4 and 6 month regimen plus a 12 months of age booster.

In addition; Data [again from Study V72P13E2] on antibody persistence one year after the two doses at 13 and 15 months of age are summarized in Table 3. This shows 18% for PorA P1.4, and 38% for NHBA.

For those aged from 11 years who have received two doses, the table shows that at least one-and-a-half year after the second dose, at least 81% were seropositive for fHBP, 93% for NadA, 75% for PorA P1.4, and 100% for NHBA. The PI text is as follows:

> *Two dose primary schedule – from 11 years*
>
> Participants aged 11 to 17 years (study V72P10) received two doses of BEXSERO with a 1, 2 or 6 month interval between doses. Baseline GMTs ranged from 2.64 to 4.11. As early as one month after the first dose, percentages of participants who achieved an hSBA ≥ 1:4 ranged from 90% to 97%.
>
> Antibody persistence was demonstrated 18 - 23 months after the second dose. (see Table 4). Independent of pre-vaccination seropositivity status, a high

percentage of participants were seropositive and achieved 4-fold increases in hSBA titres post vaccination (see Table 5).

I.5.1 ACIP recommendations

The Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine — Advisory Committee on Immunization Practices, 2016 (Weekly / May 19, 2017 / 66(19);509–513) includes the following.

> Two serogroup B meningococcal (MenB) vaccines are currently licensed for use in persons aged 10–25 years in the United States. The two vaccines are MenB-FHbp (Trumenba, Pfizer, Inc.) (1) and MenB-4C (Bexsero, GlaxoSmithKline Biologicals, Inc.) (2).
>
> In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended use of MenB vaccines among certain groups of persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease* (Category A) (3), and in June 2015, ACIP recommended that adolescents and young adults aged 16–23 years may be vaccinated with MenB vaccines to provide short-term protection against most strains of serogroup B meningococcal disease (Category B†)
>
> *Evaluator's comment*
>
> *In the context of the two available MenB vaccines, ACIP recommended that MenB vaccination may be used for those 16 to 23 years of age for short-term protection against most strains causing disease.*

The updated ACIP recommendations are as follows:

> **Persons aged ≥10 years at increased risk for serogroup B meningococcal disease (Category A recommendation).**
>
> For persons at increased risk for meningococcal disease and for use during serogroup B meningococcal disease outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1–2, and 6 months to provide earlier protection and maximize short-term immunogenicity. However, if the second dose of MenB-FHbp is administered at an interval of ≥6 months, a third dose does not need to be administered.
>
> **Adolescents and young adults aged 16–23 years (Category B recommendation).**
>
> When given to healthy adolescents who are not at increased risk for meningococcal disease, 2 doses of MenB-FHbp should be administered at 0 and 6 months. If the second dose of MenB-FHbp is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.

https://www.cdc.gov/mmwr/volumes/66/wr/mm6619a6.htm

> *Evaluator's comment*
>
> *The updated ACIP recommendations for those 16 to 23 years of age includes a two-dose regimen, if the vaccination interval is 6 months or more.*

I.6 Supporting documentation

In support of this application, the sponsor has provided the full submission as provided to the TGA, plus associated TGA assessment reports.

M1, 2 and M5.

There are multiple Clinical Overview documents.

A 22 page addendum to the 2.5-Clinical overview summarizes the main results from three studies with rMenB+OMV NZ, V72P6E1, V72P10E1, and study V72_41, for which the data became available after marketing authorization application submission in Europe (Overview addendum is dated January 2014).

I.6.1 Pharmacodynamics

Vaccine Antigens:

NadA - Neisseria adhesin A (NadA)

NadA is included in the vaccine as a single recombinant protein derived from MenB strain 2996. The NadA vaccine antigen is also referred to by the company code 961c

Neisserial Heparin Binding Antigen (NHBA) fusion protein

NHBA, derived from MenB strain NZ98/254, is included in the vaccine as recombinant protein which is fused with accessory protein coded 953, derived from MenB strain 2996.

NHBA, as an individual recombinant protein, has also been referred to by the company code 287. The 287 and 953 recombinant protein antigens are also known in publications as GNA2132 and GNA1030, respectively (GNA [genome-derived neisserial antigen]). Based on these terminologies, the NHBA recombinant fusion protein has been previously referred to as 287-953 or GNA2132-1030. For this application, the recombinant fusion protein will be referred to as NHBA, as this portion of the fusion protein is the primary inducer of bactericidal antibodies

PorA P1.4

PorA P1.4 is the immunodominant protein antigen contained in the outer membrane vesicle derived from MenB strain NZ98/254 (OMV NZ). PorA P1.4 is the main target for bactericidal antibodies generated after immunization with OMV NZ

fHBP - factor H binding protein

fHBP, derived from MenB strain MC58, is included in the vaccine as a recombinant protein which is fused with accessory protein coded 936, derived from MenB strain 2996.

fHBP, as an individual recombinant protein, has also been referred to by the company code 741.

The 936 and 741 recombinant protein antigens are also known in the literature as GNA2091 and GNA1870, respectively (GNA [genome-derived neisserial antigen]). Based on these terminologies, the fHBP recombinant fusion protein has been previously referred to as 936-741 or GNA2091-1870

For this application, the recombinant fusion protein will be referred to as fHBP, as this portion of the fusion protein is the primary inducer of bactericidal antibodies

The vaccine formulation also includes aluminium hydroxide adjuvant (1.5 mg/0.5mL, corresponding to 0.5mg/0.5mL of Al3+.

The total amount of recombinant protein (150 μ g) is within the range of other registered vaccines, and dose escalation would likely require an increase in aluminium hydroxide adjuvant content. Aluminium in the current formulation is already at the high limit of other licensed aluminium containing vaccines.

Thus, any further increase would likely render a significantly more reactogenic formulation. Most importantly, clinical immunogenicity observations suggest that the dose selected was sufficient to prime young infants for a good booster response and support the recommended dose of the proteins for the rMenB+OMV NZ vaccine

Immunogenicity endpoints

Serum bactericidal antibody (SBA) measures the level of antibodies that recognize bacterial surface antigens and are capable of directing complement-mediated bacterial lysis.

Although many factors influence SBA performance, among which are the source of complement (rabbit versus human) and the laboratory, the serum bactericidal assay using human complement (hSBA) remains the method of choice in these studies.

The primary endpoint of studies contained within this dossier is to determine the proportion of subjects with hSBA titers equal to or above the threshold of 1:4 against each of the three reference meningococcal serogroup B strains.

The use of this threshold is based on the work by Goldschneider showing that a naturally acquired serum bactericidal antibody titer of ≥1:4 (by SBA using endogenous human complement) provided protection against serogroup C among young adults. In addition efficacy data from the Norwegian OMV vaccine trials suggesting that hSBA titers ≥1:4 correlate with clinical efficacy further supports the use of serum bactericidal antibody as an appropriate surrogate marker for protection against disease caused by meningococcal serogroup B. In response to a request for Scientific Advice, the EU CHMP agreed that a serum bactericidal antibody titer ≥1:4 was an appropriate correlate of protection.

In the phase 2b and 3 studies, the threshold was set to a more conservative 1:5 as this ensures with 95% confidence that subjects with a titer of 1:5 or greater will have achieved a titer of at least 1:4. This was based on a validation of the Novartis hSBA that has shown that the lower limit of the two-sided 95% confidence interval for a titer of 1:5 is a titer of 1:4, using linear interpolated hSBA titers.

In all studies, serum samples for immunogenicity evaluation were taken at baseline (i.e., before receiving vaccination) and at least at one month after the primary course vaccination.

Reference strains

"Reference strains" (i.e., virulent strains isolated from cases of invasive disease and each uniquely susceptible to killing by serum bactericidal antibodies directed primarily against only one of the three vaccine antigens) were used in all the studies that followed.

- Strain 44/76 tests for antigen for that induced by the vaccine's **fHBP** antigen, and
- Strain 5/99 for that of **NadA**.
- [Not noted in the initial application listing of strains, but a later identified reference strain noted in a recent article, the presence of antibodies against the **NHBA antigen** can be assessed using strain M10713. This strain was also tested for in the post-approval commitment study V72_62.]
- Strain NZ98/254 assesses bactericidal antibodies induced by the immunodominant **PorA1.4 antigen in the OMV NZ.**

M10713	NHBA
44/76	fHBP
5/99	NadA
NZ98/254	PorA1.4

No evidence of impact on carriage

Although there are various studies available, from a brief perusal of the literature, the evaluator could not locate a study that claims to have firm evidence for an impact of 4CMenB vaccination on carriage of that strain. The word carriage does not occur in the draft New Zealand datasheet.

I.6.2 Vaccine development

First Vaccine Formulation and Selection of OMV for Inclusion in the Vaccine

Studies V72P1, V72P1E1, V72P2 and V72P3 were Phase 1 and 2 trials conducted in healthy adults and adolescents (V72P3).

These studies investigated immune response to the first vaccine formulation (referred to as rMenB) containing the three recombinant meningococcal proteins, i.e., 961c or NadA, fusion antigens 287-953 or NHBA and 936- 741 or fHBP, with or without OMV derived from the Norwegian strain 44/76 (OMV NW).

In these studies rMenB or rMenB+OMV NW were administered according to a 0, 1, 2, 6-month schedule (V72P1 and V72P2) or to a 0, 2, 6 month schedule (V72P2 and V72P3). In the extension study V72P1E1 a 5th dose was given 12 months after the last vaccination of the parent study.

There was a general trend towards a higher immune response in the rMenB+OMV NW groups compared with the rMenB groups although this was accompanied by slightly higher reactogenicity, especially in adolescents.

Study V72P5 was the first to evaluate safety and immunogenicity of the final vaccine formulation containing the three recombinant proteins with OMV purified from N. meningitidis serogroup B New Zealand strain NZ98/254 (i.e., rMenB+OMV NZ). Healthy adults 18 to 40 years of age received, according to a 0, 1, 2-month schedule, three doses of either:

- rMenB+OMV NZ
- rMenB OMV NW or
- rMenB.

Although all three vaccines were immunogenic with similar safety profiles, the immune response against hypervirulent ST-41/44 complex/lineage III strains was higher in the rMenB+OMV NZ group. Therefore this formulation was selected for further clinical development based on:

1) evidence of enhanced coverage against the hypervirulent ST-41/44 complex/lineage III strains,

2) the experience in manufacturing and use in mass vaccination campaigns also in the infant population with Novartis' NZ98/254 OMV-based vaccine, MeNZB, which was shown to be safe and efficacious in the control of the epidemic in New Zealand.

Phase 2 and 3 Studies with rMenB+OMV NZ

A phase 2 clinical trial (**V72P4**) evaluated safety and immunogenicity of rMenB+OMV NZ in at-risk (due to occupational exposure to N. meningitidis) adults aged 18 to 40 years according to a 0, 2, 6-month immunization schedule followed at month 7 by a single dose of Menveo™ (Novartis MenACWY conjugate vaccine). The study confirmed results of V72P5, with high immune responses to rMenB+OMV NZ even after the first vaccination and an overall good safety and acceptable tolerability profile.

rMenB+OMV NZ vaccine in infants

Novartis also conducted two phase 2 clinical studies in this population in the UK to evaluate safety and immunogenicity of rMenB and rMenB+OMV NZ vaccines.

In **study V72P6**, the administration of these vaccines was integrated within the routine infant vaccination schedule in the UK as all subjects were also to receive the recommended UK routine infant vaccinations.

In this study infants received rMenB or rMenB+OMV NZ at 2, 4, 6, and 12 months of age concomitantly (only at 2, 4 and 12 months) with UK-recommended routine infant vaccines or a single dose of rMenB or rMenB+OMV NZ at 12 months of age after having received UK-recommended routine vaccinations.

After two doses of rMenB+OMV NZ there was a good bactericidal response against N. meningitides reference strains (44/76, 5/99 and NZ98/254 with a further increase after the third vaccination.

In study V72P6, SBA responses at 6 months after the third vaccination showed a decline of GMTs against the three indicator strains, with GMTs against strain NZ98/254 being the lowest, as similarly reported for MeNZB. Results of this small study suggested that three doses of the multicomponent rMenB+OMV NZ vaccine would be required to elicit adequate immune responses to the PorA antigen and so to all three vaccine components: two doses would only produce a weak response against the NZ98/254 strain. That is, bactericidal antibodies at 6 months after the third dose declined in particular for strain NZ98/254 (PorA P1.4) but a robust booster response was observed after the fourth dose at 12 months of age.

Both vaccines showed similar safety profiles comparable to that of the routine vaccines (e.g. Prevenar™), with the exception of fever, which was more common for rMenB+OMV NZ with routine vaccines than for rMenB with routine vaccines and for the routine vaccines.

Study **V72P9** was a phase 2 study conducted in the UK in 60 infants aged 6-8 months at entry. The study evaluated safety and immunogenicity of 3 doses of either rMenB or rMenB+OMV NZ given according to a 3-dose schedule in older infants aged 6 to 8 months at enrollment (at 6-8, 8-10, and 12 months of age).

High immune responses to all three reference strains were observed at one month after both the second and the third vaccinations with rMenB+OMV NZ.

Similar to the results of study V72P6 both vaccines showed a good tolerability profile and this study confirmed the increased mild and transient fever for rMenB+OMV NZ compared to rMenB.

A 2-dose schedule administered at least 2-months apart followed by a booster dose in the second year of life (at least 2 months after the last primary vaccination) is proposed for use in unvaccinated older infants between 6 and 11 months of age based on the results of study V72P9.

The infants program continued with a phase 2b **study (V72P12)** in multiple European countries evaluating two alternative 3-dose schedules for rMenB+OMV NZ given with concomitant routine vaccines (Infanrix Hexa™ and Prevenar) at 2, 4, 6 or 2, 3, 4 months of age to adapt to commonly used routine schedules in EU countries.

The decision had been made at this time to proceed with the rMenB formulation which included the OMV NZ component. Additionally a control group received routine vaccines alone at 2, 3, 4 months and another was given rMenB+OMV NZ at 2, 4, 6 and routine vaccinations at 3, 5, 7 months of age to allow evaluation of immunogenicity and safety profile of the rMenB+OMV NZ vaccine when administered alone or in combination with the routine infants vaccines.

The study was adequately powered to demonstrate 1) sufficient immunogenicity to the three reference strains after 3-doses with the 2, 4, 6 schedule and with the more challenging accelerated 2, 3, 4 schedule and 2) that the immunogenicity of routine infant vaccines when given concomitantly with rMenB+OMV NZ at 2, 3 and 4 months of age was non-inferior to that of routine infant vaccines given alone.

Results from this study suggested that a 3-dose primary schedule either with or without concomitant routine vaccination at 2, 4, 6 months of age is able to elicit a robust immune response to all three reference strains with an acceptable safety profile.

In addition, a sufficient immunogenicity to all three reference strains and no clinically relevant interference on the immune response to concomitant vaccines antigens was observed in the more challenging accelerated 2,3,4 schedule while the safety profile was similar to that observed with the 2,4,6 schedule.

Fever rates for rMenB+OMV NZ given alone were lower than when concomitantly administered with routine vaccines and rates were comparable to the rates observed for the concomitant vaccines given alone.

An overview of the studies included in the clinical development program are summarized in Table 2.5.1-5.

Table 2.5.1-5 Studies in the Clinical Development for the Meningitis B Vaccine

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
Early Vaccine Formulation	1	V72P1 US 2004/05	19-40y (0,1,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB	15 13
		V72P1E1	Booster 12 months after last vacc in P1		rMenB+OMV (NW) rMenB	7 7
		V72P2 US 2004/06	19-40y (0,1,2,6 or 0,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB Control vaccines (Engerix B for months 0,1,6 and Menomune at month 2)	32 32 14
	2	V72P3 US 2006/07	11-18y (0,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB placebo	79 83 41

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
Final Vaccine Formulation (rMenB+OMV NZ)	1	**V72P5** Switzerland 2006	18-40y (0,1,2[c])	observer blind single center randomized	• rMenB+OMV NZ • rMenB+OMV(NW) • rMenB	28 28 14
	2	**V72P4** Italy, Germany 2007/09	18-50y (0,2,6[c]) (MenACWY at month 7)	open multicenter	• rMenB+OMV NZ	54
		V72P6 UK 2006/08	2 mo (2,4,6,12 or 12 mo)	open multicenter randomized controlled	• rMenB (2,4,6,12) • rMenB+OMV NZ(2,4,6,12) • rMenB (12) • rMenB+OMV NZ (12)	48 50 25 24
		V72P9 UK 2007/08	6-8mo (6,8,12 mo)	Single-blind single-center randomized	• rMenB • rMenB+OMV NZ	30 30
		V72P12[d] Belgium, Italy, Germany, Spain, Czech Republic 2008/10	2mo (2,4,6 or 2,3,4mo)	open multicenter randomized	• rMenB+OMV NZ 2,4,6 or 2,3,4 with concomitant Routine • rMenB+OMV NZ 2,4,6 + Routine (3,5,7) • Routine (2,3,4)	627/318[e] 628 312
	3	**V72P10**[d] Chile 2008/10	(11-17 y) 0; 0,1; 0,2;0,1,2; 0,6; 0,1,6; 0,2,6-mo schedules	observer-blind multicenter randomized controlled	8 vaccine groups injected with different chronologies of rMenB+OMV NZ at study month 0,1,2,6	1631 (placebo)
		V72P13 Italy, Germany, Austria, Czech Republic, Finland 2008/10	2mo (2,4,6 mo)	Partially blinded multicenter randomized controlled	• 3 lots rMenB+OMV NZ with concomitant Routine • Routine • Routine+MenC[f]	2481 659 490
		V72P13E1 Italy, Germany, Austria, Czech Republic, Finland 2009/10	12mo (2 catch up doses at 12, 14 or 13, 15 mo)	Open randomized multicenter extension	Each of the three groups from V72P13 were administered a booster Men at 12 mo and MMRV concomitantly or 1 month afterwards, making 6 groups in total	2249

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
	3	V72P13E2 Czech Republic, Finland	24 months, Booster (or 2 doses, 2 months apart for naive controls, 23-27 Months[g])	Open label Multi-Center Extension Study of V72P13E1	5 vaccine groups: 2 having received 3 doses rMenB+OMV NZ in V72P13 and booster dose in V72P13E1 2 having received routine vaccs in V72P13, 2 catch-up doses of rMenB+OMV NZ in V72P13E1 and booster dose in V72P13E2 1 naive group receiving 2 doses of rMenB+ONV NZ at 24 and 26 months of age[g]	508

[a] y – years; [b] mo – months; [c] schedules are in months; [d]V72P12 is phase 2b; V72P10 is phase 2b/3; [e]N=627 for the 2,4,6 rMenB+OMV NZ with concomitant Infanrix Hexa and Prevenar schedule and N= 318 for the 2,3,4 rMenB+OMV NZ with concomitant Infanrix Hexa and Prevenar schedule; [f]Menjugate, Novartis meningococcal C conjugate vaccine; [g] Results for this group not yet available. Note: the manufacturing lot numbers for rMenB+OMV NZ used in these studies are detailed in section 5.2

I.7 Efficacy

The Clinical Overview explains that there are no differences between the to-be-marketed rMenB+OMV NZ vaccine formulation and that used in phase 2b and phase 3 clinical trials.

