London, 22 March 2018
EMA/CHMP/10786/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Bexsero

International non-proprietary name: NHBA fusion protein, Neisseria meningitidis, serogroup B, recombinant , NadA protein, Neisseria meningitidis, serogroup B, recombinant, fHbp fusion protein, Neisseria meningitidis, serogroup B, recombinant , outer membrane vesicles (OMV), Neisseria meningitidis, serogroup B, strain NZ98/254

Procedure no.: EMA/H/C/002333 /P46/026

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1. Introduction

On October 30, 2017, the MAH submitted a completed paediatric study for Bexsero, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study *"A Phase 3b, Open Label, Controlled, Multi-Center, Extension Study to Assess the Persistence of Bactericidal Activity at 4 to 7.5 Years After Two Dose Primary Series of GlaxoSmithKline Biologicals Meningococcal B Recombinant Vaccine and the Response to a Third Dose in Adolescents and Young Adult Subjects who Previously Participated in Parent Studies V72_41 and V72P10, Compared to Naïve Healthy Controls" (study protocol V72_75)* is a stand alone study.

The study is not included as part of an agreed pediatric investigation plan.

It was conducted in Australia, Canada and Chile and was primarily designed to assess long term persistence of Bexsero vaccine in adolescents.

2.2. Information on the pharmaceutical formulation used in the study

GlaxoSmithKline meningococcal B vaccine was used in this study. rMenB + OMV NZ is a multicomponent recombinant vaccine with OMVs produced from N meningitides serogroup B strain NZ98/254.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- "A Phase 3b, Open Label, Controlled, Multi-Center, Extension Study to Assess the Persistence of Bactericidal Activity at 4 to 7.5 Years After Two Dose Primary Series of GlaxoSmithKline Biologicals Meningococcal B Recombinant Vaccine and the Response to a Third Dose in Adolescents and Young Adult Subjects who Previously Participated in Parent Studies V72_41 and V72P10, Compared to Naïve Healthy Controls" (study protocol V72_75)

2.3.2. Clinical study

A Phase 3b, Open Label, Controlled, Multi-Center, Extension Study to Assess the Persistence of Bactericidal Activity at 4 to 7.5 Years After Two Dose Primary Series of GlaxoSmithKline Biologicals Meningococcal B Recombinant Vaccine and the Response to a Third Dose in Adolescents and Young Adult Subjects who Previously Participated in Parent Studies V72_41 and V72P10, Compared to Naïve Healthy Controls" (study protocol V72_75)

Description

Methods

Objective(s)

Primary Safety Objective:

- To assess and compare the safety and tolerability of a single dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series, with that of 2 doses of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule.

Primary Immunogenicity Objective:

- To assess serum bactericidal activity at approximately 4 to 7.5 years following a 2 dose primary series (persistence) compared to serum bactericidal activity at baseline in vaccine naïve subjects.

Secondary Immunogenicity Objectives:

- To assess the immune response at 1 month after a third dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series, compared to the immune response at 1 month after the first dose of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule.
- To assess and compare the changes over time in the immune response (kinetics) at 3, 7 and 30 days after a third dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series, with that at 3, 7 and 30 days after the second dose of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule.
- To assess the immune response at 1 month after the second dose (primary series) of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule.

Exploratory Immunogenicity Objectives:

The exploratory immunogenicity objectives are not reported in this CSR and will be reported in an addendum when the results are available.

The immune response to rMenB+OMV NZ may also be evaluated using an additional panel of *N meningitidis* serogroup B strains (ie, M14459 (fHbp), 96217 (NadA), M07-0241084 (NHBA) and NZ98/254, according to the following exploratory objectives.

- To evaluate serum bactericidal activity at approximately 4 years following a 2 dose primary series (persistence) in follow-on subjects from parent study V72_41.
- To evaluate the immune response at 3, 7 and 30 days after a third dose (booster) of rMenB+OMV NZ administered to follow-on subjects from parent study V72_41.
- To evaluate the immune response at 30 days after the first dose, and 3, 7 and 30 days after the second dose of rMenB+OMV NZ administered to Canadian and Australian vaccine naïve subjects according to a 0, 1-month schedule.

Study design

The present study V72_75 was an extension trial from the parent studies V72_41 and V72P10. These are 2 key studies in the rMenB+OMV NZ program which enrolled adolescents aged 11 through 17 years; V72_41 enrolled subjects in Australia and Canada between August and September 2011 while V72P10 enrolled subjects in Chile between June 2008 and October 2009. In study V72P10, subjects were vaccinated with 2 rMenB+OMV NZ doses administered at a 0, 1 month, or 0, 2 month, or 0, 6 month schedules. In study V72_41, subjects were vaccinated with 2 rMenB+OMV NZ doses administered at a 0, 1 month schedule. The studies demonstrated robust response against the vaccine

antigens, absence of major safety concerns and supported the adoption of a 2-dose primary vaccine in adolescents with the 2 primary doses of rMenB+OMV NZ administered with an interval of at least 1 month.

This present study V72_75 was a phase 3b, open label, multicenter, extension study in subjects from 15 to 24 years of age who were vaccinated with 2 doses of rMenB+OMV NZ administered at either a 0, 1 month, or 0, 2 month, or 0, 6 month schedules in study V72P10 and at a 0, 1 month schedule in study V72_41. A proportional number of healthy vaccine naïve subjects aged 15 to 24 years were to be enrolled at each site to serve as a descriptive comparator for safety, persistence, immune response and antibody kinetics of primary immunization with Men B at registered 0, 1 month schedule.

Data on kinetics of immune response against serogroup B strain would be of particular relevance in outbreak management, and vaccination of travelers.

Table 2-1 Overview of V72P10, V72_41 and V72_75 Study Groups

Parent study	Parent Study groups/Schedule (# subjects enrolled)	V72_75 Extension study groups (planned # enrolled)	V72_75 Study group procedure
V72P10	Parent study groups: 1a: 0, 6 month schedule (N = 128) 2b: 0, 1 month schedule (N = 247) 3b: 0, 2 month schedule (N = 253)	Group A: Follow-on subjects (N = up to 400)	• Third booster dose of rMenB+OMV NZ at 4 or 7.5 years after last dose. • Four blood samples at: Baseline (prior to third booster dose), at 3 days, 7 days and 30 days after third booster dose.
V72_41	Parent study groups: A, B: 0, 1 month schedule (N = 344)		
		Groups B1 and B2: Vaccine naïve subjects (N = 250 total, 1:1)	• Two doses of rMenB+OMV NZ at 0, 1 month schedule. • 4 blood samples at: Baseline (prior to first dose), at 30 days post-first dose, at either 3 days (Group B1) or 7 days (Group B2) and 30 days post-second dose.

Source: Table 1, Protocol version 6 dated 14 OCT 16.

Table 2-2 Schematic Overview of the Extension (V72_75) Study Design

Study Day	Day 1	Day 4	Day 8	Day 15	Day 31	Day 34	Day 38	Day 45	Day 61
Visit number for follow-on subjects	1	2	3	4	5				
Group A: Follow-on subjects (N = 400)	Blood Draw rMenB+OMV NZ	Blood Draw	Blood Draw	Safety follow-up Call	Blood Draw Study termination				
Visit number for vaccine naïve subjects	1			2	3	4*		5	6
Group B1: Vaccine Naïve (N = 125)	Blood Draw rMenB+OMV NZ			Safety follow-up Call	Blood Draw rMenB+OMV NZ	Blood Draw		Safety follow-up Call	Blood Draw Study termination
Group B2: Vaccine Naïve (N = 125)	Blood Draw rMenB+OMV NZ			Safety follow-up Call	Blood Draw rMenB+OMV NZ		Blood Draw	Safety follow-up Call	Blood Draw Study Termination

Source: Table 2, Protocol version 6 dated 14 OCT 16.

*Vaccine naïve group B1 subjects were to attend visit 4 at day 34; Vaccine naïve Group B2 subjects were to attend visit 4 at day 38.

Note: For study conduct, the groups were divided as Group A and Groups B1 and B2. The results of Groups B1 and B2 were analyzed together as Group B_0_1 while Group A was analyzed as Group 3B.

Study population /Sample size

A preliminary feasibility assessment suggested that 400 follow-on subjects could be available to participate in the present study out of the 972 subjects who participated in studies V72_41 and V72P10 and 929 subjects who completed vaccinations with rMenB+OMV NZ according to a 2-dose schedule.