The proposed primary (infant) vaccination schedule of three doses in infants, administered at least one month apart, is based on the data generated from two large phase 3 studies: **V72P12** (N=1885), **V72P13** (N=3,630) and one phase 2 study: **V72P16** (N=372).

Three doses at least 1 month apart in young infants with or without concomitant routine infant vaccines

A three-dose primary schedule for rMenB+OMV NZ administered with (studies V72P12, V72P13, and V72P16) and without (study V72P12) concomitant routine vaccinations (Infanrix Hexa and Prevenar) in infants was investigated.

The three rMenB+OMV NZ doses were administered at 2, 4, 6, months of age (2, 4, 6 schedule) or at 2, 3, 4 months of age (2, 3, 4 schedule) to offer more flexibility in the indication and in the vaccine utilization.

Immune responses to three doses of rMenB+OMV NZ administered at 2, 4, 6 months with or without concomitant routine vaccinations (in the latter group routine vaccinations were given non concomitantly at 3, 5, 7 months) as measured at one month after the third rMenB+OMV NZ vaccination are presented in Table 2.5.4.4-2 (study V72P12).

The response at one month after the 3rd rMenB+OMV NZ dose as assessed based on hSBA GMTs and percentage of subjects achieving a hSBA ≥1:5 was remarkably similar across studies for subjects receiving a 2, 4, 6 schedule regardless of concomitant routine vaccinations (Table 2.5.4.4-2, first three columns). Subjects with a hSBA ≥1:5 were 100% for strain H44/76, ranged from 99% to 100% for strain 5/99, and from 79% to 87% for strain NZ98/254. Antibody titers to the NHBA vaccine antigen were also high as measured by ELISA GMCs in both infant studies.

Consistent with this, 84% of the subjects from study V72P13 tested by hSBA against the newly identified indicator strain (M10713) for the NHBA vaccine antigen showed a titer ≥1:5 (Table 2.5.4.4-2).

Additionally, a three-dose schedule for rMenB+OMV NZ administered at 2, 3, 4 months of age concomitantly with routine vaccination was investigated in studies V72P12 and V72P16 to provide useful additional safety and immunogenicity data for this schedule which some countries use in their routine infant vaccination programs.

Table 2.5.4.4-2 Immune Responses to rMenB+OMV NZ After a Three-dose Primary Schedule in Infants from 2 Months of Age With and Without Concomitant Routine Infant Vaccines – (PP population)

		V72P13	V72P12			V72P16		
Indicator Strain (Antigen)		2,4,6 with concomitant routine vaccinations	2,4,6 with concomitant routine vaccinations	2,4,6 with 3,5,7 routine vaccinations (non concomitant)	2,3,4 with concomitant routine vaccinations	2,3,4 with concomitant routine vaccinations	2,3,4 with concomitant routine vaccinations+ paracetamol	Vaccine group difference/ratio Paracet+MenB+R vs. MenB+R [a]
H44/76 (fHbp)	% hSBA≥1:5 (95% CI)	100% (99-100) N=1149	100% (99-100) N=525	100% (99-100) N=534	99% (97-100) N=273	100% (98-100) N=170	100% (98-100) N=167	0% (-2-2)
	hSBA GMT (95%CI)	91 (87-95) N=1149	86 (80-92) N=525	113 (105-121) N=534	82 (75-91) N=273	101 (90-113) N=170	102 (91-115) N=167	1.02 (0.87-1.18)
5/99 (NadA)	% hSBA≥1:5 (95% CI)	100% (99-100) N=1152	100% (99-100) N=527	99% (98-100) N=529	100% (99-100) N=275	99% (97-100) N=165	99% [a] (97-100) N=160	0% (-3-3)
	hSBA GMT (95%CI)	635 (606-665) N=1152	537 (494-584) N=527	699 (643-759) N=529	325 (293-362) N=275	396 (348-450) N=165	455 (399-519) N=160	1.15 (0.96-1.37)
NZ98/254 (P0rA P1.4)	% hSBA≥1:5 (95% CI)	84% (82-86) N=1152	79% (76-83) N=530	87% (84-90) N=534	81% (76-86) N=274	78% (71-84) N=171	74% [a] (67-81) N=168	-4% (-13-5)
	hSBA GMT (95%CI)	14 (13-15) N=1152	12 (11-14) N=530	18 (16-20) N=534	11 (9.14-12) N=274	10 (8.59-12) N=171	8.48 (7.24-9.93) N=168	0.85 (0.68-1.05)
Anti NHBA (287-953)	ELISA GMC (95%CI)	3370 (3270-3472) N=1823	3327 (3115-3553) N=545	4244 (3978-4527) N=557	3254 (2988-3545) N=281	3562 (3161-4013) N=173	3537 (3129-3997) N=168	-
M10713 (NHBA)	% hSBA≥1:5 (95% CI)	84% (75-91) N=100	-	-	37% (28-46) N=112	43% (26-61) N=35	-	-
	hSBA GMT (95%CI)	16 (13-21) N=100	-	-	3.24 (2.49-4.21) N=112	3.29 (1.85-5.83) N=35	-	-

Source: Seq. 0000, section 5.3.5.1, CSR V72P12, Table 14.2.1.2, Table 14.2.1.5, Table 14.2.1.6; CSR V72P13, Table 14.2.1.1, Table 14.2.1.3, Table 14.2.1.9; Seq. 0005, section 5.3.5.1, CSR V72P16, Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5; Addendum No 2 to CSR V72P12 (available on request) Table 1, Table 6; Seq. 0003, section 5.3.5.1, Addendum 1 to CSR V72P13 Table 1, Table 4; [a]MenB+R= rMenB+OMV NZ concomitantly administered with routine vaccines (InfanrixHexa and Prevenar); Paracet.+MenB+R= paracetamol administered just before or at the same time of rMenB+OMV NZ + routine vaccines followed by two further doses at 4-6 hour intervals.

In study V72P12, a modest bactericidal antibody response was observed to indicator strain M10713 in subjects in the 2, 3, 4 schedule compared with those in the 2, 4, 6 schedule, both when administered with concomitant routine vaccines. The clinical impact of the lower responses following the 2, 3, 4-month schedule as compared with the 2, 4, 6-month regimen is uncertain.

Evaluator's comment

Study V72P12 showed a lesser strain M10713 SBA response to the 2, 3, 4 schedule than to the 2, 4, 6 schedule.

Of note, in study V72P16, prophylactic paracetamol treatment did not impact the immune response to rMenB+OMV NZ antigens as no statistically significant difference was observed for both the percentage of subjects with hSBA ≥ 1:5 and hSBA GMTs and GMRs after primary vaccination course (see Table 2.5.4.4-2 above, last column on the right).

From six months of age

On page 28 of the 162 page TGA Clinical Evaluation Report Rd2 it is noted that studies show that, for subjects as young as six months of age to adolescents and adults, a two dose vaccination schedule shows a consistent and clear outcome of satisfactory immunogenicity.

Other than the general results presented above, this abbreviated evaluation will focus on selected information about the persistence of immunogenicity. The three infant studies noted above are briefly covered below, again with a focus on persistence of immunity.

I.7.1 Early UK and US experience

Early results regarding UK programme

The following from a European Centre for Disease Prevention and Control webpage:

https://ecdc.europa.eu/en/news-events/expert-opinion-meningococcal-b-vaccine-information-and-suggestions-eueea-countries

Results from the UK, where the vaccine was introduced in the national immunisation programme in a two-dose priming schedule in September 2015, estimate that two-dose 4CMenB vaccine effectiveness was 82.9% against all SgB IMD cases. The incidence of vaccine-eligible MenB cases was compared with cases diagnosed in the equivalent time period during the four years before vaccine introduction. Cases in vaccine-eligible infants halved in the first 10 months of the programme [Parikh SR, Andrews NJ, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet. 2016 Dec 03;388(10061):2775-82.]

In addition, ECDC expert opinion provides information supporting the introduction of the 4CMenB vaccine in the Member States of the EU/EEA. This expert opinion document is intended to support national decision-making by summarising the considerations and concerns of some EU/EEA countries when they discussed whether to introduce the 4CMenB vaccine into their national immunisation programmes. It also summarises the reasons behind national recommendations for the 4CMenB vaccine, points out data gaps, and presents options on how to introduce the vaccine.

https://ecdc.europa.eu/en/publications-data/expert-opinion-introduction-meningococcal-b-4cmenb-vaccine-eueea

Evaluator's comment – datasheet recommendation vs UK Health Authority

As per the draft datasheet, the proposed regimen for infants 2 months to 5 months of age at time of first dose, is three doses plus a booster in the second year of life.

The UK Health Authorities recommend a reduced two-dose priming at 2 and 4 months, plus a booster at 12 months (Basta N, Christensen H. 2016. 4CMenB vaccine effectiveness: reasons for optimism. Lancet 388 December 3).

That the 'reduced two-dose plus one schedule is still being recommended and used in the UK is confirmed by current information. As at March 2018, the NHS website states that the Men B vaccine is given as part of the childhood immunisation schedule

Given at: **8 weeks, 16 weeks and one year of age**

https://www.nhs.uk/conditions/vaccinations/childhood-vaccines-timeline/

The reduced UK 2- 4 - 12 schedule seeks to provide protection during the youngest approved period, when risk of IMD is highest.

A recently published study (Martinón-Torres et al, 2017, Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised openlabel phase 3b trial. Vaccine 35: 3548-3557.) provides information for reduced schedules; including 3.5-5-11 and 6-8-11, but does not address the UK reduced schedule.

Two doses of rMenB+OMV NZ to control New Jersey college outbreak

From March 2013 through March 2014, a meningococcal B outbreak at a university in New Jersey led to nine cases of disease, including one death. Because sustained transmission occurred during 2 academic years, the Food and Drug Administration approved the use of 4CMenB before licensure.

The vaccine was offered to nearly 6000 students, beginning in December 2013.

Among the 499 participants who received two doses of the 4CMenB vaccine 10 weeks apart, 66.1% (95% confidence interval [CI], 61.8 to 70.3) were seropositive for the outbreak strain.

That is; "only 66.1% of U.S. university students who were fully vaccinated with 4CMenB had putatively protective immunity against a meningococcal B outbreak strain. This level of seropositivity was lower than expected, given the antigenic similarity between the outbreak strain and the components of the vaccine and given that the Meningococcal Antigen Typing System predicted that 4CMenB would induce responses against the outbreak strain."

Basta NE, Mahmoud AA, et al. 2016. Immunogenicity of a Meningococcal B Vaccine during a University Outbreak. New England Journal of Medicine. 375(3):220-8, 2016 Jul 21.

Evaluator's comment

The strain specific nature of the protection afforded by the rMenB+OMV NZ vaccine was not high considering the reputed close match to the New Jersey college outbreak strain.

I.7.2 Persistence of bactericidal antibodies

Protection appears to require satisfactory antibody levels, and may not be afforded solely by immune memory as boosting antibodies may require longer than for disease to evolve to fulminant disease with poor outcomes. Therefore, an amnestic response or ability to boost is not currently understood to be important in protection from disease.

Historical comparison [from SCE Feb 2013]

The decline in bactericidal titers over the 5 months after the primary vaccination series in infants, along with the lower percentage of subjects maintaining protective titers against strain NZ98/254 at 12 months of age, support administration of a booster dose early in the second year of life.

Nonetheless, this result is very similar to the persistence of bactericidal antibodies observed after the infant series in a study in New Zealand to support the use of MeNZB in the control of the outbreak. In that study, at 4-5 months after a 3 dose infant series, 27% of subjects maintained an hSBA $\geq$ 1:4.

This is important because it provides additional linkage to the field effectiveness demonstrated by the MeNZB vaccine and the potential for protection against other strains possessing similar phenotypic characteristics.

[from EPAR] persistence of antibodies

The duration of protection is currently unknown. In infants the antibody levels declined rapidly for the PorA and NHBA antigens, i.e. within 6 months of primary vaccination, and within 12 months of booster or primary vaccination in toddlers.

The antibody titres in infants against fHbp were also shown to decline although not as much as the PorA titres. The proportion of subjects with SBA titres to fHbp ≥1:5 was 50-60% at 12 months after the fourth dose in V72P13E2.

I.7.3 Study V72P12

The phase 2b study (**V72P12**) evaluated two alternative 3-dose schedules for rMenB+OMV NZ given with concomitant routine vaccines (Infanrix Hexa™ and Prevenar) at 2, 4, 6 or 2, 3, 4 months of age to adapt to commonly used routine schedules in EU countries. A control group received routine vaccines alone at 2, 3, 4 months and another was given rMenB+OMV NZ at 2, 4, 6 and routine vaccinations at 3, 5, 7 months of age to allow evaluation of immunogenicity and safety profile of the rMenB+OMV NZ vaccine when administered alone or in combination with the routine infants vaccines.

The study's primary immunogenicity objective was to demonstrate a sufficient immune response of rMenB+OMV NZ, when given concomitantly with routine infant vaccines to healthy infants at 2, 4 and 6 and 2, 3 and 4 months of age, as measured by percentage of subjects with SBA titer ≥1:5, at 1 month after the third vaccination.

The study was undertaken in 4 centers in UK, 5 centers in Italy, 16 centers in Spain, 6 centers in Belgium, 25 centers in Germany and 4 centers in Czech Republic, from AUG 08 to JUL 10.

Subjects were randomized in a 2:2:1:1 ratio per schedule:

- Group 1: One dose of rMenB+OMV NZ at 2, 4, and 6 months of age, administered concomitantly with routine infant vaccinations.
- Group 2: One dose of rMenB+OMV NZ at 2, 4, and 6 months of age; routine infant vaccinations administered at 3, 5 and 7 months of age.
- Group 3: One dose of rMenB+OMV NZ at 2, 3, 4 months of age, administered concomitantly with routine infant vaccinations.
- Group 4: Routine infant vaccines administered at 2, 3 and 4 months of age.

Results from this study suggested that a 3-dose primary schedule either with or without concomitant routine vaccination at 2, 4, 6 months of age is able to elicit a robust immune response to all three reference strains with an acceptable safety profile. In addition, a sufficient immunogenicity to all three reference strains and no clinically relevant interference on the immune response to concomitant vaccines antigens was observed in the more challenging accelerated 2,3,4 schedule while the safety profile was similar to that observed with the 2,4,6 schedule. Fever rates for rMenB+OMV NZ given alone were lower than when concomitantly administered with routine vaccines and rates were comparable to the rates observed for the concomitant vaccines given alone.

[CSR dated 28 August 14] E2 sought to explore antibody persistence in 4-year-old children after a fourth dose boost of rMenB+OMV NZ administered at either 12, 18, or 24 months of age in study V72P12E1, in toddlers who previously received a three-dose primary series of

rMenB+OMV NZ (at 2, 3, 4 or 2, 4, 6 months of age) as infants in the original parent study V72P12.

Antibody persistence in 4-year-old children after a 4th dose boost of rMenB+OMV NZ administered to toddlers (at 12, 18, or 24 months of age) who received a three-dose primary series as infants.

The extension study was undertaken at 4 centers from the UK; 4 centers from Italy; 4 centers from Spain; 19 centers from Czech Republic from Nov 2012 to Oct 2013.

In total, 805 subjects were enrolled in the extension study V72P12E2.

The description of the vaccine groups in this study and their vaccination schedule in the previous extension trial is detailed in Table 2-1.

Table 2-1: Vaccination Schedule

V72P12E1		V72P12E2		
			Procedure	
Groups	Vaccination Schedule	Groups	Antibody Persistence	Immunogenicity and safety
B+R246 12[a] B+R246 18[b] B+R246 24[c]	rMenB+OMV NZ +Routine vac at 2, 4, 6 months Booster at 12, 18, or 24 months (N=481)	B+R246 12_48, B+R246 18_48, B+R246 24_48	Subset #1 and #2[j]: Blood sample at ~4 years of age	Subset #2[j]: Fifth dose boost of rMenB+OMV NZ at ~4 years of age Blood sample at 1 month after 5th dose boost.
B246 12[d] B246 18[e] B246 24[f]	rMenB+OMV NZ at 2, 4, 6 months + Routine vac. at 3, 5, 7 months, Booster at 12, 18, or 24 months (N=449)	B246 12_48,B246 18_48 , B246 24_48		
B+R234 12[g] B+R234 18[h] B+R234 24[i]	rMenB+OMV NZ + Routine vac at 2, 3, 4 months Booster at 12, 18, or 24months (N=244)	B+R234 12_48 B+R234 18_48 B+R234 24_48	Blood sample at ~4 years of age. Fifth dose boost of rMenB+OMV NZ at ~4 years of age. Blood sample at 1 month after 5th dose boost.	
B12 14	rMenB+OMV NZ catch up doses at 12&14 months (N=237)	B12 14_48	Blood sample at ~4 years of age. Third dose boost of rMenB+OMV NZ at ~4 years of age. Blood sample at 1 month after 3rd dose boost.	
B18 20	rMenB+OMV NZ catch up doses at 18&20 months (N=51)	B18 20_48		
B24 26	rMenB+OMV NZ catch up doses at 24&26 months (N=52)	B24 26 _48		
		B48_50 (Naïve subjects at ~4 years of age; (N=190)	Blood sample at baseline. 2 catch up doses of rMenB+OMV NZ two months apart. 2 blood samples 1 month after each dose.	

Source: Table1 of protocol version 5 issued on 14 NOV 13.

Note: Groups names as used in original study V72P12E1 - [a]Group 1a; [b]Group 1b; [c]Group 1c; [d]Group 2a; [e]Group 2b; [f]Group 2c; [g]Group 3a, [h]Group 3b, [i]Group 3c. Subjects of B+R246 (12/18/24) and B246 (12/18/24) groups from V72P12E1 were randomized in 2:1 ratio into: Nonvaccination subset #1 and vaccination subset #2.

Antibody persistence when assessed in terms of percentage of subjects with hSBA titers ≥ 5 and ≥ 8, and hSBA GMTs was observed to be highest against strain 5/99 and lowest against strain NZ98/254.

Against strains H44/76, 5/99 and NZ98/254 antibody persistence was comparable across groups B+R246 (12/18/24), B246 (12/18/24) and B+R234 (12/18/24_48) which received 4th

dose boost of rMenB+OMV NZ either at 12 or 18 or 24 months of age and was higher in these groups when compared to the baseline values for subjects in naïve group B48_50.

All the 95% CIs of vaccine group differences and vaccine group ratios were above 0% and 1 respectively (Table 2-7).

Against strain M10713, persistence at 4 years of age across groups B+R246 (12/18/24), B246 (12/18/24) and B+R234 (12/18/24_48) was comparable to the baseline values for subjects in naive group B48_50. All the 95% CIs of vaccine group differences and vaccine group ratios enclosed 0% and 1 respectively (Table 2-7).

Table 2-7: Number (%) of Subjects with hSBA Titers ≥ 5 (95% CI) at 4 Years of Age in Vaccine Groups That Received a 3-Dose Primary Series as Infants and a Booster as Toddlers – FAS (Persistence)

		rMenB+OMV NZ + Routine Vaccines at 2, 4 and 6 Months of Age			rMenB+OMV NZ at 2, 4 and 6 months, Routine Vaccines at 3, 5 and 7 Months of Age			rMenB+OMV NZ + Routine Vaccines at 2, 3 and 4 Months of Age			Vaccine-Naive
		B+R246 12	B+R246 18	B+R246 24	B246 12	B246 18	B246 24	B+R234 12	B+R234 18	B+R234 24	B48_50
H44/76		N=67	N=60	N=59	N=65	N=63	N=54	N=42	N=28	N=28	N=206
	Persistence at 4 Years of Age[a]	8 (12%) (5%-22%)	11 (18%) (10%-30%)	14 (24%) (14%-37%)	13 (20%) (11%-32%)	17 (27%) (17%-40%)	19 (35%) (23%-49%)	5 (12%) (4%-26%)	7 (25%) (11%-45%)	6 (21%) (8%-41%)	1 (0%) (0.012%-3%)
5/99		N=67	N=60	N=58	N=64	N=62	N=54	N=42	N=28	N=28	N=200
	Persistence at 4 Years of Age[a]	62 (93%) (83%-98%)	59 (98%) (91%-100%)	56 (97%) (88%-100%)	62 (97%) (89%-100%)	62 (100%) (94%-100%)	54 (100%) (93%-100%)	38 (90%) (77%-97%)	25 (89%) (72%-98%)	27 (96%) (82%-100%)	9 (5%) (2%-8%)
NZ98/254		N=67	N=60	N=60	N=66	N=63	N=54	N=42	N=28	N=28	N=206
	Persistence at 4 Years of Age[a]	6 (9%) (3%-18%)	5 (8%) (3%-18%)	7 (12%) (5%-23%)	6 (9%) (3%-19%)	7 (11%) (5%-22%)	5 (9%) (3%-20%)	4 (10%) (3%-23%)	3 (11%) (2%-28%)	3 (11%) (2%-28%)	1 (0%) (0.012%-3%)
M10713		N=65	N=59	N=58	N=62	N=60	N=54	N=40	N=28	N=28	N=192
	Persistence at 4 Years of Age[a]	35 (54%) (41%-66%)	40 (68%) (54%-79%)	43 (74%) (61%-85%)	34 (55%) (42%-68%)	32 (53%) (40%-66%)	43 (80%) (66%-89%)	27 (68%) (51%-81%)	21 (75%) (55%-89%)	21 (75%) (55%-89%)	116 (60%) (53%-67%)

Source: Table 14.2.1.1.1; Table 14.2.1.1.2; Table 14.2.1.1.3.
[a] Baseline for vaccine naïve subjects (group B48_50).

Evaluator's comment

An extension study of the phase 2b study V72P12 evaluated antibody persistence of children [who had previously received a three dose regimen of 4CMenB plus a booster at 12, 18, or 24 months of age] at 4-years of age. Most children retained antibodies against Strain 5/99; that is, the NadA (Neisseria adhesin A) antigen, but only a minority (12% or less) against Strain NZ98/254; that is, the PorA1.4 antigen.

Immunogenicity associated with protection was achieved at four years of age by:

- *about a third of subjects against strains H44/76 (35% or less)*
- *most subjects against 5/99 (89%+)*
- *few subjects against NZ98/254 (12% or less)*
- *no evidence of protective antibody levels for strain M10713 induced by vaccination (although about half the subjects had antibodies, this was comparable to the baseline values for subjects in the naive group).*

I.7.4 Phase 3 study V72P13 infants

A **phase 3 study (V72P13)** was large, with 3,630 infants aged 2 months at study entry.

The study was conducted in multiple European countries and provided safety and immunogenicity data on rMenB+OMV NZ vaccine with routine concomitant vaccines (Infanrix Hexa and Prevenar) administration at 2, 4, and 6 months of age.

15 sites in Finland, 12 sites in Germany, 5 sites in Austria, 27 sites in Czech Republic and 6 sites in Italy. Date of first enrollment: 11 FEB 09. Date of last visit: 16 AUG 10

Study groups included:

- 3 lots rMenB+OMV NZ with concomitant Routine

  Group I; Group II; Group III: one dose of rMenB+OMV NZ (Lot 1, or Lot 2, or Lot 3) at 2, 4, 6 months of age concomitantly with the routinely administered infant vaccines
- Routine

  Group IV: the routinely administered infant vaccines at 2, 4, 6 months of age
- Routine+MenC.

  Group V: the routinely administered infant vaccines + Menjugate at 2, 4 and 6 months of age

The study demonstrated the immunologic equivalence between three rMenB+OMV NZ consecutive lots administered in a 3-dose schedule at 2, 4, 6 months of age with concomitant infant routine vaccines (first co-primary objective - lot-to-lot consistency).

The second co-primary objective was also met in that antibody responses against the three reference strains were sufficient. The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥ 1:5 at 1 month following the third vaccination was ≥ 70% for all strains for the three lots combined. Responses were 100% against the 44/76 and 5/99 strains and 84% against the NZ98/254 strain.

No clinically relevant interference on the immune response to the antigens of routine infant vaccines was observed when given concomitantly with rMenB+OMV NZ in the first year of life as compared with routine infant vaccines given alone.

Higher systemic reactogenicity was observed when rMenB+OMV NZ was co-administered with routine vaccinations and in particular with regard to fever rates.

First extension study

V72P13E1 was an extension study of V72P13, in subjects (now toddlers) who completed the parent study V72P13. Toddlers had been previously primed with three doses of rMenB+OMV NZ as infants in Study V72P13.

Subjects who received three doses of rMenB+OMV NZ as infants in Study V72P13 (both observer-blinded, safety only subjects and open-label, immunogenicity subjects in V72P13) were randomized in a 1:1 ratio to receive either:

- a fourth (booster) dose of rMenB+OMV NZ at 12 months of age co-administered with routine combined measles, mumps, rubella and varicella vaccine (MMRV, Priorix-Tetra) or
- a booster dose of rMenB+OMV NZ alone at 12 months of age, followed by MMRV vaccination at 13 months of age.

The control subjects from study V72P13 who received routine vaccinations only (open-label, immunogenicity subjects in V72P13), were randomized at a 3:1 ratio to receive either:

- MMRV alone at 12 months of age as a control for this vaccination, followed by two doses of rMenB+OMV NZ at 13 and 15 months of age or
- two doses of rMenB+OMV NZ at 12 (with MMRV) and 14 months of age.

The other control subjects from Study V72P13 who received routine vaccinations co-administered with Menjugate (observer-blinded, safety only subjects in V72P13), were randomized at a 1:1 ratio to receive either:

- a single dose of rMenB+OMV NZ together with MMRV at 12 months of age or
- a single dose of rMenB+OMV NZ at 12 months of age, followed by MMRV vaccination at 13 months of age.

Among the V72P13E1 study objectives was the demonstration of 1) a sufficient immune response to the 4th dose, and 2) that the immunogenicity of routine infant vaccine (MMRV [Priorix Tetra™]) when given concomitantly with rMenB+OMV NZ was noninferior to that of MMRV given alone, 3) immunogenicity evaluation of a 2-dose schedule of rMenB+OMV NZ given to naive toddlers.

A total of 2,249 subjects were enrolled in the study out of which 2,202 subjects completed the study.

A total of 327 subjects were included in the SBA persistence per protocol (PP) analysis, 424 subjects were included in the SBA booster PP analysis, 233 subjects were included in the SBA two-dose catch-up PP analysis and 337 subjects were included in the MMRV PP analysis.

One of the secondary objectives in extension **study V72P13E1** was to evaluate the persistence of bactericidal antibodies at 12 months of age (pre-dose 4) in toddlers who had previously received three doses of rMenB+OMV NZ (as infants in Study V72P13), as measured by percentage of subjects with hSBA ≥ 1:5 (Table 3.2.4.3-a).

A summary of the study groups, together with the blood sampling and study vaccination schedules are provided in Table 2-1. The relationship of subjects in groups 1a, 1b, 2a, and 2b in V72P13E2, to the previous extension study V72P13E1 and to the original parent study V72P13 is also shown. The groups 1a, 1b, 2a, and 2b are referred to as B246_12M12, B246_12M13, B13_15_27, and B12_14_26 respectively in this report. When groups 1a and 1b, and 2a and 2b were combined they were referred to as B246_12Tot and B12+B13Tot respectively.

Table 2-1: Group Assignments and Vaccinations in the Parent Trials V72P13 & V72P13E1 and in V72P13E2

Group	V72P13	V72P13E1	V72P13E2
1a (B246_12M12)	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV concomitantly at 12 months of age	No vaccination, only blood draw at 12 months after the fourth dose rMenB+OMV NZ
1b (B246_12M13)	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV at 13 months of age	No vaccination, only blood draw at 12 months after the fourth dose rMenB+OMV NZ
2a (B13_15_27)	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 13 and 15 months of age; MMRV at 12 months of age	1 dose rMenB+OMV NZ at 12 months after the second dose
2b (B12_14_26)	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 12 and 14 months of age; MMRV concomitantly at 12 months of age	1 dose rMenB+OMV NZ at 12 months after the second dose
3 (B_24_26)	NA	NA	2 doses rMenB+OMV NZ at 24 and 26 months of age

In subjects who were vaccinated with rMenB+OMV NZ concomitantly with routine infant vaccines (InfanrixHexa® and Prevenar®) at 2, 4 and 6 months of age in V72P13 study (groups 12B12M (1a), 12B13M (1b), Men246 (combined 1a and 1b groups)), persistence of SBA antibodies at 12 months, as measured by SBA GMTs and percentages of subjects with SBA titers ≥1:5, was observed for strain 44/76-SL and strain 5/99 while for the strain NZ98/254, the SBA titers returned to the baseline level of V72P13 study but were still higher than the 12-month titers in Routine246 group who did not receive the rMenB+OMV NZ vaccination in V72P13 study.

Table 3.2.4.3-a Evaluation of Antibody Persistence as Measured by Number (Percentage) (95% CI) of Subjects with hSBA ≥ 1:5 in 12-month-old Previously Primed Toddlers - PP Population

		12B12M (1a)[a]	12B13M (1b)[b]	Men246[c]	Routine246[d]
H44/76		N=139	N=133	N=272	N=51
	1 Month After 3rd Vaccination in V72P13	139 (100%) (97-100)	132 (99%) (96-100)	271 (100%) (98-100)	0 (0%) (0-7)
	Pre-Booster Vaccination in V72P13E1	112 (81%) (73-87)	109 (82%) (74-88)	221 (81%) (76-86)	1 (2%) (0.05-10)
5/99		N=139	N=133	N=272	N=51
	1 Month After 3rd Vaccination in V72P13	139 (100%) (97-100)	132 (99%) (96-100)	271 (100%) (98-100)	0 (0%) (0-7)
	Pre-Booster Vaccination in V72P13E1	136 (98%) (94-100)	133 (100%) (97-100)	269 (99%) (97-100)	0 (0%) (0-7)
NZ98/254		N=139	N=132	N=271	N=52
	1 Month After 3rd Vaccination in V72P13	113 (81%) (74-87)	112 (85%) (78-90)	225 (83%) (78-87)	1 (2%) (0.049-10)
	Pre-Booster Vaccination in V72P13E1	29 (21%) (14-29)	26 (20%) (13-28)	55 (20%) (16-26)	0 (0%) (0-7)

Source: Seq. 0000, section 5.3.5.1, CSR V72P13E1 Table 14.2.1.1.1; **Groups**: [a]**12B12M(1a):** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster and MMRV at 12 months of age; [b]**12B13M(1b):** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster at 12 months of age and MMRV at 13 months of age; [c]**Men246:** groups 12B12M(1a) and 12B13M(1b) combined; [d]**Routine 246:** groups 12M13B15B and 12M12B14B combined. (12M13B15B: in the open-label (immunogenicity) subset of V72P13, these subjects had received routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received MMRV at 12, and rMenB+OMV NZ at 13 and 15 months of age. 12M12B14B: in the open-label (immunogenicity) subset of V72P13, these subjects had received routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received MMRV and rMenB+OMV NZ at 12 months, and a second dose of rMenB+OMV NZ at 14 months of age).

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For **strain H44/76**, the percentages of subjects with SBA titers ≥1:5 at one month after the third infant vaccination were 99%-100% across the evaluated vaccination groups. Just before the booster vaccination (at 12 months), the percentages were maintained with 81%-82% of the subjects having subjects SBA titers ≥1:5 (Table 3.2.4.3-a, see above).

At 12 months, the percentages of subjects with SBA titers ≥1:5 were much higher than that at baseline in V72P13 study and were also significantly higher than the percentage in the Routine246 group who did not receive the rMenB+OMV NZ vaccination in V72P13 study (81%-82% vs. 2%).

For **strain 5/99**, the percentages of subjects with SBA titers ≥1:5 at one month after the third infant vaccination were 99%-100% across the evaluated vaccination groups. Just before the booster vaccination (at 12 months), the percentages were maintained with 98%-100% of the subjects having subjects SBA titers ≥1:5 (Table 3.2.4.3-a, see above).

At 12 months, the percentages of subjects with SBA titers ≥1:5 were much higher than that at baseline in V72P13 study and were also significantly higher than the percentage in Routine246 group who did not receive the rMenB+OMV NZ vaccination in V72P13 study (98%-100% vs. 0%).

For **strain NZ98/254**, the percentages of subjects with SBA titers ≥1:5 at one month after the third infant vaccination were 81%-85% across the evaluated vaccination groups. Just before the booster vaccination (at 12 months), the percentages decreased with 20%-21% of the subjects having SBA titers ≥1:5 (Table 3.2.4.3-a, see above).

At 12 months, the percentages of subjects with SBA titers ≥1:5 were still higher than that at baseline in V72P13 study and were also higher than the percentage in Routine246 group who did not receive the rMenB+OMV NZ vaccination in V72P13 study (20-21% vs. 0%).

In summary, for strains H44/76 and 5/99, bactericidal antibody persistence measured at 12 months of age (**5 months after the post-third dose measurement**) showed that the titers were maintained with 81%-100% subjects having hSBA ≥ 1:5.

For strain NZ98/254, at 12 months of age, the percentages declined, with 20%-21% subjects having SBA ≥ 1:5 against strain NZ98/254.

Evaluator's comment

Study V72P13E1 - While five months after infants had received 3 vaccinations of 4CMenB [groups 12B12M (1a), 12B13M (1b), Men246 (combined 1a and 1b groups)], most retained immunogenicity correlated with protection for two antigens, the level of antibodies against the NZ98/254 strain (the PorA1.4 antigen), had fallen to non-protective levels in most children.

I.7.5 Study V72P13 toddlers

Study V72P13E2 is an extension of study V72P13E1. It was conducted as an openlabel, multi-center study. The eligible subjects from V72P13E1 who originally participated in the open-label, immunogenicity subset of parent study V72P13, conducted in Finland and the Czech Republic were planned to be enrolled.

An additional group of naive subjects, approximately 24 months of age, were recruited at the same study sites.

A summary of the study groups and study vaccination schedules are provided in Table 2-1. The relationship of subjects in groups 1a, 1b, 2a, and 2b in V72P13E2, to the previous extension study V72P13E1 and to the original parent study V72P13 is also shown.

The groups 1a, 1b, 2a, and 2b are referred to as B246_12M12, B246_12M13, B13_15_27, and B12_14_26 respectively in the E2 CSR.

When groups 1a and 1b, and 2a and 2b were combined they were referred to as B246_12Tot and B12+B13Tot respectively.

Table 2-1: Group Assignments and Vaccinations in the Parent Trials V72P13 & V72P13E1 and in V72P13E2

Group	V72P13	V72P13E1	V72P13E2
1a (B246_12M12)	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV concomitantly at 12 months of age	No vaccination, only blood draw at 12 months after the fourth dose rMenB+OMV NZ
1b (B246_12M13)	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV at 13 months of age	No vaccination, only blood draw at 12 months after the fourth dose rMenB+OMV NZ
2a (B13_15_27)	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 13 and 15 months of age; MMRV at 12 months of age	1 dose rMenB+OMV NZ at 12 months after the second dose
2b (B12_14_26)	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 12 and 14 months of age; MMRV concomitantly at 12 months of age	1 dose rMenB+OMV NZ at 12 months after the second dose
3 (B_24_26)	NA	NA	2 doses rMenB+OMV NZ at 24 and 26 months of age

Number of Subjects Planned and Analyzed: The number of subjects planned and actually enrolled in this study V72P13E2 is given in Table 2-2. The planned number for enrolment was based on the number of subjects who participated in immunogenicity and safety cohort of V72P13E1.

A lower number of subjects were actually enrolled than planned, due to slow enrolment and due to difficulties in getting subjects back after a long time for this second extension of the parent trial V72P13. Overall 98% of enrolled subjects were included in MITT persistence population and 89% of enrolled subjects were included in PP population (Table 2-2; Table 14.1.1.1; Table 14.1.1.1.1). Modified Intention-To-Treat analyses of

[page 11 of CSR] The primary objective was to explore the antibody persistence one year after a fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age to subjects enrolled in study V72P13E1 (groups B246_12M12 and B246_12M13). These subjects were previously primed with three doses of rMenB+OMV NZ (administered at 2, 4, and 6 months of age) as infants in study V72P13.

Mean age of subjects was 25.4 months (from Table 11.2 on page 99 CSR).

Subjects in groups B246_12M12 and B246_12M13 received rMenB+OMV NZ vaccination concomitantly with routine infant vaccines at 2, 4, and 6 months of age in the parent study V72P13.

Group B246_12M12 received rMenB+OMV NZ and MMRV at 12 months of age and group B246_12M13 received rMenB+OMV NZ at 12 months and MMRV at 13 months of age.

Study V72P13E2: antibody persistence 12 months after:

- 3 + 1 (12 month booster) primary infant schedule
- two-dose primary schedule in toddlers.

Study V72P13E2 Antibody persistence one year after a fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age.

When assessed across time-points after primary and booster vaccinations in B246_12M12 and B246_12M13 groups, the percentage of subjects with hSBA ≥1:5 decreased in both vaccine groups against all strains.

Persistence of immune response at 12 months after the (4th) booster dose given to 12- month-olds who had previously received the 3-dose infant series, as measured by percentages of subjects with hSBA ≥ 1:5 was most marked for

- strain 5/99 (96-99%), followed by
- strain 44/76 (60-64%),
- M10713 (32-40%), and
- NZ98/254 (17-18%) (Table 11.4.1-1).

Table 11.4.1-1: Percentage of Subjects with hSBA ≥1:5, at 12 Months Post-Booster with Previous Vaccinations at 2, 4, 6, and 12 Months of Age Compared with Naive Group - MITT Population

		Number of Subjects (Percentage) (95%CI)				Difference between vaccine group (95% CI)		
		B246_12M12	B246_12M13	B246_12Tot	B_24_26	B246_12M12 - B_24_26	B246_12M13 - B_24_26	B246_12Tot B_24_26
44/76-SL		N=147	N=152	N=299	N=112			
	12 Months after Booster	88 (60%) (51%-68%)	97 (64%) (56%-71%)	185 (62%) (56%-67%)	3 (3%) (1%-8%)	57% (48%-65%)	61% (53%-69%)	59% (52%-65%)
5/99		N=147	N=151	N=298	N=110			
	12 Months after Booster	141 (96%) (91%-98%)	149 (99%) (95%-100%)	290 (97%) (95%-99%)	1 (1%) (0.023%-5%)	95% (90%-98%)	98% (93%-99%)	96% (92%-98%)
NZ98/254		N=147	N=153	N=300	N=112			
	12 Months after Booster	26 (18%) (12%-25%)	26 (17%) (11%-24%)	52 (17%) (13%-22%)	0 (0%) (0%-3%)	18% (12%-25%)	17% (12%-24%)	17% (14%-22%)
M10713		N=143	N=148	N=291	N=109			
	12 Months after Booster	57 (40%) (32%-48%)	48 (32%) (25%-41%)	105 (36%) (31%-42%)	28 (26%) (18%-35%)	14% (3%-25%)	7% (-5%-18%)	10% (0%-20%)

Evaluator's comment

In the second extension study V72P13E2, antibody persistence one year after the fourth rMenB+OMV NZ dose was modest for the NHBA antigen/strain M10713 (32-40%), and the PorA1.4 antigen/strain NZ98/254 (17-18%).