Additionally, approximately 250 vaccine naïve subjects (Groups B1 and B2), of the same age range as follow-on subjects (approximately 15 to 24 years of age) were also to be enrolled into the study. Vaccine naïve subjects were to be recruited in proportion to the expected recruitment in each of the countries participating in the parent studies. The expected approximate proportion was 5:2:1 for Chile, Canada and Australia, respectively.

In total up to 650 study participants were estimated to take part in this study: 400 follow-on subjects and 250 vaccine naïve subjects. A total of 531 subjects were actually enrolled into the study: 276 in the follow-on subjects group and 255 in the vaccine naïve group of similar age.

Overall, the sample size was large enough to reflect important variations in the population (see confidence intervals [CIs] for the primary endpoints in statistical analysis section), but small enough to accommodate the operational constraints common to extension studies (follow-on subjects). The sample size for vaccine naïve subjects allowed for an acceptable precision in the estimation of immunogenicity responses, with particular reference to kinetics measurements at 3 and 7 days postvaccination (at each of those time points only half of all the vaccine naïve subjects were to be assessed) and 30 days postvaccination. The sample size was also estimated to allow for reliable (> 90% probability) observation of common (≥ 1%) AEs in the vaccine naïve subjects group.

From a perspective of detecting uncommon local or systemic AEs, with 250 subjects in the vaccine naïve group, the probability of observing at least one subject with an event for an underlying rate of

1% was 92%. Assuming 400 follow-on subjects were to be enrolled, the probability of observing at least one subject with an event for underlying rate of 1% was 98%.

Treatments

- Follow-on subjects (Group A): included up to 400 eligible subjects who had received 2 doses of rMenB+OMV NZ vaccine in the parent studies (V72_41 and V72P10), received no subsequent meningococcal group B vaccines, and who were to receive a booster dose of rMenB+OMV NZ vaccine in the current study. In study V72_41, 344 subjects were enrolled to receive a 2-dose primary series of rMenB+OMV NZ at a 0, 1 month schedule. In study V72P10, 1631 subjects were enrolled to receive 1, 2 or 3 doses of rMenB+OMV NZ with different vaccination schedules. Only those who received 2 rMenB+OMV NZ doses administered at either a 0, 1 month, or 0, 2 month, or 0, 6 month schedules in study V72P10 (ie, Groups 1a, 2b, 3b in parent study) and received no further meningococcal vaccine since then were to be invited to participate in the extension study V72_75.
- Vaccine naïve subjects (Groups B1 and B2): included approximately 250 subjects similar in age to subjects in the follow-on group, who had not previously received any meningococcal group B vaccine, and who were to receive 2 doses of rMenB+OMV NZ vaccine, 1 month apart, in the current study. On day 1, subjects in this group were to be randomized into 2 different blood draw schedules according to a 1:1 ratio, as described in Table 2-2.

Table 2-2 Schematic Overview of the Extension (V72_75) Study Design

Study Day	Day 1	Day 4	Day 8	Day 15	Day 31	Day 34	Day 38	Day 45	Day 61
Visit number for follow-on subjects	1	2	3	4	5				
Group A: Follow-on subjects (N = 400)	Blood Draw rMenB+OMV NZ	Blood Draw	Blood Draw	Safety follow-up Call	Blood Draw Study termination				
Visit number for vaccine naïve subjects	1			2	3	4*		5	6
Group B1: Vaccine Naïve (N = 125)	Blood Draw rMenB+OMV NZ			Safety follow-up Call	Blood Draw rMenB+OMV NZ	Blood Draw		Safety follow-up Call	Blood Draw Study termination
Group B2: Vaccine Naïve (N = 125)	Blood Draw rMenB+OMV NZ			Safety follow-up Call	Blood Draw rMenB+OMV NZ		Blood Draw	Safety follow-up Call	Blood Draw Study Termination

Source: Table 2, Protocol version 6 dated 14 OCT 16.

*Vaccine naïve group B1 subjects were to attend visit 4 at day 34; Vaccine naïve Group B2 subjects were to attend visit 4 at day 38.

Note: For study conduct, the groups were divided as Group A and Groups B1 and B2. The results of Groups B1 and B2 were analyzed together as Group B_0_1 while Group A was analyzed as Group 3B.

Follow-on subjects meeting all eligibility criteria were to be enrolled in an open label way as shown in Table 2-2.

For follow-on subjects (Group A) the study comprised 4 visits and 1 safety follow-up call for a total of 5 visits over the course of approximately 1 month during which 1 dose of rMenB+OMV NZ vaccine was to be administered and 4 blood samples were to be drawn.

All follow-on subjects were to receive a third dose (booster) of rMenB+OMV NZ at visit 1. Four blood samples were to be drawn from all follow-on subjects at visit 1 (ie, prior to rMenB+OMV NZ dose) and at visits 2, 3 and 5 (ie, approximately at 3, 7 and 30 days after the vaccination).

Vaccine naïve subjects meeting all eligibility criteria were to be enrolled in an open label way and randomized 1:1 to 1 of the 2 study groups (Group B1 or Group B2) as shown in Table 2-2. No age matching procedure between follow-on and vaccine naïve subjects was foreseen, but vaccine naïve subjects were to be enrolled in a similar age range as followon subjects, by country. Vaccine naïve subjects were to be enrolled at the same sites enrolling follow-on subjects so that vaccine naïve and follow-on subjects were drawn from populations of comparable geographical origin. Vaccine naïve subjects were to be enrolled in each participating country in proportion to the number of follow-on subjects who were expected to take part in this extension study.

For vaccine naïve subjects (ie, Groups B1 and B2, depending on blood draw schedule) the study comprised 4 visits and 2 safety follow-up calls for a total of 6 visits over the course of approximately 2 months, during which 2 doses of rMenB+OMV NZ vaccine were to be administered and 4 blood samples were to be drawn. A total of 3 diary reminder calls were to be performed over the course of 2 months' study subject participation.

All vaccine naïve subjects were to receive a first dose of rMenB+OMV NZ at visit 1 and a second dose at visit 3 (1 month after the first dose). Four blood samples were to be drawn from all vaccine naïve subjects at visit 1 (prior to the first dose) and at visits 3, 4 and 6 (approximately at 1 month after the first dose, at 3 days [vaccine naïve Group B1] or 7 days [vaccine naïve Group B2] and 30 days after the second dose).

After receiving vaccination, subjects were to be observed for at least 30 minutes for any immediate adverse events (AEs). The subject parent(s)/legal guardian(s) were to be instructed to complete a subject diary daily to report solicited local and systemic AEs occurring from the day of each vaccination and for the following 6 days as well as to indicate if any analgesic/antipyretic to prevent or to treat pain/fever was taken after injection.

From the day of each injection and for the following 30 days, any unsolicited AE and related medication were to be collected. In addition to these safety data, all serious AEs (SAEs), all medications given to treat SAEs, and all AEs leading to vaccine/study withdrawal were to be collected during the entire study period, from day 1 (from signature of informed consent) through day 31 (study termination visit) for follow-on subjects, or from day 1 through day 61 (study termination visit) for vaccine naïve subjects. These data were to be captured through interviewing the subject and/or parent(s)/legal guardian(s) and by review of available medical records.

Outcomes/endpoints

Primary Safety Endpoints:

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

Primary Immunogenicity Endpoints:

- The persistence of bactericidal activity was measured against N meningitides serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713. Data were to be summarized by calculating the percentages of subjects with human serum bactericidal assay (hSBA) ⩾ 1:4 (strains 5/99 and NZ98/254), ⩾ 1:5 (strains H44/76 and M10713), ⩾ 1:8 and ⩾ 1:16; hSBA geometric mean titers (GMTs); and geometric mean ratios (GMRs) of GMTs prevaccination versus GMTs at 1 month after the last dose of rMenB+OMV NZ in the V72_41 and V72P10 studies, to each of the 4 indicator strains.

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

Secondary Immunogenicity Endpoints:

- The immune response was measured against N meningitidis serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713. Data were to be summarized by calculating percentage of subjects with hSBA ⩾ 1:4 (strains 5/99 and NZ98/254), ⩾ 1:5 (strains H44/76 and M10713), ⩾ 1:8 and ⩾ 1:16; hSBA GMTs, GMRs of GMTs at 1 month postvaccination of a booster dose versus prebooster dose (follow-on subjects) or first dose of rMenB+OMV NZ versus pre-first dose (vaccine naïve subjects), to each of the 4 indicator strains.

  Post-first dose data in vaccine naïve subjects served as a comparator to evaluate response to a booster dose in follow-on subjects.

  Additionally, data were to be summarized by calculating the percentages of subjects with a 4-fold rise at 1 month postvaccination with a booster dose (follow-on subjects) or first dose (vaccine naïve subjects) of rMenB+OMV NZ over prevaccination, to each and any 1, 2, 3 or all 4 indicator strains.

- The changes in serum bactericidal activity over time (kinetics) were to be measured against N meningitidis serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713. Data were summarized by calculating the percentages of subjects with hSBA ⩾ 1:4 (strains 5/99 and NZ98/254), ⩾ 1:5 (strains H44/76 and M10713; section 9.8), ⩾ 1:8 and ⩾ 1:16; hSBA GMTs, and GMRs of GMTs, at 3, 7, and 30 days postvaccination with a booster dose (follow-on subjects) versus pre-booster dose or second dose (vaccine naïve subjects) of rMenB+OMV NZ versus pre-second dose, to each of the 4 indicator strains.

  Post-second dose data in vaccine naïve subjects served as a comparator to evaluate changes in bactericidal activity over time (kinetics) post-booster dose in follow-on subjects.

Additionally, data were to be summarized by calculating the percentage of subjects with 4-fold rise prevaccination compared to 3, 7 and 30 days postvaccination with a booster dose (follow-on subjects) or second dose (vaccine naïve subjects) of rMenB+OMV NZ, to each and any 1, 2, 3 or all 4 indicator strains.

- The induction of serum bactericidal activity in vaccine naïve subjects was to be measured against *N meningitidis* serogroup B indicator strains H44/76, 5/99, NZ98/254 and M10713. Data were to be summarized by calculating the percentages of subjects with hSBA ⩾ 1:4 (strains 5/99 and NZ98/254), ⩾ 1:5 (strains H44/76 and M10713; section 9.8), ⩾ 1:8, and ⩾ 1:16; hSBA GMTs, and GMRs of GMTs at 1 month after the second dose of rMenB+OMV NZ versus GMTs prevaccination, to each of the 4 indicator strains.

Additionally, data were to be summarized by calculating the percentage of subjects with 4-fold rise prevaccination with a first dose compared to 1 month postvaccination with a second dose (vaccine naïve subjects) of rMenB+OMV NZ, to each and any 1, 2, 3 or all 4 indicator strains.

Exploratory Immunogenicity Endpoints:

The exploratory immunogenicity endpoints are not reported in this CSR and will be reported in an addendum when the results are available

The immune response to rMenB+OMV NZ in both follow-on subjects from parent study V72_41 and vaccine naïve subjects from Canada and Australia might be also assessed by measuring bactericidal activity against *N meningitidis* serogroup B strains M14459, M07- 0241084, 96217, and NZ98/254 as follows:

Follow-on subjects from parent study V72_41

- GMTs at baseline (pre-booster), 3, 7 and 30 days after the administration of a third dose (booster) of rMenB+OMV NZ
- GMRs at 3, 7 and 30 days after the administration of a third dose (booster) of rMenB+OMV NZ, versus baseline (pre-booster)
- the percentage of subjects with hSBA titer ≥ Lower Limit of Quantitation (LLOQ); for each strain and for all strains (composite response) at baseline (pre-booster), 3, 7 and 30 days after the administration of a third dose (booster) of rMenB+OMV NZ
- The percentage of subjects with 4-fold increase in hSBA titers relative to baseline (prebooster) defined as:
  - for a prevaccination titer < 4, a postvaccination titer of at least 16;
  - for a prevaccination titer ≥ 4 but <LLOQ, a postvaccination titer of at least 4-fold the LLOQ;
  - for a prevaccination titer ≥LLOQ, a postvaccination titer of at least 4-fold the prevaccination titer

Vaccine naïve subjects from Canada and Australia

- GMTs at baseline and at 30 days after the first dose, then at 3, 7 and 30 days after the second dose of rMenB+OMV NZ
- GMRs at baseline and 30 days after the first dose, then at 3, 7 and 30 days after the administration of a second dose of rMenB+OMV NZ
- the percentage of subjects with hSBA titer ≥ LLOQ; for each strain and for all strains (composite response) at baseline, 3, 7 and 30 days after the administration of a second dose of rMenB+OMV NZ, and 30 days after the first and the second dose of rMenB+OMV NZ
- the percentage of subjects with 4-fold increase in hSBA titers relative to baseline defined as:
  - for a prevaccination titer < 4, a postvaccination titer of at least 16;
  - for a prevaccination titer ≥ 4 but <LLOQ, a postvaccination titer of at least 4-fold the LLOQ;
  - for a prevaccination titer ≥LLOQ, a postvaccination titer of at least 4-fold the prevaccination titer.

Statistical Methods

There was no statistical hypothesis associated with the immunogenicity or safety objectives. The primary population for each of the immunogenicity associated analysis was to be the following:

- Persistence analyses for the primary immunogenicity objective were done using FAS (full analysis set).

- After booster/first dose analyses for the first secondary immunogenicity objective were done using FAS.
- Assessment of the immune response kinetics was done using PPS (per-protocol set). The assessment after 2 doses of rMenB+OMV NZ in the vaccine naïve group was performed on PPS.
- The exploratory analyses in the naïve group were to be performed on the FAS.

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

Analyses were to be performed on V72_41 and V72P10 follow-on subjects both separately and combined.

Results

Recruitment/ Number analysed

A total of 531 subjects were enrolled into the study: 276 subjects were follow-on subjects (145 subjects from study V72_41 [Australia and Canada] and 131 subjects from study V72P10 [Chile]) who approximately 4 or 7.5 years ago had received 2 rMenB+OMV NZ primary series doses in studies V72_41 and V72P10. A total of 255 subjects (105 subjects of similar age to those in V72_41 and 150 subjects of similar age to those in V72P10) were vaccine naïve subjects. All except for 1 follow-on subject were exposed to the booster dose of rMenB+OMV NZ (Table 10.1-1).

Table 10.1-1 Summary of Study Terminations – All Enrolled Set

	Group 3B (V72_41) (N = 145)	Group 3B (V72P10) (N = 131)	Group 3B (Total) (N = 276)	Group B_0_1 (V72_41) (N = 105)	Group B_0_1 (V72P10) (N = 150)	Group B_0_1 (Total) (N = 255)	Total (N = 531)
Enrolled	145 (100%)	131 (100%)	276 (100%)	105 (100%)	150 (100%)	255 (100%)	531 (100%)
Exposed	144 (99%)	131 (100%)	275 (>99%)	105 (100%)	150 (100%)	255 (100%)	530 (>99%)
Completed study	142 (98%)	129 (99%)	271 (98%)	103 (98%)	147 (98%)	250 (98%)	521 (98%)
Premature withdrawals:	3 (2%)	2 (2%)	5 (2%)	2 (2%)	3 (2%)	5 (2%)	10 (2%)
AE	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)	2 (<1%)
Withdrawal by subject	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)
Lost to follow-up	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)
Administrative Reason	0	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Other[a]	0	1 (<1%)	1 (<1%)	1 (1%)	2 (1%)	3 (1%)	4 (<1%)

Source: Table 14.1.1.2, Table 16.2.2.1.

Abbreviation: AE, adverse event.

[a] Time constraints due to a busy work/school schedule.

Baseline data

All demographic and baseline characteristics were balanced across the follow-on and vaccine naïve subjects groups (Table 11.2-1). The mean age of the subjects enrolled into the study V72_41 was 18

± 1.88 years for the follow-on subjects and 17.5 ± 1.85 years for the vaccine naïve group; for study V72P10, the mean age was 21.2 ± 1.73 years and 21.7 ± 1.56 years, in the respective groups. Among the enrolled subjects, in study V72_41, males were 55% in the follow-on group and 49% in the vaccine naïve group while in study V72P10, males were 48% in the follow-on group and 51% in the vaccine naïve group. The race of majority of subjects in study V72_41 was categorized as 'white', (68% in the follow-on group and 70% in the vaccine naïve group). The race of all of the subjects in study V72P10 was categorized as 'other'. Among the overall enrolled subjects, 99% met the protocol-defined study entry criteria.