As infants, these children had received a three-dose rMenB+OMV NZ regimen at 2, 4, 6 months of age in the V72P13 study, plus a fourth (booster) dose at 12 months of age in the V72P13E1 study.

That is, related to the primary objective of Study V72P13E2 - of children two years of age, who had one year previously finished the 3+1 (four dose) regimen, 17% to 18% remained protected against strain NZ98/254 at one year post-booster.

This extension study V72P13E2 evaluated antibody persistence at approximately 24 months of age (12 months after last dose) in subjects who received four doses of rMenB+OMV NZ at 2, 4, 6, and 12 months of age in the studies V72P13 and V72P13E1.

The draft datasheet provides persistence data, showing that in Study V72P12E1, following a three-dose schedule (at 2, 3, and 4 months), before the 12 month booster, 58% had antibodies against fHBP, 97% for NadA, 19% for PorA, and 25% for NHBA. The Table also shows results of Study V72P13E2, where 12 months after the 3+1 schedule persistence of antibodies was found for 62% had antibodies against fHBP, 97% for NadA, 17% for PorA, and 36% for NHBA.

Find below the text and table 3 from the proposed datasheet.

> Table 3 summarises antibody persistence pre-booster dose 8 months after primary vaccination at 2, 3 and 4 months of age and at 6 months after vaccination at 2,4 and 6 months of age.
>
> Table 3 also summarises an antibody response for both regimens one month after a booster dose administered at 12 months of age, and antibody persistence 12 months after the booster dose for the 2,4 and 6 month regimen.
>
> Seroprotection rates and hSBA GMTs one month following the fourth dose at 12 months were indicative of a booster response for both regimens.

Table 3: Serum bactericidal antibody responses following a booster at 12 months of age after a primary series administered at 2, 3 and 4 (Study V72P12E1) or 2, 4 and 6 months of age (Study V72P13E1), and persistence of bactericidal antibody one year after the booster (Study V72P13E2).

Antigen*	Response (95% CI)	2, 3, 4, 12 months	2, 4, 6, 12 months
fHBP	pre-booster**	N=81	N=426
	% seropositive***	58% (47-69)	82% (78-85)
	hSBA GMT****	5.79 (4.54-7.39)	10 (9.55-12)
	1 month after booster	N=83	N=422
	% seropositive	100% (96-100)	100% (99-100)
	hSBA GMT	135 (108-170)	128 (118-139)
	12 months after booster		N=299
	% seropositive	-	62% (56-67)
	hSBA GMT		6.5 (5.63-7.5)
NadA	pre-booster	N=79	N=423
	% seropositive	97% (91-100)	99% (97-100)
	hSBA GMT	63 (49-83)	81 (74-89)
	1 month after booster	N=84	N=421
	% seropositive	100% (96-100)	100% (99-100)
	hSBA GMT	1558 (1262-1923)	1465 (1350-1590)
	12 months after booster		N=298
	% seropositive	-	97% (95-99)
	hSBA GMT		81 (71-94)
PorA P1.4	pre-booster	N=83	N=426
	% seropositive	19% (11-29)	22% (18-26)
	hSBA GMT	1.61 (1.32-1.96)	2.14 (1.94-2.36)
	1 month after booster	N=86	N=424
	% seropositive	97% (90-99)	95% (93-97)
	hSBA GMT	47 (36-62)	35 (31-39)
	12 months after booster		N=300
	% seropositive	-	17% (13-22)
	hSBA GMT		1.91 (1.7-2.15)

NHBA	pre-booster % seropositive hSBA GMT	N=69 25% (15-36) 2.36 (1.75-3.18)	N=100 61% (51-71) 8.4 (6.4-11)
	1 month after booster % seropositive hSBA GMT	N=67 76% (64-86) 12 (8.52-17)	N=100 98% (93-100) 42 (36-50)
	12 months after booster % seropositive hSBA GMT	-	N=291 36% (31-42) 3.35 (2.88-3.9)

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254
- NHBA antigen: strain M10713

** pre-booster time point represents persistence of bactericidal antibody at 8 months after BEXSERO vaccination at 2, 3 and 4 months of age and 6 months after BEXSERO vaccination at 2, 4 and 6 months of age.
*** % seropositive = the percentage of participants who achieved an hSBA ≥ 1:5
**** GMT = geometric mean titre.

Evaluator's comment

From the available information in the above table from Study V72P13 and its extensions, in infants, the more widely spaced 2, 4, 6, 12 months achieves better persistence than the 2, 3, 4, 12 months regimen for the fHBP and NHBA antigens.

Persistence and Booster Response After a Two-Dose Primary Schedule in Toddlers

Study V72P13E2 also explored antibody persistence at one year after two doses of rMenB+OMV NZ, previously administered to vaccine-naïve-toddlers at either 12 and 14, or 13 and 15 months of age in study V72P13E1. The study title was: A Phase 3, Open-Label, Multi-Center, Extension Study of V72P13E1 to Assess Antibody Persistence at One Year After a Fourth Dose Boost or Two Catch-Up Doses of Novartis Meningococcal B Recombinant Vaccine Administered Starting at 12 Months of Age and to Evaluate the Response to a Third Dose Boost or Two Catch-Up Doses Starting at 24 Months of Age.

An additional group of naive subjects, (defined as subjects who have never previously received any meningococcal B vaccine) approximately 24 months of age, was recruited at the same study sites (group B_24_26).

Study V72P13E2 explored antibody persistence at one year after two doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1.

This study also included a group of naive subjects received two doses of rMenB+OMV NZ and, as such, provided catch-up vaccination data in children approximately 24 months of age. The following groups (among others) received routine vaccinations, as well as the rMenB+OMV NZ vaccine, as follows:

- Groups B13_15_27 and B12_14_26 received routine vaccines at 2, 4, 6 months of age followed by MMRV at 12 months of age.
- Group B13_15_27 received rMenB+OMV NZ at 13 and 15 months of age and
- Group B12_14_26 received rMenB+OMV NZ at 12 and 14 months of age.

In this trial (V72P13E2), subjects who were vaccinated with two catch-up doses of rMenB+OMV NZ vaccine in study V72P13E1 had a blood sample drawn for serological analyses 12 months (-30/+60 days) after the second dose. At the same visit, subjects were vaccinated with a booster (third) dose of rMenB+OMV NZ, followed by a blood sample drawn for serological analyses one month later. A third blood sample was drawn after 6 months of safety follow-up to assess antibody persistence at this time point.

The baseline antibody titers for these subjects served as a control for assessing antibody persistence one year post-vaccination for groups B246_12M12, B246_12M13, B13_15_27, and B12_14_26.

The Secondary objectives included persistence after two catch-up doses. The first of the secondary objectives was to explore antibody persistence at one year after two catch-up doses of rMenB+OMV NZ, previously administered to children at either 12 and 14 or 13 and 15 months of age in study V72P13E1 (groups B13_15_27 and B12_14_26), as measured by hSBA GMTs and the percentage of subjects with hSBA ≥1:5 and ≥1:8, directly against N. meningitidis serogroup B indicator strains H44/76-SL, 5/99, NZ98/254, and M10713.

Subjects in groups B13_15_27 and B12_14_26 received routine infant vaccines at 2, 4, and 6 months of age in the parent study V72P13.

Percentage of subjects with hSBA ≥1:5:

At 12 months after the two dose catch-up, the percentages of subjects in groups B13_15_27 and B12_14_26 with hSBA ≥1:5 were 75% and 56% for strain H44/76-SL, 97% and 94% for strain 5/99, 18% and 6% for strain NZ98/254, and 39% and 28% for strain M10713 respectively (Table 11.4.1-9).

Table 11.4.1-9: Percentage of Subjects with hSBA ≥1:5, 12 Months after Two-Dose Catch-Up (at 13 & 15 Months or 12 &, 14 Months of Age) Compared with Naive Group - MITT Population

		Number of subjects (Percentage) (95% CI)				Difference between vaccine groups (95% CI)		
		B13_15_27	B12_14_26	B12+B13Tot	B_24_26	B13_15_27 - B_24_26	B12_14_26 - B_24_26	B12+B13Tot B_24_26
H44/76-SL		N=67	N=18	N=85	N=112			
	12 Months after 2-Dose Catch-Up	50 (75%) (63%-84%)	10 (56%) (31%-78%)	60 (71%) (60%-80%)	3 (3%) (1%-8%)	72% (60%-81%)	53% (31%-73%)	68% (57%-77%)
5/99		N=67	N=18	N=85	N=110			
	12 Months after 2-Dose Catch-Up	65 (97%) (90%-100%)	17 (94%) (73%-100%)	82 (96%) (90%-99%)	1 (1%) (0.023%-5%)	96% (89%-99%)	94% (73%-98%)	96% (89%-98%)
NZ98/254		N=67	N=18	N=85	N=112			
	12 Months after 2-Dose Catch-Up	12 (18%) (10%-29%)	1 (6%) (0%-27%)	13 (15%) (8%-25%)	0 (0%) (0%-3%)	18% (11%-29%)	6% (1%-26%)	15% (9%-24%)
M10713		N=64	N=18	N=82	N=109			
	12 Months after 2-Dose Catch-Up	25 (39%) (27%-52%)	5 (28%) (10%-53%)	30 (37%) (26%-48%)	28 (26%) (18%-35%)	13% (-1%-28%)	2% (-16%-27%)	11% (-2%-24%)

In the naive group B_24_26, the percentage of subjects with such titers at baseline was low against H44/76- SL, 5/99, and NZ98/254 strain while against M10713 26% of subjects showed hSBA ≥1:5.

Both groups which received two catch-up doses showed significantly higher percentage of subjects with hSBA titers ≥1:5 after 12 months when compared with the naive group at baseline against H44/76-SL, 5/99, and NZ98/254 strains.

Against M10713 strain although a higher percentage of vaccinated subjects showed such titers, the difference was not significant based on overlapping 95% CIs (Table 11.4.1-9).

Persistence of immune response at 12 months after the second of two doses given two months apart to naive 12- or 13-month-old toddlers as measured by percentages of subjects with hSBA ≥ 1:5 was most marked for strain

- 5/99 (94-97%), followed by
- 44/76 (56-74%),
- M10713 (28-38%), and
- NZ98/254 (6-18%).

Evaluator's comment

Related to the secondary objective of Study V72P13E2 - of children two years of age, who had one year previously received two doses of finished rMenB+OMV NZ (that is, two catch-up doses at either 12 and 14 or 13 and 15 months of age), persistence of antibody levels was variable.

For naïve 12-13 month old toddlers, 12 months after two doses the persistence of response to M10713 (28-38%), and NZ98/254 (6-18%), was modest.

The proportion who had immunogenicity correlated with protection for the M10713 strain was not statistically different from that of the naïve group.

I.7.6 Study V72P6 E1 small phase 2

In **study V72P6**, infants had received rMenB or rMenB+OMV NZ at 2, 4, 6, and 12 months of age (integrated within the routine infant vaccination schedule in the UK).

The phase 2 extension study **V72P6E1** evaluated bactericidal antibody persistence at approximately 40 months of age (28 months after the last vaccination) in subjects who received 4 doses of rMenB ± OMV NZ at 2, 4, 6, and 12 months of age, or a single dose at 12 months of age, in the parent study V72P6 [this measurement of persistence was the extension-study's primary objective].

The study was a single-centre study in Oxford UK, with Study Initiation in JAN 10, and Completion in MAY 12.

This evaluation report focuses on Group 5rMenB+OMV (referred to as Group II in protocol). This refers to Subjects who were vaccinated at 2, 4, 6, and 12 months of age with rMenB+OMV NZ vaccine in Study V72P6 were vaccinated with a single booster vaccination of the same vaccine at 40 months of age.

Subjects were also boosted [with a 5th dose] at 40 months of age with the same vaccine received as infants.

Antibody persistence was measured at 18 months to 20 months after these vaccinations when the subjects were 60 months [5 years] of age.

For the primary objective, the sample sizes were selected to explore bactericidal antibody persistence in children at 40 months of age who previously received 4 vaccinations of rMenB (group 5rMenB) or rMenB+OMV NZ (group 5rMenB+OMV) at 2, 4, 6, and 12 months of age in parent study V72P6. The power for superiority of antibody persistence (eg, hSBA ≥ 1:4) at 40 months of age of rMenB ± OMV NZ after vaccinations **compared to naive subjects at 40 months of age**, for different sample sizes was calculated.

A total of 163 subjects were enrolled in this study. The immunogenicity MITT analyses for persistence at 40 months included 108 subjects.

Two groups of naive subjects, aged 40 and 60 months, were recruited in the study to serve as a baseline comparator for antibody persistence at these ages for the vaccinated groups.

For subjects in group 5rMenB+OMV, a clear difference between antibody levels at 40 months was observed only against strain NZ98/254, and not against strains H44/76 and M10713, when compared to Naive_4042 group subjects (Table 2-3 [from pages 46-47 of CSR]).

[Group 5rMenB (referred to as Group I in protocol): Subjects who were vaccinated at 2, 4, 6, and 12 months of age with rMenB vaccine in study V72P6 were vaccinated with a single booster vaccination of the same vaccine at 40 months of age.]

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

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

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

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

Evaluator's comment

For infants who, in study V72P6, had received the four-dose schedule rMenB or rMenB+OMV NZ at 2, 4, 6, and 12 months of age (integrated within the routine infant vaccination schedule in the UK) persistence of antibodies before a 40 month booster (slightly over two years after vaccination) was shown solely for strain NZ98/254 (the PorA1.4 antigen).

- *For Strain NZ98/254, the proportion of subjects prebooster with antibody hSBA ≥ 1:4 was higher than that for vaccine-naïve subjects (41% vs 0%).*
- *For Strain 5/99, the proportion of subjects prebooster with antibody hSBA ≥ 1:4 was higher than that for vaccine-naïve subjects (76% vs 3%) [a reasonable rate/percentage estimate cannot be based on the low number available; the three percent is based solely on one subject].*
- *For Strain H44/76 the proportion of subjects prebooster with antibody hSBA ≥ 1:4 was the same as that for vaccine-naïve subjects (65% vs 63%).*
- *For Strain M10713 the proportion of subjects prebooster with antibody hSBA ≥ 1:4 was the same as that for vaccine-naïve subjects (67% vs 68%).*

That is, the extension of study V72P6 showed that slightly over two years after a 2, 4, 6, and 12 months schedule there was no demonstrated persistence of antibodies for the fHBP, NadA and PorA1.4 antigens.

As the bulk of strain coverage in Australia according to the MATS study was conferred primarily by the fHbp and NHBA vaccine antigens, either singly or in combination with other antigens; persistence for strain 44/76 and strain 5/99 is of particularly importance.

Persistence 18 months after 2-dose catch-up rMenB+OMV NZ of 40-42 month olds, at 60 months of age

Additionally, data from this study provide information on bactericidal antibody persistence at 60 months of age, ie, 18 months after a 2-dose catch-up regimen of rMenB+OMV NZ administered at 40 months and 42 months of age.

The comparison group was composed of vaccine naive subjects 60 months of age. Baseline bactericidal titers in vaccine naive subjects 60 months of age from study V72P6E1 were very low except for strains H44/76 and M10713 (32% and 84% of subjects, respectively, had hSBA ≥ 1:4) (see Table 11.4.1-10 below).

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

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

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

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

When the percentages of subjects with an hSBA ≥ 1:4 were compared to those measured in vaccine naive subjects recruited at 60 months of age, good persistence was observed against strains H44/76, 5/99 and [to a lesser degree] NZ98/254 as shown by the higher percentages reaching this titer cut-off (subjects after a 2-dose catch up regimen vs. vaccine-naïve subjects:

- H44/76: 71% [CI: 51-87%] vs 33% [CI: 20-48%]
- 5/99: 100% [CI: 88-100%] vs 2% [CI: 0.055-12%]
- NZ98/254: 31% [CI: 15-51%] vs 2% [CI: 0.055-12%]) (Table 2.5.4.1-2).

No persistence was observed against strain M10713 as the percentages of subjects with an hSBA ≥ 1:4 were similar in the two groups (81% [CI: 62-94%] vs 83% [CI: 69-92%]).

Evaluator's comment

The extension of study V72P6 included cohorts additional to children who had received 4CMenB as infants. The cohort who had received two (catch-up) doses of 4CMenB at 40-42 month olds were 18 months later found to have persistence for the NadA and fHBP antigens.

I.7.7 Study V72P9 E1 Phase 2 study in older infants

Study V72P9 was a phase 2 study conducted in the UK in 60 infants. The study evaluated safety and immunogenicity of 3 doses of either rMenB or rMenB+OMV NZ given according to a 3-dose schedule in older infants aged 6 to 8 months at enrollment (at 6-8, 8-10, and 12 months of age).

High immune responses to all three reference strains were observed at one month after both the second and the third vaccinations with rMenB+OMV NZ.

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

Study V72P9E1 evaluated bactericidal antibody persistence at approximately 40 months of age, 28 months after a three-dose (at 6-8, 10, and 12-months) schedule as infants in study V72P9, and the effect of a fourth (booster) dose at 40 months of age.

Bactericidal antibody persistence at 40 months of age, 28 months after a third dose of rMenB and rMenB+OMV NZ administered to subjects at 12 months of age enrolled in study V72P9 (4rMenB and 4rMenB+OMV NZ vaccine groups), when compared to the baseline values of naive subjects (Naive_4042 vaccine group) was evident against strain 5/99 (hSBA ≥1:4 93%-100% vs. 0%; GMT 29-41 vs. 1;).

For the 4rMenB+OMV NZ group, antibody also appeared to persist against the other strains when compared to the baseline of the naive subjects (Naive_4042 vaccine group), but to a lesser extent than against strain 5/99:

- strain H44/76: hSBA ≥1:4 36% vs. 3%; and GMT 2.55 vs. 1.08;
- strain NZ98/254: hSBA ≥1:4 14% vs. 0% and GMT 1.74 vs. 1;
- strain M10713: hSBA ≥1:4 79% vs. 53% and GMT 7.11 vs. 4.82).

GMTs and percentages of subjects with hSBA ≥1:4 are provided in Table 3.2.4.4-1.

Table 3.2.4.4-1 **GMTs (95% CI) and Percentages of Subjects with hSBA ≥1:4 (95% CI) Before, at 1 Month After Booster at 40 Months of Age, Given to Subjects who Received a 3-Dose Primary Series as Infants, Study V72P9E1 - MITT Population**

Strain (antigen)		GMTs		% hSBA ≥1:4	
	Group	4rMenB+OMV	Control	4rMenB+OMV	Control
		N=14	N=39	N=14	N=39
H44/76 (fHbp)	P9 Baseline	2.33 (1.2-4.49) N=11	-	45% (17-77) N=11	-
	P9 1 Month Post 2nd	281 (179-439) N=11	-	100% (72-100) N=11	-
	P9 1 Month Post 3rd at 12 Months of Age	234 (170-322) N=11	-	100% (72-100) N=11	-
	P9E1 Pre-Booster (Persistence)	2.55 (1.15-5.66)	1.08[a] (0.97-1.21)	36% (13-65)	3%[a] (0.065-13)
	P9E1 1 Month Post Booster	114 (59-222)	8.89[b] (5.83-14)	100% (77-100)	72%[b] (55-85)
5/99 (NadA)	P9 Baseline	1 (1-1) N=11	-	0% (0-28) N=11	-
	P9 1 Month Post 2nd	562 (362-873) N=11	-	100% (72-100) N=11	-
	P9 1 Month Post 3rd at 12 Months of Age	1143 (732-1783) N=11	-	100% (72-100) N=11	-
	P9E1 Pre-Booster (Persistence)	29 (18-47)	1[a] (1-1) N=40	100% (77-100)	0%[a] (0-9) N=40
	P9E1 1 Month Post Booster	926 (432-1988)	27[b] (16-44)	100% (77-100)	87%[b] (73-96)
NZ98/ 254 (PorA 1.4)	P9 Baseline	1 (1-1) N=11	-	0% (0-28) N=11	-
	P9 1 Month Post 2nd	26 (14-50)	-	90% (55-100)	-

Strain (antigen)	GMTs		% hSBA ≥1:4	
Group	4rMenB+OMV	Control	4rMenB+OMV	Control
	N=14	N=39	N=14	N=39
P9 1 Month Post 3rd at 12 Months of Age	N=10 56 (33-95) N=11	-	N=10 100% (72-100) N=11	-
P9E1 Pre-Booster (Persistence)	1.74 (0.91-3.33)	1[a] (1-1)	14% (2-43)	0%[a] (0-9)
P9E1 1 Month Post Booster	32 (14-71)	1.91[b] (1.35-2.71)	93% (66-100)	23%[b] (11-39)

Source: Seq. 0003, section 5.3.5.1, CSR V72P9E1_40 Months Table 14.2.1.5.1, Table 14.2.1.5.2, Table 14.2.1.5.3. Group 4rMenB+OMV received a 3 dose primary series at 6-8, 10 and 12 months of age, with a booster at 40 months of age. Group Naive_4042 received 2 doses of rMenB+OMV NZ at 40 and 42 months of age. [a]Naive 40-42 group, baseline; [b]Naive 40-42 group, 1 month post 1st dose.

Evaluator's comment

Study V72P9E1 - Slightly more than 2 years (2.3 years) after older infants received three doses of rMenB+OMV NZ (that is, 4CMenB) at 6-8, 8-10, and 12 months of age, most retained bactericidal antibody persistence against NadA strain, but solely 36% continued to be protected against fHbp, and 14% against NZ98/254/ PorA1.4.

The application includes an addendum to the 2.5 Clinical Overview that summarizes the final data obtained at 60 months of age from one study with rMenB+OMV NZ, V72P9E1 (dated March 2014).

Antibody Persistence at 60 Months of Age

Bactericidal antibody persistence at 60 months of age was observed 18 months after a booster dose of rMenB+OMV NZ administered to subjects at 40 months of age, when compared to the baseline values of naïve subjects recruited at 60 months of age, against:

- strain H44/76 (GMT, 4.69 vs 1.09 and hSBA ≥ 1:4, 67% vs 4%),
- strain 5/99 (GMT, 119 vs 1.17 and hSBA ≥ 1:4, 100% vs 4%) and to a lesser extent against
- strain NZ 98/254 (GMT, 1.63 vs 1, hSBA ≥ 1:4, 17% vs 0%); Table 2.5.4.1-1.

[for example in page 142 of CSR] Persistence of antibody at 60 months of age could not be demonstrated for strain M10713 (GMT, 5.51 vs 8.09 and hSBA ≥ 1:4, 45% vs 67%); Table 2.5.4.1-1.

Table 2.5.4.1-1 Geometric Mean hSBA Titers (GMTs; 95% CI) and Percentage of Subjects with hSBA ≥ 1:4 (Persistence at 60 Months of Age) - MITT Set, Study V72P9E1

		GMTs		% hSBA ≥ 1:4	
		rMenB+OMV NZ	Naïve_6062[a]	rMenB+OMV NZ	Naïve_6062[a]
H44/76 (fHbp)		N=14	N=46	N=14	N=46
	P9E1 (1 month post booster)	114 (59-222)	-	100% (77%-100%)	-
	P9E1 20 months post booster /baseline	4.69 (1.98-11) N=12	1.09 (0.96-1.25)	67% (35%-90%) N=12	4% (1%-15%)
5/99 (NadA)		N=14	N=46	N=14	N=46
	P9E1 (1 month post booster)	926 (432-1988)	-	100% (77%-100%)	-
	P9E1 20 months post booster /baseline	119 (56-252) N=11	1.17 (0.96-1.42)	100% (72%-100%) N=11	4% (1%-15%)
NZ98/254 (PorA P1.4)		N=14	N=46	N=14	N=46
	P9E1 (1 month post booster)	32 (14-71)	-	93% (66%-100%)	-
	P9E1 20 months post booster /baseline	1.63 (0.86-3.08) N=12	1 (1-1)	17% (2%-48%) N=12	0% (0%-8%)
M10713 (NHBA)		N=14	N=45	N=14	N=45
	P9E1 (1 month post booster)	23 (13-41)	-	93% (66%-100%)	-
	P9E1 20 months post booster /baseline	5.51 (2.19-14) N=11	8.09 (5.13-13)	45% (17%-77%) N=11	67% (51%-80%)

Source: section 5.3.5.1, CSR V72P9E1 Table 14.2.1.1.2, Table 14.2.1.5.2; hSBA = serum bactericidal assay; GMT = geometric mean titer; MenB = *N meningitidis* serogroup B; CI = confidence interval; [a] Naïve subjects recruited at 60 months of age were vaccinated with two doses of rMenB+OMV NZ, given two months apart, at 60 and 62 months of age. Baseline antibody levels measured in naïve subjects at 60 months of age served as a descriptive comparator to evaluate antibody persistence at 60 months of age for the groups which received rMenB+OMV NZ in this study.

Evaluator's comment

In the extension of Study V72P9, about one-and-a-half year after a booster dose of rMenB+OMV NZ administered to subjects at 40 months of age (that is; at 60 months of age), antibodies persisted in 67% of subjects against strain H44/76 (fHBP antigen), 100% against strain H44/76 (fHBP), and there was a low level of persistence against strain NZ 98/254 [against PorA1.4] (17% vs 0%) and no persistence for strain M10713 [against NHBA] (45% vs 67%).

I.7.8 Study V72P10 adolescents

A phase 2b/3 study (V72P10) was conducted in Chile to evaluate different schedules in adolescents 11 to 17 years of age.

Subjects received either 1-dose, 2-doses (either one or two months apart), or 3-doses one month apart of rMenB+OMV NZ followed by another vaccination (booster) at month 6 or placebo.

Data supporting the two-dose series comes from Groups 0-1 and 0-2 in Table 3.2.1.1-1, which included subjects who were randomized into the 0-1 month and 0-2 month schedules respectively, and from Group 0-1-2, where immune responses were evaluated one month after the second dose in subjects who went on to have a third dose.

Table 3.2.1.1-1 Number of Subjects (Percentage) (95% CI) with hSBA ≥1:4 in Adolescents by Schedule, Study V72P10

		0-1	0-2	0-1-2	0 Schedule	Placebo
		N=679	N=342	N=335	N=1357	N=116
H44/76	Pre	289 (43%) (39-46)	149 (44%) (38-49)	155 (46%) (41-52)	591 (44%) (41-46)	53 (46%) (36-55)
	Month 1				1261 (93%) (92-94) N=1356	50 (43%) (34-53) N=115
	Month 2	637 (100%) (99-100) N=638				54 (50%) (40-59) N=109
	Month 3		319 (100%) (99-100) N=319	303 (100%) (98-100) N=304		52 (48%) (38-58) N=108
		N=679	N=342	N=335	N=1357	N=116
5/99	Pre	223 (33%) (29-37)	119 (35%) (30-40)	119 (36%) (30-41)	467 (34%) (32-37)	34 (29%) (21-38)
	Month 1				1310 (97%) (96-98) N=1355	40 (35%) (26-44) N=115
	Month 2	638 (100%) (99-100) N=639				34 (31%) (23-41) N=109
	Month 3		318 (99%) (98-100) N=320	304 (100%) (99-100) N=304		35 (32%) (24-42) N=108
		N=678	N=342	N=334	N=1356	N=116
NZ98/254	Pre	227 (33%) (30-37)	123 (36%) (31-41)	110 (33%) (28-38)	474 (35%) (32-38)	44 (38%) (29-47)
	Month 1				1263 (93%) (92-94) N=1355	44 (38%) (29-48) N=115
	Month 2	637 (100%) (99-100) N=639				42 (39%) (29-48) N=109
	Month 3		319 (100%) (99-100) N=319	300 (99%) (97-100) N=303		46 (43%) (33-52) N=108

Compared with the 2- dose schedules, there was no increase in hSBA response to the three reference strains in subjects receiving the 3-dose schedule. At four to six months after the primary vaccination course (at month-6), the antibody response showed good persistence.

In the (0-Schedule) group that received one dose of the vaccine (N=1357), although most of the subjects showed hSBA ≥1:4, the response was relatively lower (93% to 97% across the strains) compared to the two-dose series.

A second dose at 6 months for subjects who had received one dose only at month 0 produced hSBA responses very similar to those observed after 2 doses one or two months apart.

The vaccine was safe with no increase in reactogenicity or adverse events with incremental doses.

Therefore, immunogenicity and safety results from this study, together with those of the two adult studies, support the use of a 2-dose schedule in individuals aged 11 years and older.

For the primary vaccination period and persistence (visit-1 to visit-4 and visit-5) these groups have been combined into 5 groups as given in Table 9.1-1; the groups that were combined differed in their schedules only for booster vaccination.

Table 9.1-1: Overview of Vaccination and Blood Draw Schedule

Vaccine Groups (until Visit-4)	Month 0	Month 1	Month 2	Month 3	Vaccine Groups from Visit-5	Month 6	Month 7	Month 12
1a & 1b (rMenB0) N=375	BD +Vacc	BD +P	BD +P	BD	1a (rMenB06) N=125	BD + Vacc	BD	Safety follow up
					1b (rMenB0) N=250	BD + P	BD	Safety follow up
2a & 2b (rMenB01) N=375	BD +Vacc	BD +Vacc	BD +P	BD	2a (rMenB016) N=125	BD + Vacc	BD	Safety follow up
					2b (rMenB01) N=250	BD + P	BD	Safety follow up
3a & 3b (rMenB0Y) N=375	BD +Vacc	BD +P	BD +Vacc	BD	3a (rMenB026) N=125	BD + Vacc	BD	Safety follow up
					3b (rMenB02) N=250	BD + P	BD	Safety follow up
4 (rMenB012) N=375	BD +Vacc	BD +Vacc	BD +Vacc	BD	4 (rMenB012) N=375	BD + P	BD	Safety follow up
5 (Placebo) N=125	BD +P	BD +P	BD +P	BD	5 (rMenB6) N=125	BD + Vacc	BD	Safety follow up

BD: Blood draw; Vacc: rMenB+OMV NZ; P: Placebo

Evaluator's comment

The Visit-5 column provides the numbers who received a booster, or not. Visit-5 was the month-6, pre-booster visit.

For example: rMenB012 stands for subjects who received three doses, at month 0, month 1, and month 2. rMenB0 is the group who received only one vaccination, at month 0.

Booster dose:

At four to six months after the primary vaccination, at month-6, a booster dose of the candidate vaccine rMenB+OMV NZ, was administered to one-third of the subjects within each combined vaccine group (rMenB0, rMenB01, rMenB02), other two-thirds received a placebo.

In this study, adolescents were administered two doses either one (N=679), two (N=342) or 6 (N=112) months apart. Subjects from Group 0-1-2, went on to have a third dose.

99% to 100% of subjects achieved hSBA of ≥1:4 against the 44/76, 5/99 and NZ98/254 reference strains after all these two-dose schedules.

In the (0-Schedule) group that received one dose of the vaccine (N=1357), although most of the subjects showed hSBA ≥1:4, the response was relatively lower (93% to 97% across the strains) compared to the two-dose schedules.

At four to six months after the primary vaccination course (at month-6), the persistence of the antibody response was substantially higher in the two-dose and three-dose primary vaccine groups (rMenB01, rMenB02 and rMenB012) than the one-dose primary vaccine group (rMenB0) in terms of percentage of subjects with hSBA≥1:4, and GMTs/GMCs (Table 11.4.1.1-1;

Table 11.4.1.1-1: Percentages (95% CI) of Subjects With hSBA ≥ 1:4 in the Primary Vaccination Course and Persistence (Months 1 to 6) – PP Population

		rMenB0_C	rMenB01_C	rMenB02_C	rMenB012	Placebo	Dose 0[a]	Dose 01[b]
Strain 44/76-SL		**N=335**	**N=344**	**N=342**	**N=334**	**N=116**	**N=1355**	**N=678**
	Month 0	45%(40-51)	39%(34-44)	44%(38-49)	46%(41-52)	46%(36-55)	44%(41-46)	43%(39-46)
	Month 1	**92%(89-95)**	93%(90-96)	92%(88-94)	95%(92-97) N=333	43%(34-53) N=115	93%(91-94) N=1354	94%(92-96) N=677
	Month 2	91%(87-94) N=321	**100%(99-100)** N=330	89%(85-92) N=324	100%(98-100) N=307	50%(40-59) N=109		100% (99-100) N=637
	Month 3	86%(82-90) N=315	99%(98-100) N=320	**100%(99-100)** N=319	**100%(98-100)** N=303	48%(38-58) N=108		
	Month 6	74%(68-79) N=288	93%(89-95) N=298	97%(95-99) N=300	97%(94-99) N=278	46%(36-56) N=100		
Strain 5/99		**N=335**	**N=344**	**N=342**	**N=334**	**N=116**	**N=1355**	**N=678**
	Month 0	37%(32-42)	30%(25-35)	35%(30-40)	36%(30-41)	29%(21-38)	34%(32-37)	33%(29-37)
	Month 1	**97%(94-98)** N=334	97%(94-98)	96%(94-98)	97%(94-98) N=333	35%(26-44) N=115	97%(96-98) N=1353	97%(95-98) N=677
	Month 2	94%(91-97) N=321	**100%(99-100)** N=330	93%(90-96) N=324	100%(98-100) N=308	31%(23-41) N=109		100% (99-100) N=638
	Month 3	90%(86-93) N=316	100%(98-100) N=320	**99%(98-100)** N=320	**100%(99-100)** N=303	32%(24-42) N=108		
	Month 6	76%(70-81) N=288	99%(97-100) N=298	99%(98-100) N=300	100%(98-100) N=278	28%(19-38) N=100		
Strain NZ98/254		**N=335**	**N=344**	**N=342**	**N=333**	**N=116**	**N=1354**	**N=677**
	Month 0	37%(32-42)	34%(29-39)	36%(31-41)	33%(28-38)	38%(29-47)	35%(32-37)	33%(30-37)
	Month 1	**93%(89-95)** N=334	94%(91-96)	92%(88-94)	95%(92-97)	38%(29-48) N=115	93%(92-94) N=1353	94%(92-96)
	Month 2	83%(78-87) N=320	**100%(98-100)** N=330	83%(78-87) N=323	100%(98-100) N=308	39%(29-48) N=109		100% (99-100) N=638
	Month 3	78%(73-82) N=315	97%(95-99) N=320	**100%(99-100)** N=319	**99%(97-100)** N=302	43%(33-52) N=108		
	Month 6	73%(68-78) N=287	91%(87-94) N=298	96%(94-98) N=299	97%(94-99) N=278	45%(35-55) N=100		

Source: Table 14.2.1.1; Bold font: one month after the last dose of rMenB+OMV NZ; a: Dose 0 =All the subjects receiving rMenB+OMV NZ at Month-0 (rMenB0 + rMenB01 + rMenB02 + rMenB012); b: Dose 01 = All the subjects receiving rMenB+OMV NZ at Months-0 and 1 (rMenB01 + rMenB012)

Evaluator's comment

As noted in the conclusions of the CSR, at four to six months after the primary vaccination course (at month-6), the persistence of the antibody response (percentage of subjects with hSBA≥1:4) was substantially higher in the two-dose and three-dose primary

vaccine groups (rMenB01, rMenB02 and rMenB012) than the one-dose primary vaccine group (rMenB0).

In the two-dose primary vaccine groups (rMenB01, rMenB02) at four to six months after the primary vaccination course there is good persistence in terms of percentage of subjects with hSBA≥1:4 for the three vaccine antigens measured (91% and over).

No substantial difference was noted among the two-dose and three-dose vaccine groups in terms of percentage of subjects with hSBA≥1:4, and ≥1:8.

The GMTs at month-6 supported good persistence of the antibody response in the two-dose and three-dose vaccine groups as these titers were markedly higher than the original titers at baseline, as well as the titers of the placebo group at month-6.

Extension study V72P10 E1

Overall 817 subjects (666 follow-on subjects from V72P10 and 151 vaccine-naive subjects) were enrolled into the present study to assess the 18 months antibody persistence after completion of vaccination course in the parent study V72P10.

Please note that no vaccine was administered in study V72P10E1 and only safety data related to the blood draw procedure were collected.

As the last vaccine dose was administered at study month 0, 1, 2 or 6 depending on the schedule, this study provides persistence data 18 to 24 months after the last rMenB+OMV NZ vaccination.

At 18 months after completion of vaccination course in V72P10, a majority of subjects in groups vaccinated in the parent study showed hSBA ≥1:4 against each reference strain tested. Across rMenB+OMV NZ vaccinated groups the hSBA ≥1: 4 persisted in

- 73% to 92% subjects against 44/76-SL strain,
- 65% to 100% of subjects against 5/99 strain and
- 61% to 96% of subjects against NZ98/254 strain.

When compared with the vaccine-naive group at baseline, in all previously rMenB+OMV NZ vaccinated groups, a significantly higher percentage of subjects showed hSBA ≥1:4, against all the three strains.

Overall, the percentages of subjects with hSBA ≥1:4 were higher in groups with a three-dose vaccination schedule (rMenB016, rMenB026 and rMenB012), and in groups with a two-dose vaccination schedule (rMenB01, rMenB02, rMenB06), for all three strains when compared with groups receiving a single dose (rMenB0, rMenB6) (Table 11.4.1.1-1).