Table 11.2-1 Demographic and Baseline Characteristics – All Enrolled Set

	Group 3B (V72_41) (N = 145)	Group 3B (V72P10) (N = 131)	Group 3B (Total) (N = 276)	Group B_0_1 (V72_41) (N = 105)	Group B_0_1 (V72P10) (N = 150)	Group B_0_1 (Total) (N = 255)
Age (years)	18±1.88	21.2±1.73	19.5±2.42	17.5±1.85	21.7±1.56	20±2.69
Age group:						
Adolescents (12-17 years)	65 (45%)	0	65 (24%)	56 (53%)	1 (1%)	57 (22%)
Adults (18-64 years)	80 (55%)	131 (100%)	211 (76%)	49 (47%)	149 (99%)	198 (78%)
Sex: N (%):						
Male	80 (55%)	63 (48%)	143 (52%)	51 (49%)	76 (51%)	127 (50%)
Female	65 (45%)	68 (52%)	133 (48%)	54 (51%)	74 (49%)	128 (50%)
Race: N (%):						
American Indian or Alaska native	11 (8%)	0	11 (4%)	1 (1%)	0	1 (<1%)
Asian	22 (15%)	0	22 (8%)	18 (17%)	0	18 (7%)
Black or African American	3 (2%)	0	3 (1%)	2 (2%)	0	2 (1%)
Native Hawaiian or other Pacific Islander	3 (2%)	0	3 (1%)	8 (8%)	0	8 (3%)
White	98 (68%)	0	98 (36%)	74 (70%)	0	74 (29%)
Other	8 (6%)	131 (100%)[a]	139 (50%)	2 (2%)	150 (100%)	152 (60%)
Country of enrollment:						
Australia	38 (26%)	0	38 (14%)	25 (24%)	0	25 (10%)
Canada	107 (74%)	0	107 (39%)	80 (76%)	0	80 (31%)
Chile	0	131 (100%)	131 (47%)	0	150 (100%)	150 (59%)
Weight (kg)	72.4±18.42	69.1±16.3	70.8±17.49	70.6±18.17	67.8±13.18	68.9±15.46

	Group 3B (V72_41) (N = 145)	Group 3B (V72P10) (N = 131)	Group 3B (Total) (N = 276)	Group B_0_1 (V72_41) (N = 105)	Group B_0_1 (V72P10) (N = 150)	Group B_0_1 (Total) (N = 255)
Height (cm)	170.7±9.78	166.5±8.71	168.7±9.51	170±10.06	167.5±9.21	168.5±9.63
Met protocol criteria	144 (99%)	131 (100%)	275 (>99%)	105 (100%)	148 (99%)	253 (99%)
Average persistence period (years from last vaccination in parent study to day 1)	4.27±0.08 N = 144	6.91±0.34	5.53±1.34 N = 275	NA	NA	NA

Source: Table 14.1.1.3, Table 14.1.1.5.1.

Abbreviations: NA, not applicable.

[a] As reported in the in study V72P10 CSR, most of the subjects enrolled were of 'Hispanic' ethnic origin.

Note: Categorical parameters: Number (%) of subjects; non-categorical parameters: mean±standard deviation.

Note: Chilean centers recorded "Other" as race because "Hispanic" was not available in the V72_75 CRF.

Immunogenicity results

Immune Response Persistence - (Primary Immunogenicity Objective)

Serum bactericidal activity at approximately 4 to 7.5 years following a 2-dose primary series (persistence) compared to serum bactericidal activity at baseline in vaccine naïve subjects.

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

- In the follow-on subjects, at approximately 4 or 7.5 years after the 2-dose primary series hSBA GMTs, although declined (except for strain M10713 in V72_41 subjects) compared to 1 month after

the second primary series dose, were higher than for vaccine naïve subjects of similar age (Table 2-4).

Table 2-4 **Geometric Mean hSBA Titers at 4 or 7.5[a] Years after the Last Dose of MenB+OMV NZ in the Parent Study in Follow-on Subjects and at the Baseline in V72_75 in Vaccine Naïve Subjects and Vaccine Group Ratios – FAS Persistence**

		hSBA GMT (95% CI)						Vaccine Group Ratio (95% CI)	
Strain (Antigen)		Group 3B (V72_41) (N = 144)	Group 3B (V72P10) (N = 131)	Group 3B (Total) (N = 275)	Group B_0_1 (V72_41) (N = 105)	Group B_0_1 (V72P10) (N = 150)	Group B_0_1 (Total) (N = 255)	Group 3B vs Group B_0_1 (V72_41)	Group 3B vs Group B_0_1 (V72P10)
H44/76 (fHbp)	GMT 1 month after the last dose in parent study	99 (82-119)	197 (165-235)	124 (108-143)	NA	NA	NA	NA	NA
	GMT Day 1[a] (V72_75)	2.43 (2.04-2.89)	4.51 (3.57-5.69)	3.05 (2.61-3.56)	1.14 (0.93-1.40)	1.52 (1.23-1.90)	1.20 (1.02-1.42)	2.13 (1.66-2.72)	2.96 (2.15-4.07)
5/99 (NadA)	GMT 1 month after the last dose in parent study	180 (153-211) N = 134	606 (492-746) N = 120	270 (234-311) N = 254	NA	NA	NA	NA	NA
	GMT Day 1[a] (V72_75)	24 (19-30) N = 134	31 (23-42) N = 120	26 (21-31) N = 254	1.20 (0.91-1.58) N = 100	2.30 (1.75-3.04) N = 139	1.57 (1.26-1.95) N = 239	20 (14-28)	14 (9.05-20)
NZ98/254 (PorA P1.4)	GMT 1 month after the last dose in parent study	11 (8.67-14)	93 (75-117) N = 129	22 (19-27) N = 273	NA	NA	NA	NA	NA
	GMT Day 1[a] (V72_75)	1.31 (1.17-1.45)	2.56 (2.07-3.17) N = 129	1.66 (1.46-1.89) N = 273	1.01 (0.89-1.14)	1.50 (1.23-1.84) N = 148	1.11 (0.97-1.27) N = 253	1.30 (1.11-1.51)	1.70 (1.27-2.28)
M10713 (NHBA)	GMT 1 month after the last dose in parent study	10 (7.65-14) N = 140	66 (53-81)	19 (16-24) N = 271	NA	NA	NA	NA	NA
	GMT Day 1[a] (V72_75)	13 (9.86-18) N = 140	22 (16-29)	16 (13-20) N = 271	10 (7.13-15)	18 (14-24)	12 (9.86-16)	1.32 (0.85-2.05)	1.20 (0.81-1.78)

Source: Table 14.2.1.3.1. Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; GMT, geometric mean titer; hSBA, human serum bactericidal assay; NA, not applicable; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A.
[a] 4 years persistence for follow-on subjects in study V72_41 (Canada, Australia), 7.5 years persistence for follow-on subjects in study V72P10 (Chile), and prevaccination for vaccine naïve subjects.

- At approximately 4 or 7.5 years after a 2-dose primary series, for all 4 indicator strains the percentage of subjects with hSBA titer of at least 4 in follow-on subjects was higher (except for strain M10713 in V72P10 subjects) than for vaccine naïve subjects of similar age (Table 2-3).

Table 2-3 **Percentages of Subjects With hSBA Titer of at Least 4 at 4 or 7.5 Years[a] After the Last Dose of rMenB+OMV NZ in the Parent Study in Follow-on Subjects and at Baseline in V72_75 in Vaccine Naïve Subjects, and Vaccine Group Differences – FAS Persistence**

	Number (%) of Subjects (95% CI)						Vaccine Group Differences (95% CI)	
Strain (Antigen)	**Group 3B (V72_41) (N = 144)**	**Group 3B (V72P10) (N = 131)**	**Group 3B (Total) (N = 275)**	**Group B_0_1 (V72_41) (N = 105)**	**Group B_0_1 (V72P10) (N = 150)**	**Group B_0_1 (Total) (N = 255)**	**Group 3B minus. Group B_0_1 (V72_41)**	**Group 3B minus. Group B_0_1 (V72P10)**
H44/76 (fHbp)	38 (26%) (19.4%-34.4%)	54 (41%) (32.7%-50.2%)	92 (33%) (27.9%-39.4%)	5 (5%) (1.6%-10.8%)	17 (11%) (6.7%-17.5%)	22 (9%) (5.5%-12.8%)	22% (13.2%-30.1%)	30% (20%-39.6%)
5/99 (NadA)	113 (84%) (77%-90%) N = 134	101 (84%) (76.4%-90.2%) N = 120	214 (84%) (79.2%-88.5%) N = 254	7 (7%) (2.9%-13.9%) N = 100	33 (24%) (16.9%-31.7%) N = 139	40 (17%) (12.2%-22.1%) N = 239	77% (68.1%-84.1%)	60% (49.9%-69.2%)
NZ98/254 (PorA P1.4)	13 (9%) (4.9%-14.9%)	37 (29%) (21.1%-37.3%) N = 129	50 (18%) (13.9%-23.4%) N = 273	0 (0%) (0%-3.5%)	21 (14%) (9%-20.9%) N = 148	21 (8%) (5.2%-12.4%) N = 253	9% (5.3%-14.8%)	14% (4.9%-24.2%)
M10713 (NHBA)	102 (71%) (63.2%-78.6%) N = 143	102 (78%) (69.8%-84.6%)	204 (74%) (68.9%-79.5%) N = 274	62 (59%) (49%-68.5%)	117 (78%) (70.5%-84.3%)	179 (70%) (64.2%-75.7%)	12% (0.33%-24.2%)	0% (-10%-9.5%)

Source: Table 14.2.1.1, Table 14.2.1.1.1.2.

Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A.

[a] 4 years persistence for follow-on subjects in study V72_41 (Canada. Australia), 7.5 years persistence for follow-on subjects in study V72P10 (Chile), and prevaccination for vaccine naïve subjects.

Note: Results for strains 5/99 and NZ98/254 are computed with a cut-off of hSBA ≥ 1:4; for strains H44/76 and M10713 with a cut-off of hSBA ≥ 1:5.

In the follow-on subjects, the percentages of subjects with hSBA titer of at least 4 and the hSBA GMTs after the last vaccination in the parent study were similar at 4 years (V72_41) vs 7.5 years (V72P10) across serogroup B indicator strains, except for the strain NZ98/254 for which the titers were higher (Table 2-3; Table 2-4).

Across the 4 serogroup B indicator strains, the highest persistence was observed for strain 5/99, followed by strain M10713, strain H44/76, and strain NZ98/254, in that order (Table 2-3; Table 2-4).

Assessor's comment:

Although decreasing for all strains over time, immune persistence was observed 4-7.5 years after vaccination with 2 doses of rMenB+OMV NZ as demonstrated by GMT ratios (hSBA) > 1 for all strains when comparing vaccinated and vaccine naïve subjects. However, the lower limit of the 95% CI for the GMT ratio for M10713 was below 1.

Of note and as demonstrated with hSBA titers measured in the vaccine naïve population, basal absolute GMT titers and rates for hSBA titer ≥ 4 in this population were highest for strain M10713, and there was little difference between vaccinated and unvaccinated groups for this antigen. Based on the GMT ratios for hSBA (vaccinated individuals/naïve individuals) highest persistence of immunogenic response was reached for strain 5/99 followed by H44/76, and was lowest for NZ98/254 and M10713 (table 2.4).

Secondary Immunogenicity Objectives:

1) Immune response at 1 month after a third dose (booster) of rMenB+OMV NZ in follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series compared to the immune response at 1 month after the first dose of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule.

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

- The percentages of subjects with hSBA titer of at least 4 at 1 month after the booster dose in follow-on subjects were higher than after a single vaccine dose in vaccine naïve subjects for all 4 indicator strains, ranging across the 4 strains from 94%-100% in Group 3B (V72_41) and 93%-100% in Group 3B (V72P10). Comparatively, at 1 month following 1 dose of rMenB+OMV NZ in vaccine naïve subjects, responses were lower, ranging from 41%-87% in Group B_0_1 (V72_41) and 62%-92% in Group B_0_1 (V72P10) (Table 11.4.1-3).
- The hSBA GMTs achieved after booster in follow-on subjects were higher than after a single vaccine dose in vaccine naïve subjects for all 4 indicator strains. In V72_41 subjects, the GMRs in follow-on subjects ranged from 4.69 (for strain M10713) to 100 (for strain 5/99) while the GMRs in vaccine naïve subjects of similar age ranged from 2.37 (for strain M10713) to 25 (for strain 5/99). Similarly, in V72P10 subjects, the GMRs in follow-on subjects ranged from 5.16 (for strain M10713) to 64 (for strain 5/99) while the GMRs in vaccine naïve subjects of similar age ranged from 2.58 (for strain M10713) to 16 (for strain H44/76) (Table 11.4.1-4).

Table 11.4.1-3 Percentages of Subjects With hSBA Titer of at Least 4 at 1 Month after Booster Dose/First Dose of rMenB+OMV NZ and Vaccine Group Differences – FAS Booster

	Number (%) of Subjects (95% CI)						Vaccine Group Differences (95% CI)	
Strain (Antigen)	Group 3B (V72_41) (N = 142)	Group 3B (V72P10) (N = 127)	Group 3B (Total) (N = 268)	Group B_0_1 (V72_41) (N = 104)	Group B_0_1 (V72P10) (N = 149)	Group B_0_1 (Total) (N = 253)	Group 3B minus. B_0_1 (V72_41)	Group 3B minus. Group B_0_1 (V72P10)
H44/76 (fHbp)	138 (98%) (93.9%-99.56%) N = 141	127 (100%) (97.1%-100%)	265 (99%) (96.8%-99.77%)	83 (80%) (70.8%-87%)	117 (79%) (71.1%-84.8%)	200 (79%) (73.5%-83.9%)	18% (10.7%-27%)	21% (15.6%-28.8%)
5/99 (NadA)	124 (100%) (97.1%-100%) N = 124	102 (100%) (96.4%-100%) N = 102	226 (100%) (98.4%-100%) N = 226	84 (87%) (78.2%-92.7%) N = 97	115 (84%) (76.7%-89.7%) N = 137	199 (85%) (79.8%-89.4%) N = 234	13% (8%-21.6%)	16% (10.8%-23.1%)
NZ98/254 (PorA P1.4)	134 (94%) (89.2%-97.5%)	112 (93%) (87.3%-97.1%) N = 120	246 (94%) (90.3%-96.5%) N = 262	42 (41%) (31.2%-50.9%) N = 103	92 (62%) (53.8%-70%) N = 148	134 (53%) (47%-59.7%) N = 251	54% (43%-63.3%)	31% (22%-40.1%)
M10713 (NHBA)	140 (99%) (96.1%-99.98%) N = 141	125 (98%) (94.4%-99.81%)	265 (99%) (96.8%-99.77%)	82 (80%) (70.5%-86.9%) N = 103	137 (92%) (86.4%-95.8%)	219 (87%) (82.1%-90.8%) N = 252	20% (12.8%-28.6%)	6% (1.5%-12.2%)

Source: Table 14.2.1.1.2, Table 14.2.1.1.2.2.

Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A.

Note: Group 3B subjects (follow-on subjects) - hSBA titers were measured at baseline (day 1, ie, 4-7.5 years after the 2-dose primary series administered in the parent study) and 1 month after booster dose; Group B_0_1 subjects (vaccine naïve subjects) - hSBA titers were measured at baseline (day 1) and 30 days after first vaccination.

Note: Results for strains 5/99 and NZ98/254 are computed with a cut-off of hSBA ≥ 1:4; for strains H44/76 and M10713 with a cut-off of hSBA ≥ 1:5.

Table 11.4.1-4 Geometric Mean hSBA Titers, Geometric Mean Ratios After Booster Dose/First Dose of rMenB+OMV NZ and Vaccine Group Ratios – FAS Booster

Strain (Antigen)		GMT/GMR (95% CI) Group 3B (V72_41) (N = 142)	Group 3B (V72P10) (N = 127)	Group 3B (Total) (N = 268)	Group B_0_1 (V72_41) (N = 104)	Group B_0_1 (V72P10) (N = 149)	Group B_0_1 (Total) (N = 253)	Vaccine Group Ratio (95% CI) Group 3B vs. Group B_0_1 (V72_41)	Group 3B vs. Group B_0_1 (V72P10)
H44/76 (fHbp)	GMT Day 1 before booster or first dose	2.45 (2.06-2.92) N = 141	4.65 (3.66-5.89)	3.10 (2.65-3.62)	1.13 (0.92-1.38)	1.53 (1.23-1.90)	1.19 (1.01-1.41)	2.18 (1.70-2.79)	3.04 (2.20-4.20)
	GMT 1 month after booster or first dose	158 (123-204) N = 141	269 (206-351)	188 (155-228)	13 (10-18)	24 (19-31)	16 (13-20)	12 (8.22-17)	11 (7.75-16)
	GMR 1 month after the dose/Day 1	65 (49-85) N = 141	58 (44-76)	61 (50-74)	12 (8.69-16)	16 (12-20)	14 (11-17)	5.42 (3.66-8.01)	3.66 (2.54-5.27)
5/99 (NadA)	GMT Day 1 before booster or first dose	22 (17-28) N = 118	31 (22-43) N = 93	24 (19-30) N = 211	1.19 (0.89-1.59) N = 96	2.19 (1.65-2.92) N = 129	1.51 (1.21-1.88) N = 225	18 (13-26)	14 (8.99-22)
	GMT 1 month after booster or first dose	2191 (1681-2856) N = 124	1951 (1425-2671) N = 102	2089 (1690-2582) N = 226	30 (22-40) N = 97	31 (24-41) N = 137	31 (25-38) N = 234	74 (51-107)	63 (41-95)
	GMR 1 month after the dose/Day 1	100 (72-139) N = 118	64 (44-93) N = 93	87 (67-112) N = 211	25 (18-36) N = 96	14 (9.90-19) N = 129	20 (16-26) N = 225	3.96 (2.51-6.25)	4.69 (2.87-7.66)
NZ98/254 (PorA P1.4)	GMT Day 1 before booster or first dose	1.31 (1.18-1.46)	2.48 (1.99-3.09) N = 118	1.64 (1.44-1.86) N = 260	1 (0.88-1.13) N = 103	1.51 (1.24-1.84) N = 146	1.11 (0.97-1.28) N = 249	1.32 (1.13-1.54)	1.64 (1.22-2.20)
	GMT 1 month after booster or first dose	30 (23-38)	41 (30-56) N = 120	32 (26-39) N = 262	3.58 (2.70-4.76) N = 103	9.43 (7.15-12) N = 148	5.39 (4.33-6.72) N = 251	8.27 (5.83-12)	4.36 (2.88-6.58)
	GMR 1 month after the dose/Day 1	23 (18-29)	16 (12-22) N = 118	19 (16-24) N = 260	3.60 (2.69-4.81) N = 103	6.43 (4.95-8.34) N = 146	4.92 (3.97-6.1) N = 249	6.28 (4.4-8.97)	2.55 (1.72-3.77)
M10713 (NHBA)	GMT Day 1 before booster or first dose	14 (10-19) N = 140	22 (16-29)	16 (13-20) N = 267	9.82 (6.87-14) N = 103	18 (14-23)	12 (9.62-15) N = 252	1.40 (0.90-2.18)	1.23 (0.82-1.82)
	GMT 1 month after booster or first dose	65 (52-81)	113 (90-142)	78 (66-92)	23 (18-30) N = 103	46 (37-57)	30 (25-36) N = 252	2.79 (2.04-3.81)	2.45 (1.79-3.36)
	GMR 1 month after the dose/Day 1	4.69 (3.72-5.92) N = 140	5.16 (4.14-6.42)	4.85 (4.1-5.72) N = 267	2.37 (1.81-3.1) N = 103	2.58 (2.11-3.16)	2.44 (2.04-2.91) N = 252	1.98 (1.42-2.75)	2 (1.48-2.7)

Source: Table 14.2.1.3.2.

Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A.

Note: Group 3B subjects (follow-on subjects) - hSBA titers were measured at baseline (Day 1, before booster) and 1 month after booster dose. Group B_0_1 subjects (vaccine naïve subjects) - hSBA titers were measured at baseline (Day 1, before vaccination) and 30 days after first vaccination.

- Similarly, the percentage of subjects achieving at least a 4-fold increase in hSBA titers after booster in the follow-on subjects were higher than after a first dose in vaccine naïve subjects for all 4 indicator strains (Table 11.4.1-5).

Table 11.4.1-5 Percentages of Subjects with at Least 4-fold Increase[a] in hSBA Titers at 1 Month After Booster Dose/First rMenB+OMV NZ Dose Over Day 1 – FAS Booster

	Number (%) of Subjects (95% CI)						Vaccine Group Differences (95% CI)	
Strain (Antigen)	Group 3B (V72_41) N = 142	Group 3B (V72P10) N = 127	Group 3B (Total) N = 268	Group B_0_1 (V72_41) N = 104	Group B_0_1 (V72P10) N = 149	Group B_0_1 (Total) N = 253	Group 3B minus. Group B_0_1 (V72_41)	Group 3B minus. Group B_0_1 (V72P10)
H44/76 (fHbp)	134 (95%) (90%-98%) N = 141	124 (98%) (93.3%-99.51%)	258 (96%) (93.2%-98.2%)	69 (66%) (56.4%-75.3%)	107 (72%) (63.9%-78.9%)	176 (70%) (63.5%-75.2%)	29% (19.3%-38.7%)	26% (18.3%-33.9%)
5/99 (NadA)	116 (98%) (94%-99.79%) N = 118	90 (97%) (90.9%-99.3%) N = 93	206 (98%) (94.6%-99.2%) N = 211	76 (79%) (69.7%-86.8%) N = 96	95 (74%) (65.2%-81%) N = 129	171 (76%) (69.9%-81.4%) N = 225	19% (11.5%-28.5%)	23% (14.6%-31.9%)
NZ98/254 (PorA P1.4)	118 (83%) (75.9%-88.9%)	91 (77%) (68.5%-84.3%) N = 118	209 (80%) (75%-85%) N = 260	29 (28%) (19.7%-37.9%) N = 103	77 (53%) (44.3%-61.1%) N = 146	106 (43%) (36.3%-49%) N = 249	55% (43.5%-64.7%)	24% (12.9%-35.1%)
M10713 (NHBA)	68 (49%) (40%-57.2%) N = 140	62 (49%) (39.9%-57.8%)	130 (49%) (42.6%-54.9%) N = 267	25 (24%) (16.4%-33.7%) N = 103	40 (27%) (19.9%-34.7%)	65 (26%) (20.5%-31.7%) N = 252	24% (12.2%-35.5%)	22% (10.6%-32.9%)

Source: Table 14.2.1.2.1.

Abbreviations: CI, confidence interval; FAS, full analysis set; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; LOD, limit of detection; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A.

[a] The percentage of subjects with 4-fold increase in hSBA titers relative to baseline defined as: for a prevaccination titer < 2 x (LOD), a postvaccination titer of at least 8; for a prevaccination titer ≥ 2 a postvaccination titer of at least 4 x prevaccination titer.

Note: Group 3B subjects (follow-on subjects) - hSBA titers were measured 1 month after booster dose. Group B_0_1 subjects (vaccine naïve subjects) - hSBA titers were measured 1 month after first vaccination.

- Thus, administration of a booster dose of rMenB+OMV NZ in previously primed subjects (follow-on group) showed a stronger immune response with higher increase of hSBA titers, as compared to the response to a first dose of rMenB+OMV NZ vaccine in vaccine naïve subjects of similar age, inducing an anamnestic response (Table 11.4.1-3; Table 11.4.1-4).
- A booster dose administered 4 years (V72_41) or 7.5 years (V72P10) after the last vaccination induced a similar immune response (Table 11.4.1-3; Table 11.4.1-4).

Assessor's comment:

The rate of subjects with hSBA titer ≥ 4 at 1 month after the booster dose in follow-on subjects were higher than after a single vaccine dose in vaccine naïve subjects for all 4 indicator strains. The same is observed for hSBA GMTs. The GMT ratios following booster compared to first dose indicate the presence of immunological memory (Table 11.4.1-4).

The strongest immune response as evaluated by hSBA GMTs and an at least 4fold increase of hSBA titers reached one month after the booster dose were obtained for strain 5/99 followed by H44/76 and were lowest for NZ98/254 and M10713.

2) Changes over time in the immune response (kinetics) at 3, 7 and 30 days after a third dose (booster) of rMenB+OMV NZ in follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series compared with that the immune response at 3, 7 and 30

days after the second dose of rMenB+OMV NZ in vaccine naïve subjects according to a 0, 1 month schedule.

- For all 4 strains, the percentages of subjects with hSBA titer of at least 4 in follow-on subjects 3 days after receiving the booster dose were similar to those before vaccination, highly increased 7 days after vaccination and remained unchanged or further increased at 1 month after the booster dose (Table 11.4.1-6). In vaccine naïve subjects 3 days after receiving the second vaccine dose, the percentages of subjects with hSBA titer of at least 4 were similar compared with baseline, increased 7 days after vaccination except for the strain M10713 which remained similar to day 4, and remained unchanged or further increased at 1 month after the second vaccine dose (Table 11.4.1-6).