Table 11.4.1.1-1: Number (Percentages) (95% CI) of Subjects With hSBA ≥ 1:4, at 18 months after Month-6 Vaccination in V72P10, and in Naive Subjects, by Strain – MITT Population

		rMenB 06	rMenB 0	rMenB 016	rMenB 01	rMenB 026	rMenB 02	rMenB 012	rMen B6	Naive
44/76 SL		N=49	N=95	N=53	N=102	N=57	N=106	N=153	N=51	N=151
	18 months after last vaccination in V72P10	41 (84%) (70-93)	69 (73%) (63-81)	49 (92%) (82-98)	84 (82%) (74-89)	49 (86%) (74-94)	86 (81%) (72-88)	127 (83%) (76-89)	37 (73%) (58-84)	76 (50%) (42-59)
5/99		N=49	N=95	N=53	N=102	N=57	N=106	N=153	N=51	N=151
	18 months after last vaccination in V72P10	46 (94%) (83-99)	62 (65%) (55-75)	52 (98%) (90-100)	95 (93%) (86-97)	57 (100%) (94-100)	101 (95%) (89-98)	147 (96%) (92-99)	37 (73%) (58-84)	38 (25%) (18-33)
NZ 98/254		N=49	N=95	N=53	N=102	N=57	N=106	N=153	N=51	N=151
	18 months after last vaccination in V72P10	42 (86%) (73-94)	59 (62%) (52-72)	52 (98%) (90-100)	76 (75%) (65-83)	55 (96%) (88-100)	80 (75%) (66-83)	131 (86%) (79-91)	31 (61%) (46-74)	60 (40%) (32-48)

In groups with a single vaccine dose (rMenB0, rMenB6), although the percentage of subjects with hSBA ≥1:4 were relatively lower, these were still higher when compared with the vaccine-naive subjects.

Evaluator's comment

One-and-a-half year following a two dose schedule, the majority (75% or more) of adolescents continued to have antibodies associated with protection against fHBP, NadA and PorA P1.4.

Except for a higher proportion of subjects still being covered for PorA P1.4/ Strain NZ98/254 (86% vs 75%) for the months 0 and 6 schedule there is no difference between the B02 and B06 schedules.

The application reasonably argues that a 2 dose rMenB+OMV NZ regimen in adolescents at least 1 month apart is supported by antibody persistence data from study V72P10E1.

I.7.9 Study V72 28 different infant schedules

Although this study may provide comparative information about safety profile compared to, for example, the pneumococcal vaccine Synflorix, the Clinical Overview explains that regarding groups receiving: " … Synflorix only and is not within the scope of this document."

[information from the June 2016 Clinical Overview and SCE, the CSR was not located.] Study V72_28 was a phase 3b, open-label, multicenter study to evaluate the safety, tolerability and immunogenicity of rMenB+OMV NZ when administered alone or concomitantly with MenC-CRM to healthy infants according to different immunization schedules and to healthy children aged 2 through 10 years. Among others, the study groups included:

- Group II – 2-doses, at 3½ and 5 months of age
- Group III – 2-doses, at 6 and 8 months of age
- The Clinical Overview further notes that: "subjects receiving a 2- or 3-dose primary vaccination series starting at 2½, 3½ or 5 months of age followed by a booster dose at 11 months of age (study groups I, II, and III)". Therefore, Group I is likely to be two doses, starting at 2½ months.
- subjects 2 to 10 years of age receiving a 2-dose catch-up series (study group IV), and

- subjects receiving a 2-dose primary vaccination series at 3 and 5 months of age followed by a booster dose of MenC-CRM at 12 months of age, with or without concomitant rMenB+OMV NZ vaccination at 13 and 15 months of age (study groups V and VI).

In Groups I, II and III a total of 253, 250 and 251 subjects were enrolled, respectively, with the majority of subjects across groups (91% to 96%) included in the FAS data sets for analyses of primary series, persistence and booster responses.

The mean age of subjects enrolled in Groups I, II and III was 2, 3 and 6 months, respectively. The majority of subjects across the 3 groups were white (83%-92%) and of non-Hispanic ethnicity (85%-91%). Other baseline characteristics were balanced across groups, and reflected the different age categories of the subjects.

The study consisted of 2 parts. In Part 1, infants 2½ months through 6 months of age (Group 1 - III) and children 2 through 10 years of age (Group IV) were enrolled and stratified by age and vaccination schedule. Infants in Groups I, II and III received a 2- or 3-dose primary series followed by a booster dose of rMenB+OMV NZ, and children in Group IV received a 2-dose catch up series of 2 rMenB+OMV NZ vaccinations

Evaluator's comment

The CSR for Study V72_28 could not be located, nor were results of Part 1 of the study otherwise found reported. As a post-approval commitment, the Sponsor should provide the final CSR for the total study.

In Part 2 of the study (conducted in Brazil), information of which is provided in the Clinical Overview (June 2016), infants 3 months of age were enrolled to receive rMenB+OMV NZ with or without concomitant administration of meningococcal (group C) oligosaccharide diphtheria CRM-197 conjugate vaccine (Men C-CRM), at 3 and 5 months of age, and then a booster dose at 12 months of age.

The study showed that the immune response after rMenB+OMV vaccination is noninferior when co-administered with or without MenC-CRM, after a 2-dose primary vaccination schedule and a booster vaccination, as determined by percentages of subjects with hSBA titers ≥ 8.

A Secondary Objective was to explore the bactericidal antibody persistence at 11 months of age in subjects who previously received a primary series of 2 or 3 doses of rMenB+OMV NZ (Groups I, II and III), as measured (among others) by the percentages of subjects with hSBA titers ≥ 4 (≥ 5 against strain M10713).

Prior to the booster vaccination at 11 months of age, the percentages of subjects with hSBA titers ≥ 4 against strains H44/76 (86% to 100% across groups) and 5/99 (93% to 100%) were similar or slightly lower than those observed at 1 months after the primary vaccination series.

- The percentages against NZ98/254 at 11 months had decreased in all groups, with Groups I and II having 54% and 41% of subjects with hSBA titers ≥ 4 and 90% in Group III.
- Against strain M10713, the percentage of subjects with hSBA titers ≥ 5 had decreased to 23% to 42% across groups.

Evaluator's comment

*Of subjects who'd receiving a 2- dose primary vaccination course starting after at least 2½ months of age, 41-54% had response against NZ98/254 (*PorA1.4) *at 11 months, while response to M10713 (*NHBA) *was 42% or less across groups.*

According to the SCEv7228.pdf, the above information refers to CSR V72_28 Table 14.2.1.1.3.2.

Available information from Study V72 28 suggests that a 2- dose primary vaccination course starting after at least 2½ months of age results in only moderate immunity at 11 months, only 41-54% of subjects still have protective levels against PorA1.4 and 42% or less would be expected to have protection against NHBA.

I.7.10 Study V72 62 complement deficiency or asplenia

Study V72_62 (a post authorization measure)

The European Pediatric Committee (PDCO) requested that the Company conduct a study in pediatric populations at special risk of meningococcal disease.

Study V72_62 was a phase 3, open label, multicenter study in subjects 2 to 17 years of age with increased risk of meningococcal disease because either of complement deficiencies or of asplenia or splenic dysfunction to assess the antibody response after 2 doses of rMenB+OMV NZ (administered at day 1 and day 61) to determine the functional immune responses to rMenB+OMV NZ in immunocompromised patients predisposed to invasive meningococcal disease.

In study V72_62 hSBA for testing each single vaccine antigen, and a specific enzyme-linked immunosorbent assay (ELISA) validated for the Neisseria heparin binding antigen (NHBA), were used to measure the induction of antibodies directed against serogroup B meningococci following vaccination with rMenB+OMV NZ vaccine.

In total, 239 subjects (40 with complement deficiencies ["CompDef" group], 112 in the Asplenia group and 87 in the Healthy group) were enrolled in study V72_62 and included in the FAS.

Percentage of Subjects with hSBA ≥ 1:5 at One Month after Second Vaccination

Pre-existing (baseline) bactericidal antibody levels were generally low across the vaccine groups for 3 of the 4 tested indicator strains (exception was M10713.

At 1 month following the second vaccination, across the CompDef and Asplenia groups, the percentage of subjects with hSBA ≥1:5 ranged 87% to 97% against strain H44/76, 95% to 100% against strain 5/99, 68% to 86% against strain NZ98/254 and 73% to 94% against strain M10713.

Percentage of Subjects with 4-fold Increase in hSBA Titers at One Month after Second Vaccination

At 1 month after second vaccination, a high percentage of subjects achieved a 4-fold increase in hSBA titers, in both the CompDef and Asplenia groups, against serogroup B strains H44/76, 5/99, and NZ98/254, ranging 87% to 94% against strain H44/76, 92% to 100% against strain 5/99, 61% to 80% against strain NZ98/254.

The percentage of subjects achieving 4-fold increase against strain M10713 across CompDef and Asplenia groups was lower than those observed against the other 3 serogroup B strains, ranging 25% to 33%. However these results were comparable to those observed in the Healthy group against strain M10713. [from page 10 of SCE v7262.]

Evaluator's comment

The response in terms of increase compared to baseline to test strain M10713, corresponding to meningococcal B strain/antigen NHBA (which at 22% made up the largest MATS coverage), is noted to be limited; a 4-fold increase, at one month after the second vaccination, was achieved by only 25% to 33% of complement deficient or

aspenic vaccine recipients – this was noted to be comparable to those observed in the Healthy group against this (strain) M10713.

It is reassuring that in the immune compromised groups, the percentage of subjects with hSBA ≥1:5 ranged 73% to 94% against strain M10713.

I.7.11 Summary of persistence

Large phase 2 study V72P12 (E1 and E2) in toddlers. Children [who had previously received a three dose regimen of 4CMenB plus a booster at 12, 18, or 24 months of age] had antibody persistence assessed at 4-years of age.

Most children retained antibodies against Strain 5/99; that is, the NadA (Neisseria adhesin A) antigen, but only a minority (12% or less) against Strain NZ98/254; that is, the PorA1.4 antigen.

Immunogenicity associated with protection was achieved at four years of age by:

- about a third of subjects against strains H44/76 (35% or less)
- most subjects against 5/99 (89%+)
- few subjects against NZ98/254 (12% or less)
- about half the subjects against strain M10713 (53% and over).

Large phase 3 study V72P13 (E1 and E2) infant schedule.

At 12 months of age, five months after infants had received 3 vaccinations of 4CMenB, the level of antibodies against the NZ98/254 strain (the PorA1.4 antigen) had fallen to non-protective levels in most children.

In children who had received a 3+1 (booster at 12 months) regimen, persistence of immune response at 12 months after the (4th) booster dose, as measured by percentages of subjects with hSBA ≥ 1:5 was:

- strain 5/99 (96-99%), followed by
- strain 44/76 (60-64%),
- M10713 (32-40%), and
- NZ98/254 (17-18%) (Table 11.4.1-1).

The study also included a group of naive subjects, who received two doses of rMenB+OMV NZ (that is, a catch-up schedule at about 24 months of age). Persistence of immune response at 12 months after the second of two doses given two months apart to naive 12- or 13-month-old toddlers as measured by percentages of subjects with hSBA ≥ 1:5 was most marked for strain

- 5/99 (94-97%), followed by
- 44/76 (56-74%),
- M10713 (28-38%), and
- NZ98/254 (6-18%).

Small phase 2 study V72P6 E1 infant schedule and toddlers. For infants who, in study V72P6, had received the four-dose schedule rMenB or rMenB+OMV NZ at 2, 4, 6, and 12 months of age (integrated within the routine infant vaccination schedule in the UK) persistence of antibodies was assessed before a 40 month booster (slightly over two years after vaccination).

The extension of study V72P6 showed clear evidence of persistence of antibodies solely for strain NZ98/254 (the PorA1.4 antigen).

Toddlers who received two doses at about 3.3 years of age. The study further showed that the cohort who had received two (catch-up) doses of 4CMenB as 40-42 month olds were 18 months later found to have persistence for the NadA and fHBP antigens.

Study V72 28, available information from this study suggests that a 2- dose primary vaccination course starting after at least 2½ months of age results in only moderate immunity at 11 months, only 41-54% of subjects still have protective levels against PorA1.4 and 42% or less would be expected to have protection against NHBA.

Small phase 2 study V72P9 in toddlers and children. The study was conducted in the UK in 60 older infants. In the extension Study V72P9E1, at 40 months of age (about 2.3 years after older infants received three doses of 4CMenB at 6-8, 8-10, and 12 months of age), most retained bactericidal antibodies against NadA strain, but solely 36% continued to be protected against fHbp, and 14% against NZ98/254/ PorA1.4.

About one-and-a-half year after the booster at 40 months of age (that is; at 60 months of age), antibodies persisted in subjects against strain H44/76 (fHBP antigen) and strain H44/76 (fHBP), with 17% having persistence against strain NZ 98/254 [against PorA1.4], and no persistence for strain M10713 [against NHBA] (45% vs 67%).

Large phase 2b/3 study V72P10 of adolescents in Chile. This study was conducted in Chile to evaluate different schedules in adolescents 11 to 17 years of age. Subjects received either 1-dose, 2-doses (either one or two months apart), or 3-doses one month apart of rMenB+OMV NZ, followed by another vaccination (booster) at month 6 or placebo.

One-and-a-half year following a two dose schedule, the majority (75% or more) of adolescents continued to have antibodies associated with protection against fHBP, NadA and PorA P1.4. The application reasonably argues that a 2 dose rMenB+OMV NZ regimen in adolescents at least 1 month apart is supported by antibody persistence data from study V72P10E1.

I.8 Safety

There is a SCS Sept 2011, plus two additional SCS reports regarding studies 728 and 762 both dated May 2016.

There are studies in infants as well as in adolescents and adults to inform regarding the safety profile; in addition there is post-marketing experience.

This report will briefly characterise the safety profile in infants and toddlers, and adolescents, and briefly consider the following issues:

- Injection site reactogenicity and pyrogenicity in infants, toddlers and adolescents
- Limb swelling
- Kawasaki Disease
- PSUR report.

I.8.1 Infants and toddlers

In the Clinical Overview, the development of the vaccine is covered, including experience with the rMenB and rMenB+OMV NZ vaccines in infants.

Both vaccines showed similar safety profiles and overall comparable to that of the routine vaccines (e.g. Prevenar™), with the exception of fever, which was more common for rMenB+OMV NZ with routine vaccines than for rMenB with routine vaccines and for the routine vaccines.

Evaluator's comment

Given the ability to induce fever in children, especially when coadministered with other vaccines, the possibility of febrile seizures may be more commonly associated with this vaccine.

As per TGA liaison with the Sponsor, the possibility of febrile seizures is noted in the draft New Zealand datasheet. The draft datasheet appropriately includes under 'undesirable effects' for Infants, Toddlers, and Children (up to 10 years of age):

Nervous system disorders

Very common: sleepiness, unusual crying, headache

Uncommon: seizures (including febrile seizures)

Most of the safety data for rMenB+OMV NZ in young infants comes from subjects in studies V72P12 and V72P13 who received a 3-dose schedule at 2,4,6 months of age given concomitantly with routine infant vaccines (i.e., Infanrix Hexa [DTaP-IPV-HBV-Hib combined vaccine] and the heptavalent pneumococcal conjugate vaccine, Prevenar).

A pooled analysis was conducted on 3,102 infants exposed to at least one dose of rMenB+OMV NZ with concomitant routine vaccinations from both studies.

Tenderness followed by erythema and induration were the most commonly reported local reactions after vaccination with rMenB+OMV NZ with concomitant routine vaccinations (i.e., rMenB+OMV NZ + Routine group).

A higher percentage of subjects in the rMenB+OMV NZ with concomitant routine vaccinations experienced these local reactions than in the group receiving Novartis meningococcal C conjugate vaccine with concomitant routine vaccines (i.e., MenC + Routine group) or routine vaccines alone (i.e., Routine group; study V72P13).

Evaluator's comment – reactogenicity when co-admistered

Very high incidence of local reactions at the injection site, as well as solicited systemic reactions (including very high incidence of fever) – but TGA report concedes incidence is similar to that of routine childhood vaccinations, if given separately.

Eg. Table 2.5.5.2-2 not reproduced here shows that severe 'tenderness' is much more commonly reported when routine vaccines are coadministered with the MenB vaccine; often 10-11% and 14% vs while the MenC vaccine given together with routine vaccines commonly has incidence of severe tenderness of 5% or less.

The majority of the local reactions were mild or moderate in nature and transient; few continued past the day 7 observation window. This is consistent with data in the literature for other vaccines containing OMV and aluminum.

Fever (i.e., body temperature ≥38.0° C) was reported in a high percentage of infants and was more frequently reported after receiving rMenB+OMV NZ with routine vaccinations than after routine vaccinations only and routine vaccinations concomitantly administered with MenC vaccine (69%-79% vs. 42%-63% across the three vaccinations for rMenB+OMV NZ +Routine group pooling V72P12 and V72 P13 and MenC + Routine group.

Similar percentages of subjects reported fever after the first, second, or third vaccination within each vaccine group.

Fever ≥39.5° C across the three vaccinations was reported by 4%-7% of the rMenB+OMV NZ +Routine group, from 1% to 2% of the routine only group, and from <1% to 2% of MenC + Routine group.

When it occurred, fever associated with rMenB+OMV NZ + Routine group was very predictable and transient with onset mainly between 6 hours and one day post vaccination. The majority of fever resolved within 48 hours after vaccination.

Except for tenderness, local reactogenicity to rMenB+OMV NZ was similar for subjects in the rMenB+OMV NZ + Routine concomitant 2,4,6 schedule and subjects who received rMenB+OMV NZ alone.

Systemic reactogenicity was generally lower when rMenB+OMV NZ was administered alone than for the concomitant rMenB+OMV NZ + Routine 2,4,6 schedule (Table 2.5.5.2-3).