Table 11.4.1-6 Percentages of Subjects With hSBA Titer of at Least 4 after Booster Dose/Second Dose of rMenB+OMV NZ and Vaccine Group Differences – PPS Kinetics

		Number (%) of Subjects (95% CI)						Vaccine Group Difference (95% CI)	
Strain (Antigen)		Group 3B (V72_41) (N = 130)	Group 3B (V72P10) (N = 112)	Group 3B (Total) (N = 242)	Group B_0_1 (V72_41) (N = 94)	Group B_0_1 (V72P10) (N = 109)	Group B_0_1 (Total) (N = 203)	Group 3B minus Group B_0_1 (V72_41)	Group 3B minus Group B_0_1 (V72P10)
H44/76 (fHbp)	prebooster or second dose	35 (27%) (19.5%-35.4%)	47 (42%) (32.7%-51.7%)	82 (34%) (27.9%-40.2%)	75 (80%) (70.2%-87.4%)	86 (79%) (70%-86.1%)	161 (79%) (73.1%-84.7%)	-53% (-63%--40.8%)	-37% (-48.2%--24.5%)
	3 days after booster or second dose	37 (28%) (20.9%-37%)	51 (46%) (36.1%-55.2%)	88 (36%) (30.3%-42.8%)	37 (74%) (59.7%-85.4%) N = 50	47 (85%) (73.3%-93.5%) N = 55	84 (80%) (71.1%-87.2%) N = 105	-46% (-58.4%--29.8%)	-40% (-51.8%--25.4%)
	7 days after booster or second dose	126 (97%) (92.3%-99.2%)	111 (99%) (95.1%-99.98%)	237 (98%) (95.2%-99.3%)	44 (100%) (92%-100%) N = 44	53 (98%) (90.1%-99.95%) N = 54	97 (99%) (94.4%-99.97%) N = 98	-3% (-7.7%-5.1%)	1% (-3.3%-9%)
	1 month after booster or second dose	127 (98%) (93.4%-99.52%)	112 (100%) (96.8%-100%)	239 (99%) (96.4%-99.74%)	93 (99%) (94.2%-99.97%)	108 (99%) (95%-99.98%)	201 (99%) (96.5%-99.88%)	-1% (-5.7%-3.7%)	1% (-2.4%-5%)
5/99 (NadA)	prebooster or second dose	81 (81%) (71.9%-88.2%) N = 100	62 (83%) (72.2%-90.4%) N = 75	143 (82%) (75.2%-87.1%) N = 175	71 (87%) (77.3%-93.1%) N = 82	73 (84%) (74.5%-90.9%) N = 87	144 (85%) (78.9%-90.2%) N = 169	-6% (-16.3%-5.6%)	-1% (-13.3%-10.4%)
	3 days after booster or second dose	80 (78%) (68.4%-85.3%) N = 103	66 (80%) (70.3%-88.4%) N = 82	146 (79%) (72.3%-84.6%) N = 185	36 (82%) (67.3%-91.8%) N = 44	37 (88%) (74.4%-96%) N = 42	73 (85%) (75.5%-91.7%) N = 86	-4% (-17%-11.4%)	-8% (-20%-7.3%)
	7 days after booster or second dose	103 (100%) (96.5%-100%) N = 103	82 (100%) (95.6%-100%) N = 82	185 (100%) (98%-100%) N = 185	40 (100%) (91.2%-100%) N = 40	47 (98%) (88.9%-99.95%) N = 48	87 (99%) (93.8%-99.97%) N = 88	0% (-3.6%-8.8%)	2% (-2.5%-11%)
	1 month after booster or second dose	103 (100%) (96.5%-100%) N = 103	82 (100%) (95.6%-100%) N = 82	185 (100%) (98%-100%) N = 185	84 (100%) (95.7%-100%) N = 84	88 (98%) (92.2%-99.73%) N = 90	172 (99%) (95.9%-99.86%) N = 174	0% (-3.6%-4.4%)	2% (-2.3%-7.8%)
NZ98/254 (PorA P1.4)	prebooster or second dose	13 (10%) (5.4%-16.5%)	28 (28%) (19.3%-37.5%) N = 101	41 (18%) (13%-23.3%) N = 231	37 (40%) (29.8%-50.5%) N = 93	68 (63%) (53.1%-72.1%) N = 108	105 (52%) (45.1%-59.3%) N = 201	-30% (-41%--18.7%)	-35% (-47.2%--22.1%)
	3 days after booster or second dose	15 (12%) (6.6%-18.3%)	29 (28%) (19.7%-37.9%) N = 103	44 (19%) (14.1%-24.5%) N = 233	16 (32%) (19.5%-46.7%) N = 50	33 (60%) (45.9%-73%) N = 55	49 (47%) (36.9%-56.7%) N = 105	-20% (-35.2%--7.5%)	-32% (-46.5%--15.7%)

		Number (%) of Subjects (95% CI)						Vaccine Group Difference (95% CI)	
Strain (Antigen)		Group 3B (V72_41) (N = 130)	Group 3B (V72P10) (N = 112)	Group 3B (Total) (N = 242)	Group B_0_1 (V72_41) (N = 94)	Group B_0_1 (V72P10) (N = 109)	Group B_0_1 (Total) (N = 203)	Group 3B minus Group B_0_1 (V72_41)	Group 3B minus Group B_0_1 (V72P10)
M10713 (NHBA)	7 days after booster or second dose	95 (73%) (64.6%-80.5%)	82 (80%) (70.5%-86.9%) N = 103	177 (76%) (70%-81.3%) N = 233	35 (80%) (64.7%-90.2%) N = 44	44 (81%) (68.6%-90.7%) N = 54	79 (81%) (71.4%-87.9%) N = 98	-6% (-19.2%-9.2%)	-2% (-14.1%-12.3%)
	1 month after booster or second dose	122 (94%) (88.2%-97.3%)	97 (94%) (87.8%-97.8%) N = 103	219 (94%) (90.1%-96.7%) N = 233	77 (82%) (72.6%-89.1%)	86 (79%) (70%-86.1%)	163 (80%) (74.1%-85.5%)	12% (3.6%-21.6%)	15% (6.4%-24.6%)
	prebooster or second dose	90 (70%) (61.6%-78.1%) N = 128	88 (79%) (69.8%-85.8%)	178 (74%) (68.1%-79.6%) N = 240	76 (82%) (72.4%-89%) N = 93	101 (93%) (86%-96.8%)	177 (88%) (82.3%-91.8%) N = 202	-11% (-22.3%-0.17%)	-14% (-23.5%--5%)
	3 days after booster or second dose	92 (71%) (62.7%-78.9%) N = 129	96 (86%) (77.8%-91.6%)	188 (78%) (72.2%-83.1%) N = 241	38 (76%) (61.8%-86.9%) N = 50	48 (87%) (75.5%-94.7%) N = 55	86 (82%) (73.2%-88.7%) N = 105	-5% (-17.8%-10.6%)	-2% (-11.8%-11%)
	7 days after booster or second dose	126 (98%) (93.4%-99.52%) N = 129	109 (97%) (92.4%-99.4%)	235 (98%) (94.7%-99%) N = 241	42 (95%) (84.5%-99.4%) N = 44	52 (96%) (87.3%-99.55%) N = 54	94 (96%) (89.9%-98.9%) N = 98	2% (-3.2%-13%)	1% (-4.6%-10.1%)
	1 month after booster or second dose	128 (99%) (95.8%-99.98%) N = 129	111 (99%) (95.1%-99.98%)	239 (99%) (97%-99.9%) N = 241	85 (90%) (82.6%-95.5%)	104 (95%) (89.6%-98.5%)	189 (93%) (88.7%-96.2%)	9% (3.7%-16.5%)	4% (-0.8%-9.5%)

Source: Table 14.2.1.1.3, Table 14.2.1.1.3.2.
Abbreviations: CI, confidence interval; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A; PPS, per-protocol set.
Note: Group 3B subjects (follow-on subjects) - hSBA titers were measured at day 1 (pre-booster dose), 3 days, 7 days and 1 month after booster dose of rMenB+OMV NZ. Group B_0_1 subjects (vaccine naïve subjects) - hSBA titers were measured at pre-second dose, 3 days, 7 days and 1 month after second dose of rMenB+OMV NZ.
Note: Results for strains 5/99 and NZ98/254 are computed with a cut-off of hSBA ≥ 1:4; for strains H44/76 and M10713 with a cut-off of hSBA ≥ 1:5.

- For all 4 strains, hSBA GMTs in follow-on subjects 3 days after receiving the booster dose remained similar to those before vaccination, increased 7 days after vaccination and further increased or remained high at 1 month after the booster dose. In vaccine naïve subjects 3 days after receiving the second vaccine dose GMTs also remained similar to those at baseline, increased 7 days after vaccination and remained high at 1 month after the second dose. For all 4 strains hSBA titers at 1 month after booster were higher than at 1 month after the second dose in naïve subjects (Table 11.4.1-7).

Table 11.4.1-7 Geometric Mean hSBA Titers, Geometric Mean Ratios After Booster/Second Dose Over Before Booster/Second Dose and Vaccine Group Ratios – PPS Kinetics

		hSBA GMT/GMR (95% CI)						Vaccine Group Ratio (95% CI)	
Strain (Antigen)		Group 3B (V72_41) (N = 130)	Group 3B (V72P10) (N = 112)	Group 3B (Total) (N = 242)	Group B_0_1 (V72_41) (N = 94)	Group B_0_1 (V72P10) (N = 109)	Group B_0_1 (Total) (N = 203)	Group 3B vs Group B_0_1 (V72_41)	Group 3B vs Group B_0_1 (V72P10)
H44/76 (fHbp)	GMT Before booster or second dose	2.41 (1.86-3.13)	4.61 (3.34-6.38)	2.99 (2.41-3.7)	14 (10-19)	27 (19-37)	17 (14-22)		
	GMT 3 days after booster or second dose	2.68 (2.06-3.48)	4.57 (3.38-6.18)	3.2 (2.6-3.94)	14 (9.55-22) N = 50	24 (16-37) N = 55	17 (13-23) N = 105		
	GMT 7 days after booster or second dose	97 (77-123)	153 (123-191)	115 (98-136)	62 (42-90) N = 44	60 (44-83) N = 54	57 (44-73) N = 98		
	GMT 1 month after booster or second dose	157 (127-193)	285 (234-345)	196 (170-228)	57 (45-73)	64 (52-78)	56 (48-66)	2.73 (2.02-3.69)	4.46 (3.38-5.88)
	GMR 1 month after booster or second dose/before booster or second dose	65 (49-85)	62 (49-78)	66 (55-79)	4.21 (3.05-5.80)	2.37 (1.87-3)	3.27 (2.66-4.03)		
5/99 (NadA)	GMT Before booster or second dose	20 (14-29) N = 100	30 (20-47) N = 75	24 (18-32) N = 175	33 (23-50) N = 82	30 (20-44) N = 87	31 (23-41) N = 169		
	GMT 3 days after booster or second dose	23 (16-34) N = 103	25 (17-35) N = 82	24 (18-31) N = 185	27 (15-49) N = 44	28 (17-47) N = 42	27 (19-41) N = 86		
	GMT 7 days after booster or second dose	1969 (1516-2556) N = 103	1547 (1191-2009) N = 82	1787 (1477-2162) N = 185	294 (197-439) N = 40	365 (259-514) N = 48	337 (257-442) N = 88		
	GMT 1 month after booster or second dose	2147 (1749-2635) N = 103	1903 (1469-2466) N = 82	2026 (1714-2395) N = 185	224 (179-281) N = 84	276 (215-353) N = 90	248 (208-295) N = 174	9.58 (7.17-13)	6.90 (4.82-9.87)

Strain (Antigen)		hSBA GMT/GMR (95% CI) Group 3B (V72_41) (N = 130)	Group 3B (V72P10) (N = 112)	Group 3B (Total) (N = 242)	Group B_0_1 (V72_41) (N = 94)	Group B_0_1 (V72P10) (N = 109)	Group B_0_1 (Total) (N = 203)	Vaccine Group Ratio (95% CI) Group 3B vs Group B_0_1 (V72_41)	Group 3B vs Group B_0_1 (V72P10)
	GMR 1 month after booster or second dose/before booster or second dose	105 (76-145) N = 100	62 (41-96) N = 75	85 (65-111) N = 175	6.86 (4.82-9.78) N = 82	9.09 (6.1-14) N = 87	8.1 (6.12-11) N = 169		
NZ98/254 (PorA P1.4)	GMT Before booster or second dose	1.31 (1.06-1.63)	2.4 (1.72-3.37) N = 101	1.57 (1.29-1.92) N = 231	3.44 (2.66-4.43) N = 93	9.79 (7.07-14) N = 108	5.11 (4.1-6.38) N = 201		
	GMT 3 days after booster or second dose	1.4 (1.15-1.7)	2.34 (1.72-3.2) N = 103	1.62 (1.35-1.96) N = 233	2.75 (2.02-3.74) N = 50	8.94 (5.84-14) N = 55	4.45 (3.38-5.84) N = 105		
	GMT 7 days after booster or second dose	10 (7.8-13)	18 (13-25) N = 103	12 (10-15) N = 233	11 (6.96-17) N = 44	15 (9.79-24) N = 54	12 (8.46-16) N = 98		
	GMT 1 month after booster or second dose	32 (25-40)	44 (33-59) N = 103	35 (29-42) N = 233	12 (9.04-16)	17 (13-23)	14 (11-17)	2.65 (1.89-3.73)	2.51 (1.67-3.78)
	GMR 1 month after booster or second dose/before booster or second dose	24 (19-30)	18 (14-24) N = 101	22 (19-27) N = 231	3.42 (2.59-4.51) N = 93	1.76 (1.36-2.29) N = 108	2.63 (2.15-3.21) N = 201		
M10713 (NHBA)	GMT Before booster or second dose	13 (9.76-18) N = 128	22 (16-29)	15 (12-19) N = 240	25 (18-35) N = 93	50 (38-67)	32 (25-41) N = 202		
	GMT 3 days after booster or second dose	14 (9.96-19) N = 129	24 (18-32)	16 (13-21) N = 241	18 (11-30) N = 50	37 (24-56) N = 55	23 (17-33) N = 105		
	GMT 7 days after booster or second dose	48 (39-59) N = 129	68 (56-82)	54 (46-62) N = 241	42 (30-59) N = 44	56 (42-73) N = 54	45 (36-57) N = 98		

Strain (Antigen)		hSBA GMT/GMR (95% CI) Group 3B (V72_41) (N = 130)	Group 3B (V72P10) (N = 112)	Group 3B (Total) (N = 242)	Group B_0_1 (V72_41) (N = 94)	Group B_0_1 (V72P10) (N = 109)	Group B_0_1 (Total) (N = 203)	Vaccine Group Ratio (95% CI) Group 3B vs Group B_0_1 (V72_41)	Group 3B vs Group B_0_1 (V72P10)
	GMT 1 month after booster or second dose	64 (52-80) N = 129	116 (94-143)	78 (67-92) N = 241	34 (26-44)	61 (49-75)	41 (35-49)	1.88 (1.37-2.59)	1.91 (1.41-2.58)
	GMR 1 month after booster or second dose/before booster or second dose	4.87 (3.92-6.05) N = 128	5.3 (4.29-6.55)	5.07 (4.33-5.94) N = 240	1.36 (1.06-1.75) N = 93	1.2 (0.97-1.49)	1.27 (1.07-1.52) N = 202		

Source: Table 14.2.1.3.3.

Abbreviations: CI, confidence interval; fHbp, factor H binding protein; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A; PPS, per protocol set.

Note: Group 3B subjects (follow-on subjects) - hSBA titers were measured at day 1 (pre booster dose), 3 days, 7 days and 1 month after booster dose of rMenB+OMV NZ. Group B_0_1 subjects (vaccine naïve subjects) - hSBA titers were measured at pre-second dose, 3 days, 7 days and 1 month after second dose of rMenB+OMV NZ.

- Across serogroup B strains and across vaccine groups, the percentages of subjects with at least 4-fold increase were higher at 7 days and at 1 month after the booster dose in the follow on subjects compared than after the second dose in the vaccine naïve subjects (Table 14.2.1.2.2).

Assessor's comment:

Booster vaccination 4 to 7 years after a two dose vaccination schedule with rMenB+OMV NZ led to strong increases of both hSBA titers and hsBA GMTs of all 4 strains as measurable 7 days and 30 days later. Best results were obtained for the strains H44/76, 5/99 and M10713 showing proportions of 98-100% for individuals with hSBA titers ≥ 4 after the booster vaccination (compared to 94% for strain NZ98/254). The kinetics of these immune responses is in agreement with persisting immune memory 4-7.5 years following two priming doses.

Similar observations were made when comparing the time dependent outcome before and after the second dose of vaccination. Also here, a strong increase in both hSBA titers and hsBA GMTs against all 4

strains were measurable 7 days and 30 days later, although the increases were of a lower magnitude compared to the booster dose.