Table 2.5.5.2-3 Summary of Systemic Reactions by Vaccination Following a Three-dose Schedule of rMenB+OMV NZ With and Without Concomitant Vaccines in Infants

		Percentages of Subjects With Any (Severe) Reaction								
		2,4,6 Schedule							2,3,4 Schedule	
	Group Study	MenB+R Total P12+P13	MenB+R P13	MenC+R P13	Routine P13	MenB+R P12	MenB+R3,5,7 P12		MenB+R P12	Routine P12
	Vacc.	N=3102	N=2478	N=490	N=659	N=624	MenB N=627	Routine N=627	N=318	N=311
Change Eat. Habits	1st	51(3)	50(3)	31(1)	30(2)	56(4)	46(3)	36(2)	59(4)	33(3)
	2nd	44(3)	43(2)	32(1)	25(<1)	50(4)	35(2)	34(2)	56(5)	31(2)
	3rd	43(3)	42(2)	29(1)	25(2)	47(4)	32(1)	29(1)	44(3)	23(1)
Sleepiness	1st	72(3)	73(3)	58(4)	56(2)	67(4)	61(3)	52(2)	73(6)	59(3)
	2nd	64(2)	63(1)	45(1)	42(<1)	65(3)	48(2)	44(2)	69(4)	49(<1)
	3rd	53(1)	53(1)	35(1)	32(<1)	54(3)	37(2)	34(2)	55(1)	38(2)
Vomiting	1st	13(1)	12(<1)	11(<1)	7(<1)	17(1)	14(1)	12(<1)	14(0)	15(<1)
	2nd	13(<1)	12(<1)	11(1)	6(<1)	14(<1)	10(<1)	11(1)	17(1)	12(0)
	3rd	11(<1)	11(<1)	9(<1)	7(<1)	16(1)	9(0)	9(1)	15(1)	11(<1)
Diarrhea	1st	24(1)	24(<1)	20(1)	17(1)	23(1)	20(1)	17(1)	25(1)	21(1)
	2nd	22(1)	21(1)	15(<1)	17(<1)	23(2)	20(1)	19(1)	27(1)	21(2)
	3rd	18(1)	17(1)	13(1)	12(<1)	21(1)	12(<1)	16(1)	15(<1)	18(<1)
Irritability	1st	79(6)	81(5)	55(3)	61(2)	74(8)	63(5)	56(5)	79(8)	57(3)
	2nd	79(5)	80(6)	58(4)	62(3)	74(11)	61(8)	54(5)	75(10)	54(4)
	3rd	76(6)	77(5)	49(3)	54(1)	71(10)	53(5)	45(3)	66(6)	44(4)
Unusual Crying	1st	69(5)	71(5)	52(3)	41(2)	64(7)	53(5)	45(2)	68(8)	36(4)
	2nd	66(5)	66(4)	50(4)	40(2)	66(9)	52(4)	43(3)	65(6)	42(4)
	3rd	56(4)	55(4)	39(3)	30(2)	60(7)	40(3)	30(2)	61(5)	33(2)
Rash	1st	5(1)	5(1)	4(<1)	3(1)	5(<1)	4(20	5(1)	6(10	5(2)
	2nd	6(2)	6(2)	4(<1)	5(1)	7(1)	5(1)	5(1)	4(<1)	3(1)
	3rd	5(1)	5(1)	3(0)	5(1)	5(<1)	6(1)	4(1)	5(1)	5(2)
Fever [Body Temp. ≥38°C (≥40°C)][b]	1st	75(<1)	78(<1)	46(0)	44(<1)	61(<1)	38(<1)	32(<1)	58(<1)	31(<1)
	2nd	79(1)	84(1)	63(<1)	59(<1)	62(1)	41(<1)	37(<1)	59(0)	36(0)
	3rd	69(1)	73(1)	42(0)	50(1)	51(<1)	26(0)	25(1)	44(0)	23(0)
Medically Attended Fever	1st	1(-)	1(-)	1(-)	1(-)	3(-)	1(-)	1(-)	1(-)	1(-)
	2nd	1(-)	1(-)	1(-)	<1(-)	1(-)	1(-)	1(-)	3(-)	1(-)
	3rd	1(-)	1(-)	2(-)	1(-)	2(-)	1(-)	1(-)	1(-)	1(-)
Other Indicators of Reactogenicity										
Analge. Antipyr. Med. Used[a]	1st	75(-)	79(-)	40(-)	43(-)	60(-)	41(-)	34(-)	60(-)	29(-)
	2nd	81(-)	85(-)	52(-)	52(-)	66(-)	42(-)	36(-)	59(-)	35(-)
	3rd	71(-)	74(-)	36(-)	45(-)	58(-)	27(-)	31(-)	46(-)	19(-)

Source: section 5.3.5.3 ISS: Table 2.7.4.7.23; section 5.3.5.1, CSR V72P12, Table 14.3.1.1.3.4, Table 14.3.1.1.3.5; [a]In study V72P12 only antipyretic use was collected and their use was discouraged for prophylactic purpose; in study V72P13 subject's parents/legal guardians were asked retrospectively if an analgesic or an antipyretic medication was used; [b]as defined by the Brighton Collaboration (Marcy et al, 2004)

Evaluator's comment

Fever was reported by similar percentages of subjects after rMenB+OMV NZ given separately and after routine vaccinations. However, the 4CMenB vaccine co-administered with routine vaccines results in higher rates of fever.

- *26%-41% - only rMenB+OMV NZ 2,4,6 + Routine 3,5,7 group*

- *25%-37% - only the routine vaccinations*
- *44%-59% - rMenB+OMV NZ concomitantly with the routine vaccines.*

Immunologically naïve older infants

In study V72P9 immunologically naive older infants received rMenB+OMVNZ or rMenB (i.e., the vaccine formulation without OMV) at 6, 8 and 12 months of age. Overall, the reactogenicity profile was similar to that of younger infants.

Toddlers: Booster at 12 Months and two doses of rMenB+OMV NZ with or without concomitant routine vaccinations in immunologically naïve toddlers

The most commonly reported local and systemic reactions after vaccination with the fourth (booster) dose of rMenB+OMV NZ were tenderness followed by erythema, and induration, and irritability [information mainly from study V72P13E1].

Similar results were obtained for local reactions to rMenB+OMV NZ alone or concomitantly with MMRV.

Fever ≥38° C within 7 days of vaccination was reported more when concomitantly administered with the MMRV vaccine than when rMenB+OMV NZ was given alone (46% vs. 37%,

Comparison 4CMenB and MMRV (Study V72P13E1)

Daily fever rates for the month (days 1-28) after the 12 months of age vaccination in groups rMenB+OMV NZ alone (12B13M group), MMRV alone (12M13B15B group) and concomitant vaccination (12B12M group) were compared.

Fever was mostly reported during the 1-4 days after the rMenB+OMV NZ vaccination alone and during the 5-28 days after the MMRV vaccination alone.

- Assessed on study days 1-4, the percentage of subjects reporting fever after a dose of rMenB+OMV NZ given alone (either as a fourth (booster) dose at 12 months or as part of the two-dose schedules starting at 12 or 13 months) ranged from 35% to 54%.
- During the 5-28 day period fever was mainly contributed to by MMRV vaccination, with 53% of subjects reporting fever during this period following MMRV vaccination alone [from synopsis, page 44 of CSR].

When rMenB+OMV NZ was given concomitantly with the MMRV vaccine, the fever rates showed a trend towards an additive effect; i.e. fever reported during the 1-3 day period as well as during the 5-28 day period after the vaccinations.

The majority of fever was of mild to moderate in intensity throughout. The rate and magnitude of fever were similar between rMenB+OMV NZ and MMRV vaccines.

Booster 12 Months following two doses of rMenB+OMV NZ in the second year of life

In study V72P13E2, safety data was collected for 30 days following a booster (third) dose of rMenB+OMV NZ administered at one year after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1.

Most subjects (89%-99%) in the V72P13E2 groups who had received 2 toddler doses in study V72P13E1 experienced solicited local or systemic reactions within 7 days after booster vaccination with rMenB+OMV NZ; most of the reactions were mild to moderate in severity, and transient. The most common local reaction after vaccination with the third (booster) dose was tenderness which was reported in 94% of the subjects with 18% of the subjects having severe tenderness (crying when the injected limb was moved). A total of 70%-76% subjects had

erythema with 3% of subjects having severe erythema (>100mm). Other local reactions reported were induration and swelling.

The most common systemic reaction after the booster dose was irritability, reported in 60%-82% of the subjects with 1%-6% of the subjects having severe irritability.

Fever (≥38°C) was reported in 33% of subjects in both groups, with none of the subjects reporting temperature ≥40°C. Antipyretic medications were administered as treatment to 30%-35% of the subjects and none of the subjects had medically attended fever.

I.8.2 Adolescents and adults

rMenB+OMV NZ Safety Profile in Adolescents and Adults (11 Years and Above)

The characterization of the safety profile of rMenB+OMV NZ in the adolescent and adult population is based on the data from 3 studies: V72P10 in subjects aged 11 to 17 years; and V72P4 and V72P5 in adults (18 to 50 and 18 to 40 years of age, respectively).

Reactogenicity to a second or third dose was lower than to the first.

For subjects aged 11 years and older the most commonly reported local reaction after any rMenB+OMV NZ dose was pain, followed by erythema in adolescents and induration in adults [Table 2.5.5.2-1, which is not reproduced here, shows that 13% to 18% of adolescent subjects report 'severe' pain after any of their three vaccinations]. In the adolescent study V72P10, all local reactions were reported less frequently after placebo than after rMenB+OMV NZ except for pain, which was similarly reported.

The most commonly reported systemic reactions after any rMenB+OMV NZ dose were malaise, myalgia and headache. In the adolescent study V72P10, each systemic reaction was similarly or slightly less frequently reported after placebo than after rMenB+OMV NZ.

Fever was similarly reported in the rMenB+OMV NZ and placebo groups (3%-5% and 2%-4% across vaccinations, respectively) and rates were low and similar for both adolescents and adults. The frequency of reports for local and systemic reactions was generally lower with subsequent administrations. Most of the local and systemic reactions were mild or moderate in severity and were transient.

I.8.3 Study V72P16 prophylactic antipyretic treatment

Evaluator's comment

The application in a Clinical Overview notes that fever is a characteristic feature of OMV vaccines when administered in the first year of life. In addition, the MeNZB experience showed self-limited mild to moderate fever, not accompanied by either increased rates of medical attention or, more specifically, increased rates of febrile seizures.

The rate of fever when rMenB+OMV NZ was given to infants concomitantly with routine vaccines was higher than for routine vaccines alone, however when rMenB+OMV NZ was administered alone fever rates were lower and similar to those of the routine vaccines.

When it occurred, the fever observed after concomitant rMenB+OMV NZ and routine vaccines followed a predictable pattern with resolution on the day after vaccination.

Study P16 was a phase 2, partially observer-blind, randomized, controlled study in healthy infants aged approximately 2 months at the time of enrolment.

The study, with a three-dose primary infant schedule administered at 2, 3 and 4 months of age and a booster administered at 12 months of age, was aimed at assessing the safety and

immunogenicity of different doses and formulations (including decreasing OMV content) to guide future development of a new Novartis Meningococcal B Recombinant Vaccine (rMenB+OMV NZ [the group receiving this vaccine, that is; the MenB group with full dose of antigens was designated as: B+OMV]).

Reduction in OMV by one-half or more resulted in reduced immune response to the OMV component of the vaccine, although responses to the other antigens appeared unaffected.

In addition, this study assessed whether prophylactic administration of paracetamol could decrease the incidence of febrile reactions following vaccination without impacting the immunogenicity of rMenB+OMV NZ and the concomitantly administered routine infant vaccines and provided information about vaccine produced using the original phase 2 manufacturing process.

rMenB+OMV NZ vaccination was co-administered with InfanrixHexa and Prevenar in infants at the 2, 3, 4-month schedule. Subjects receiving prophylactic antipyretics (N=183) received one dose of paracetamol (10-15 mg/kg per dose) just before study vaccination and two further doses at 4-6 hour intervals after vaccination.

A control group (N=184) received no prophylactic paracetamol. Rectal temperatures were measured in both groups for seven days postvaccination.

Prophylactic paracetamol can also reduce local and systemic reactions overall and, importantly a reduction in rates of fever, without a negative effect on rMenB+OMV responses and without interference with most of the concomitant routine vaccine antigens.

Paracetamol just before vaccination is able to reduce fever rates by [up to] approximately 50% after the first dose.

[page 197 of CSR] Subjects who were administered paracetamol prophylactically [that is; group Par+B+OMV], had fever (≥38.5°C) in up to 36% subjects after vaccine dose while those in group B+OMV had fever (≥38.5°C) in up to 52% subjects.

Evaluator's comment

With preventative paracetamol, up to a third of infants who received 4CMenB had Fever (≥ 38.5°C). The likelihood of such fever is up to halved when paracetamol is given from before the vaccination, plus two further doses.

While not reproduced here, the following table shows that the text refers solely to the booster dose: Table 12.2.3-2a: Numbers (%) of Subjects with Systemic Reactions during 1 to 7 Days after Each Vaccination - Safety Set. This table shows that for the first injection, 52% of subjects in the B+OMV group had Fever (≥ 38.5°C), while the corresponding number was 26% of the Par+ B+OMV group. For the second 30% vs 11%, and for the booster 52% vs 36%.

In the study, subjects receiving prophylactic antipyretics received one dose of paracetamol (10-15 mg/kg per dose) just before study vaccination and two further doses at 4-6 hour intervals after vaccination.

The draft datasheet (and the package inset) appropriately have under 'interactions with other medicines and other forms of interaction' that:

> The safety profiles of the co-administered vaccines were unaffected by concomitant administration of BEXSERO with the exception of more frequent occurrence of fever, tenderness at the injection site, change in eating habits and irritability. Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either BEXSERO or routine

vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied.

The CMI includes:

The incidence of fever may be decreased by the use of paracetamol. Before you or your child receives vaccination, ask your doctor about the risks of fever and how to treat it, including what to do if fever does not respond to initial treatment.

I.8.4 Limb swelling and persistent nodules added to PI

The proposed datasheet includes limb swelling and persistent nodules in the section: Adverse reactions from post-marketing spontaneous reports:

General disorders and administration site conditions Fever (adolescents from 11 years of age and adults) Injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site and injection site nodule which may persist for more than one month).

The addendum to the Clinical Overview (Dec 2016) explains that spontaneous report cases with events coded to MedDRA preferred term "extensive swelling of the vaccinated limb" should be considered as a signal (ie, the cases contained sufficient evidence suggesting a causal association between rMenB+OMV NZ and occurrence of the event to justify further investigation).

The pathophysiology of **extensive swelling of the vaccinated limb (ESL)** is unknown, however, it is considered to potentially represent an exaggerated injection-site reaction. Per Woo, "That local reactions may span a continuum from minor injection-site reactions to ESL is biologically plausible and suggests substantial variability in individual susceptibility to this adverse event."

While ESL has been reported following over 20 vaccines, it is most closely associated with diphtheria containing vaccines.

Overall, the evaluation of 47 cases of ESL that were retrieved from GSK worldwide safety database from launch until July 29, 2016 which were adjudicated both to meet the GSK case definition of ESL and to be reasonably causally related to rMenB+OMV NZ administration resulted in the conclusion that there is sufficient evidence of a causal association between this event and vaccination with rMenB+OMV NZ.

The observed events were generally well-tolerated and self-limiting, resolving without sequelae, normally within 7 days. The safety profile in subjects experiencing ESL was otherwise consistent with the known rMenB+OMV NZ safety profile.

Based on these findings, the Company proposes to amend the current rMenB+OMV NZ PI to include ESL.

In addition, evaluation of 24 confirmed or suspected cases of **persistent nodules** at the injection site retrieved from GSK worldwide safety database from launch until August 2016 which were adjudicated both to meet an ad hoc case definition of "injection site nodule" and to be reasonably causally related to rMenB+OMV NZ administration resulted in the conclusion that there is sufficient evidence of a causal association between this event and vaccination with rMenB+OMV NZ.

In many of the SRs, the nodules persisted for longer than 1 month; in slightly less than half of the identified cases, it was observed that the nodule persisted from 1 to as long as 3 months

post vaccination. An etiology for the nodule, including possible hypersensitivity to aluminium of rMenB+OMV NZ formulation, could not be determined.

I.8.5 Kawasaki Disease

The 2011 SCS includes that there were 7 cases of suspected Kawasaki Disease (KD) reported in clinical studies of rMenB+OMV NZ: 4 cases in Study V72P13, 2 cases in Study V72P12 and 1 case in Study V7213E1.

Six cases were in recipients of the rMenB+OMV NZ and one in a control subject receiving Men C conjugate.

An external, independent KD Expert Panel was organized by Novartis to review the KD cases. The Expert Panel included two pediatric infectious disease physicians and a pediatric cardiologist, all of whom are recognized experts in the KD field. The Chair of the Data Monitoring Committee, which has oversight of the safety of the subjects participating in the rMenB+OMV NZ clinical studies, was also involved with the Expert Panel in the review of the KD cases.

A "confirmed" case of KD was defined by the Expert Panel as one that met the classical case definition of KD: fever of >5 days duration and the presence of at least 4 of the 5 other principal clinical signs (rash, cervical lymphadenopathy, bilateral conjunctiva injection, oral mucosal changes and peripheral extremity changes).

Patients whose illness did not meet the KD case definition, but who had coronary artery abnormalities consistent with KD were also classified as a confirmed case.

Patients whose illness did not meet the above KD case definition and had no coronary artery abnormalities were classified as having "incomplete" KD. For these cases, additional clinical and laboratory findings were taken into consideration to judge the case as a "likely or probable" case of KD or "unlikely" KD.

The Expert Panel was also asked to judge the causal relationship of the cases as either "unrelated" or "possibly related" to study vaccinations. The Expert Panel utilized the concept of a latency period of up to 30 days between the time of study vaccination and onset of fever as an aid in determining whether the case could be considered related to study vaccination. Such a latency period is reasonable to postulate based on:

(1) strong evidence suggesting that KD is precipitated by an infectious agent;

(2) the occurrence of a well-defined precipitating event in selected instances of KD reported in the medical literature;

(3) the typical and reproducible clinical evolution of the syndrome and associated pathophysiological processes; and

(4) previous publications that also support the concept of a 30-day latency period.

The application notes that the occurrence of these cases is consistent with the known epidemiology of KD in terms of geographic and temporal clustering, and seasonal variation.

The first two cases of KD reported were clustered geographically and in time, both being reported from Finland in October of 2008, despite a long enrollment period in the country.

The two cases reported from Belgium were also clustered in time and space, although one of the cases is unlikely to be KD.

Seasonal variation was striking in that two cases occurred in Finland in October of 2009, and the remaining five cases occurred in March, April and May of 2009, and in April 2010.

This epidemiology is consistent with the proposed infectious etiology of KD.

The six suspected KD cases in infants from Studies V72P12 and V72P13 are summarized in Table 2.1.6-4 by adjudication outcome and by onset interval ≤30 days or >30 days after the last dose of study vaccine.

Table 2.1.6-4 Summary of Suspected Cases of Kawasaki Disease in Studies V72P12 and V72P13 by Onset Interval ≤ 30 Days and > 30 Days from Last Dose of Study Vaccine

	Onset Interval from Last Study Vaccination	
Adjudication Outcome	**≤ 30 days**	**> 30 days**
rMenB+OMV NZ (N=4050*)		
Confirmed KD	2 (0.05%)	1 (0.02%)
Incomplete but likely KD	0	1 (0.02%)
Unlikely KD	1 (0.02%)	0
MenC or Routine Vaccines (N=1461*)		
Confirmed KD	0	1 (0.07%)

*Number of exposed subjects receiving at least one study vaccination in combined studies V72P12 and V72P13.

Based on the cumulative total of 2,915 person-years of follow-up time for the rMenB+OMV NZ vaccinees in both studies V72P12 and V72P13, the estimated (equivalent) annual incidence of KD is:

- 137 [95% CI: (37, 351)] per 100,000 children when the four confirmed and incomplete KD cases are considered,
- 103 [95% CI: (21, 301)] per 100,000 when only the 3 confirmed cases are considered, and
- 69 [95% CI: (8, 248)] per 100,000 when only the two confirmed and possibly related cases are considered (within the 30-day period after vaccination).

In comparison, the estimated (equivalent) annual incidence rate for the confirmed KD case in the control arms, based on 1,529 person-years of follow-up time (subjects receiving MenC conjugate co-administered with routine vaccines or routine vaccines only), is 65 [95% CI: (2, 364)] per 100,000 children.

The point estimates are in the similar range and, with the limited number of cases, the confidence intervals are wide and overlapping indicating that there are no significant differences in KD incidence rates between the rMenB+OMV NZ and control groups.

I.8.6 PSUR to January 2017

Post-marketing experience

The application includes an EMA Pharmacovigilance Risk Assessment Committee (PRAC) PSUR assessment report covering from 14 January 2016 to 13 January 2017.

The number of subjects exposed since launch until the data lock point (DLP) of this PSUR is estimated as being between a minimum of 3,569,743 and a maximum of 7,139,487 subjects.

Signals have been investigated.

No actions related to investigational use or related to marketing experience have been undertaken. A withdrawal of the MAA in Morocco was performed due to limitations in the product sample delivery needed for registration purposes in the country.

The overall benefit/risk balance of Bexsero remains unchanged.

I.9 Product information

There is a question relating to the product information; see below.

The application cover implies that that the approved Australian PI was the reference document for the New Zealand datasheet.

The application cover letter includes the following information.

> GSK intends providing the Australian Product Information (PI) as a package insert in each carton BEXSERO.
>
> An assurance is provided that the package insert will be kept in alignment with the approved New Zealand Data Sheet and approved product details.

I.10 Risk management plan

The PhV team is assessing the RMP.

Documentation [data received December 2017 – Attachment 7.3] includes RMP_26Nov15 and RMP_26Oct16.

Routine risk minimisation and an educational program are proposed. The education programme will consist of the provision of a booklet for HCPs, and a tear-off leaflet for patients and their caregivers following each administration of Bexsero.

Distribution of Bexsero educational materials in Australia as of December 1, 2015

Since registration, the HCP Booklet and Patient Leaflet have been distributed as hardcopy versions alongside supply of Bexsero vaccine to prescribers. As of December 1, 2015, these educational materials will be accessed via the GSK website health.gsk.com.au.

Currently Bexsero is not PBS listed and has not yet been adopted by the National Immunisation Program (NIP). Therefore, GSK Australia commits to implementing a second Australian education program for Healthcare Professionals (HCPs; i.e. prescribers, pharmacists and nurses) and patients and their caregivers for Bexsero once adopted on the NIP.

As of December 1, 2015, the Australian approved PI and the CMI for Bexsero are available on the GSK Australia website www.gsk.com.au and the TGA website www.ebs.tga.gov.au.

I.11 Benefit risk assessment

Background: international approvals

Bexsero is one of the two internationally approved meningococcal B vaccines. Bexsero was approved in Europe (January 2013), Australia (August 2013), Canada (December 2013), and the USA (January 2015), as well as in other countries. The vaccine was introduced to the UK schedule in September 2015.

In the US, Bexsero is approved for use in individuals 10 through 25 years of age. In other countries, infants are covered; for example: in the EU from 2 months of age and older; in Canada from 2 months through 17 years old, in Australia from 2 months of age and older.

Background: factors influencing efficacy

The efficacy of the 4CMenB vaccine can be expected to change, as the epidemiology of meningococcal B strains changes. Such changes in epidemiology are not expected to be rapid, but to evolve over multiple years. There will likely be adequate information on changes of epidemiology relevant to epidemiology in New Zealand to ensure appropriate use of the Bexsero vaccine, given the licensure of the vaccine internationally and programme-wide implementation in the UK.

MenB vaccines are not expected to protect against all serogroup B strains. The level of meningococci group B immunogenic-protein expression varies greatly, and these proteins are antigenically diverse.

Benefit risk balance

The benefit risk balance of Bexsero (Multicomponent Meningococcal group B Vaccine; rMenB+OMV NZ, 4CMenB) suspension for injection for protection against invasive disease caused by N. meningitidis group B strains for individuals from 2 months of age and older is positive.

- Efficacy is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent MenB strains specimens isolated in Australia during the period January 2007- December 2011; the strains are also prevalent in the US and Europe. In infants and toddlers, antibody levels do not appear to persist long-term. In addition, efficacy is inferred from the rapid decrease [in addition to the already decreasing trend prior to the vaccination programme] in incidence of group B disease in the UK following introduction of the MenB vaccine to the UK schedule in September 2015.
- The vaccine has been shown to have an acceptable safety profile, although tenderness at the injection site is very common (eg up to 10%-14% of infants are noted to have severe tenderness when routine vaccines are co-administered with the MenB vaccine), and fever is also common, especially if given together with other vaccinations (eg if co-administered, body temperature ≥38.0° C was reported in 69%-79% of infants). Among adolescents, 13% to 18% report 'severe' pain after any of their three vaccinations).

Issues to be taken into account regarding efficacy

There is no comparative data regarding the UK reduced infant schedule. The proposed datasheet variously notes the need for a booster dose with particular vaccination schedules, although for some age groups it is noted that: "The need for a booster dose after this vaccination schedule has not been established."

Information regarding need for booster doses

Information about likely duration of protection can assist decisions about the need for booster doses. Available information suggests that, in infants and toddlers, the vaccine provides short to intermediate term protection against key prevalent strains in countries with western-European meningococcal B strain epidemiology. (Even limited duration of protection is important, as it may cover the young who experience the highest rates of disease.) In the young, there is variable waning of antibody levels against each of the four vaccine antigens. The datasheet should include comprehensive, clear information about antibody levels following vaccination. This should include two plus one schedules, to facilitate interpretation of the UK reduced schedule.

The Sponsor will be asked to provide an updated datasheet, that includes comprehensive, clear information about likely duration of protection. The information could, for example, be in the form of tables as follows.

Infant schedules and antibody persistence at approximate ages

study		Infant schedule	1 year of age	2 years of age	3 years of age	4 years of age
V72P12E2	N=805	3+1 (booster at 12, 18, or 24 months of age)	Pre 12 month booster 25% NHBA 58% fHBP 97% NadA 19% PorA1.4			Nil NHBA ≤35% fHBP ≥89% NadA ≤12% PorA1.4
V72P13E2		3	Pre 12 month booster not tested NHBA 91-82% fHBP 98-100% NadA 20-21% PorA1.4	12 months after booster 32-40% NHBA 60-64% fHBP 96-99% NadA 17-18% PorA1.4		
V72P6	N=108 for persistence at 40 months	3+1			Pre- booster at 40 months (5th dose) Nil NHBA Nil fHBP - NadA 41% PorA1.4	
V72 28		2 doses starting at 2.5 and 3.5 months of age	At 11 months 42% NHBA 86-100% fHBP 93-100% NadA 41-54% PorA1.4			

Toddler schedules and antibody persistence at approximate ages

study		schedule	2 years of age	3 years of age	4 years of age	5 years of age
V72P9E1	N=60	3-dose schedule at 6-8, 8-10, and 12 months of age			At 40 months of age, 28 months after a third dose 79% NHBA 36% fHBP 93-100% NadA 14% PorA1.4	At 60 months of age, 20 months after booster Nil NHBA 67% fHBP 100% NadA 17% PorA1.4
V72P13E2			Schedule: 2-dose at 24 months of age	12 months after last dose 28-38% NHBA 56-74% fHBP 94-97% NadA 6-18% PorA1.4		
V72P6				Schedule: 2-dose at 40-42 months of age		18 months after vaccination Nil NHBA 71% fHBP 100% NadA 31% PorA1.4

Note:

nil refers to the situation where antibody levels in the vaccination group are no different from those in the vaccine naïve comparison group.

- refers to instances when the presence of the antigen was tested.

I.12 Conclusion

Subject to an appropriately updated datasheet, based on review of the information provided, and taking account of the information relating to the TGA and EMA assessment, the Evaluator considers that under Section 20 of the Medicines Act consent to distribute Bexsero (Multicomponent Meningococcal group B Vaccine) suspension for injection can be recommended for the following indication:

> BEXSERO is indicated for active immunisation against invasive disease caused by N. meningitidis group B strains. See section 5.1 for information on protection against specific group B strains.
>
> BEXSERO is indicated for vaccination of individuals from 2 months of age and older.
>
> The use of BEXSERO should be in accordance with official recommendations.

As a post-approval commitment, the Sponsor should provide the final CSR for the Study V72_28.

The Sponsor should note that the application cover letter states that subject to approval in New Zealand, a recent clinical variation in Australian PI (regarding an additional dosing schedule) will be submitted subject on approval in Australia.

TT Number	TT50-10296
Date of this report:	March 2018

I.13 Appendix

I.13.1 Glossary

ESL	extensive swelling of the vaccinated limb
4CMenB	Bexsero; the rMenB+OMV NZ (4-component MenB vaccine)
hSBA	human serum bactericidal antibody
LPS	lipopolysaccharide
MATS	Meningococcal Antigen Typing System
rMenB	Vaccine formulation containing only the three recombinant protein antigens fHBP, and NadA, and NHBA. Originally named 5CVMB (5-Component Vaccine against MenB) in some publications. Evaluated in studies V72P1, V72P1E1, V72P2, V72P3, V72P5, V72P6 and V72P9
rMenB+OMV NW	Vaccine formulated with fHBP, NadA, NHBA and OMV Norwegian strain antigens. Evaluated in studies V72P1, V72P2, V72P3 and V72P5
rMenB+OMV NZ	The final Phase 2b/3 vaccine formulation containing the three recombinant protein antigens (fHBP, NadA, and NHBA,) and OMV NZ derived from Neisseria meningitidis serogroup B strain

	NZ98/254 (New Zealand strain). Evaluated in studies V72P4, V72P5, V72P6, V72P9, V72P10, V72P12, V72P13, and V72P13E1
OMV NZ	Outer membrane vesicle derived from Neisseria meningitides serogroup B strain NZ98/254 (New Zealand strain) OMV NW Outer membrane vesicle derived from Neisseria meningitidis serogroup B strain 44/76 (Norwegian strain)

I.13.2 Background

Epidemiology

Neisseria meningitidis is an encapsulated gram-negative bacterium. In Europe, the majority of disease occurs in infants under 1 year of age, followed by children through from 1 to 5 years of life. A second peak occurs in adolescents 15 to 19 years of age.

In contrast to serogroup A and C epidemics, which usually resolve in 1 to 3 years, serogroup B epidemics begin slowly but may persist for 10 years or longer, as seen in Cuba, Norway, areas of Chile, and New Zealand.

Data from the New Zealand epidemic of meningococcal B disease collected from 1998 to 2003, also showed that the highest rates of disease consistently occurred in those under 5 years of age.

The application cover letter explains that

> Outbreaks continue to occur in specific areas of New Zealand. In September 2016, the New Zealand MOH enquired about the feasibility of sourcing unregistered meningococcal vaccine to curb potential outbreak in Southland, New Zealand.
>
> There had been 12 cases of meningococcal B notified in the Southern District Health Board area, seven of which were the New Zealand epidemic strain. These were in the adolescent age group.

Selected information from the notifiable diseases in New Zealand annual report 2016 is given below. In 2016, 75 cases of meningococcal disease were notified. The notification rate (1.6 per 100,000) was slightly higher than the 2015 rate (1.4 per 100,000, 64 cases).

The rate was also a significant decrease from the peak rate (16.7 per 100,000 in 2001) experienced during the New Zealand meningococcal disease epidemic (driven by the B:P1.7-2,4 strain). The 2016 rate is similar to the rate of 1.5 per 100,000 observed in the immediate pre-epidemic years (1989–1990).

Seventy (93.3%) cases were laboratory-confirmed and the strain type was determined for 67 cases:

- group B (47 cases, including 23 B:P1.7-2,4 [70% of the 67 cases were group B; 47 cases]),
- group C (8 cases) [12% of the 67 cases were group C; 8 cases],
- group Y (7 cases), and
- group W (5 cases) (Table 20).

Of the 26 laboratory-confirmed cases in children <5 years of age, all were able to be typed and, of these, 17 (65.4%) were determined to be group B strain.

https://surv.esr.cri.nz/PDF_surveillance/AnnualRpt/AnnualSurv/2016/2016AnnualNDReportFinal.pdf

Evaluator's comment

In New Zealand in 2016, Group B meningococcal disease made up the majority of strain-typed disease generally, and also for children <5 years of age.

The number of cases covered by the MenACWY vaccine (20) is less than the group B cases (47).

Meningococcal B vaccine development

Capsular polysaccharide vaccines have been used successfully in preventing disease and limiting epidemics and outbreaks caused by meningococcal serogroups A, C, W135, and Y. However, the capsular polysaccharide of meningococcal serogroup B is poorly immunogenic. Therefore, research has focused on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines.

Serogroup B vaccines based on protein-containing outer membrane vesicles (OMV) have been safe and effective in controlling epidemic disease caused by strains homologous to the vaccine strain in Cuba, Brazil, Chile, Norway, and New Zealand. [Strain replacement due to capsular switching, which has been noted for polysaccharide vaccines, may not be an issue for this protein-based vaccine.]

The use of these OMV vaccines to combat serogroup B meningococcal disease has been limited, however, due to the strain-specific nature of the protection and the lack of consistent efficacy and persistence of protection in young children.

Novartis' serogroup B meningococcal vaccine (rMenB+OMV NZ) used knowledge gained during vaccine development for the Norwegian (MenBvac) and New Zealand (MeNZB) epidemics, together with the identification of the N. meningitidis serogroup B genome sequence to develop an effective serogroup B vaccine.

The availability of the bacterial genome sequence allowed identification of conserved surface-exposed outer membrane proteins of serogroup B strains that were targets for bactericidal antibodies. The first vaccine formulation of the recombinant serogroup B meningococcal vaccine consisted of a single recombinant vaccine antigen, the conserved, recombinant Neisseria Heparin-Binding Antigen (NHBA or 287) formulated with and without OMV derived from N. meningitidis Norwegian strain 44/76. This vaccine was safe in clinical studies in healthy adult volunteers; however, to improve immunogenicity and cross-strain protection, the vaccine was redesigned.

The redesign of the single recombinant vaccine antigen involved inclusion of additional recombinant protein antigens in the formulation. To further increase the immunogenicity of the antigens, protein-protein fusions of the candidate antigens were generated and vaccines formulated with aluminium hydroxide and with or without OMV derived from either:

- the Norwegian strain 44/76 (OMV NW) or
- the New Zealand strain NZ98/254 (OMV NZ)

were then evaluated in preclinical and clinical studies.

Bexsero (4CMenB) relationship to New Zealand meningoccal B vaccine (in 2000s)

A meningococcal B vaccine has been used to help control epidemic disease in New Zealand. At that time, questions remained about the persistence of antibodies following vaccination, especially of young children.

Various from the literature

Carriage can persist from weeks to months. Carriage of non-groupable stains has less invasive disease potential. Nasopharyngeal carriage peaks during late adolescence – often 20-30%, but can be up to 70% in closed communities such as residential colleges and military barracks. Antibodies can be acquired naturally through asymptomatic carriage.

Meningococci group B surface (outer membrane) proteins are antigenically diverse, and can be sparse (level of expression can vary greatly). MenB vaccines are not expected to protect against all serogroup B strains.

Incidence of meningococcal disease fluctuates.

Group C vaccination was introduced in UK in 1999, and the Netherlands in 2002. In both countries there was a substantial reduction in disease over the next years.

In the UK, before the September 2015 introduction of the vaccination programme, serogroup B meningococcal disease more than halved from 2007-08 and 2014-15 (Parikh et al 2017. Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007-08 and 2014-15: a qualitative and quantitative assessment, Lancet);

In New Zealand where there has not been a childhood meningococcal C immunisation programme, group B now makes up the majority of disease. Group B disease is also the most prevalent in many other western countries, including those who've had group C immunisation programmes and where this could be a partial explanatory factor.

For the past 20 years, serogroup B disease has been decreasing in both England and the Netherlands.

Serogroup W disease is currently increasing in Europe, including England. Deaths have included patients with predominantly gastrointestinal symptoms.

Factor H binding protein (FHbp) of sub-family A makes up about 40-50% of meningococcal B disease in the US (the fHbp antigen is contain in both the Pfizer and GSK vaccines).

The **bivalent Trumenba vaccine** (Pfizer) contains equal amounts of two fHbp variants. The amount of fHbp expressed by different MenB strains is genetically determined and can vary at least 15-fold. In addition, there is wide genetic diversity in [presumably AA detail] fHbp. Clinical development of the developmental form of the Trumenba vaccine in infants was suspended when high rates of fever were observed among those receiving low doses of the vaccine.

The 4CMenB vaccine also contains fHbp.

The Pfizer and the GSK vaccines have both been used in US college outbreaks.

In the US, in addition to use in those at risk, both vaccines are recommended for individual clinical decision making for use in 16-23 year olds (preferred age 16-18 years).

FHbp and NHBA together cover most disease in Europe, England and Wales, Greece and Canada.

Outer membrane vesicle (OMV) antigens consist of outer membrane proteins, lipopolysaccharides, phospholipids, and proteins generally.

LIST OF QUESTIONS

Major objections

Product information

Although the proposed datasheet provides antibody persistence data for children vaccinated as infants before the 12 month booster (Study V72P12E1), and 12 months after the 3+1 schedule (Study V72P13E2), additional persistence data is now available and should be provided.

Prescribers require comprehensive and clear information to guide decisions about boosters, as recommendations are not always available, as there is waning of antibodies. Information about duration of likely protection further supports' the prescribers' communication regarding the need for parents and caregivers to be vigilant about the signs and symptoms of meningococcal disease, even though a child may be immunised. In addition, immunogenicity of various schedules is of interest, as in the UK a reduced 2- 4 - 12 schedule is implemented.

1. The Sponsor should provide an updated datasheet with comprehensive and clear antibody persistence data, for children immunised as infants and toddlers. For example, the data could be provided in a format similar to the tables below.

Infant schedules and antibody persistence at approximate ages

study		Infant schedule	1 year of age	2 years of age	3 years of age	4 years of age
V72P12E2	N=805	3+1 (booster at 12, 18, or 24 months of age)	Pre 12 month booster 25% NHBA 58% fHBP 97% NadA 19% PorA1.4			Nil NHBA ≤35% fHBP ≥89% NadA ≤12% PorA1.4
V72P13E2		3	Pre 12 month booster not tested NHBA 91-82% fHBP 98-100% NadA 20-21% PorA1.4	12 months after booster (3+1 schedule) 32-40% NHBA 60-64% fHBP 96-99% NadA 17-18% PorA1.4		
V72P6	N=108 for persistence at 40 months	3+1			Pre- booster at 40 months (5th dose) Nil NHBA Nil fHBP - NadA 41% PorA1.4	
V72 28		2 doses starting at 2.5 and 3.5 months of age	At 11 months 42% NHBA 86-100% fHBP 93-100% NadA 41-54% PorA1.4			

Toddler schedules and antibody persistence at approximate ages

study		schedule	2 years of age	3 years of age	4 years of age	5 years of age
V72P9E1	N=60	3-dose schedule at 6-8, 8-10, and 12 months of age			At 40 months of age, 28 months after a third dose 79% NHBA 36% fHBP 93-100% NadA 14% PorA1.4	At 60 months of age, 20 months after booster Nil NHBA 67% fHBP 100% NadA 17% PorA1.4
V72P13E2			Schedule: 2-dose at 24 months of age	12 months after last dose 28-38% NHBA		

				56-74% fHBP 94-97% NadA 6-18% PorA1.4		
V72P6				Schedule: 2-dose at 40-42 months of age		18 months after vaccination Nil NHBA 71% fHBP 100% NadA 31% PorA1.4

Note:

nil refers to the situation where antibody levels in the vaccination group are no different from those in the vaccine naïve comparison group.

- refers to instances when the presence of the antigen was tested.

Points for clarification

Product information

2. The Sponsor should consider whether the following suggested addition [in bold] to the draft datasheet (under 'interactions with other medicines and other forms of interaction') would be helpful to prescribers, by specifying the prophylactic paracetamol regimen used in Study V72P16.

> The safety profiles of the co-administered vaccines were unaffected by concomitant administration of BEXSERO with the exception of more frequent occurrence of fever, tenderness at the injection site, change in eating habits and irritability. Prophylactic use of paracetamol **[for example, one dose before vaccination, followed by two further doses 4 to 6 hours apart]** reduces the incidence and severity of fever without affecting the immunogenicity of either BEXSERO or routine vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied.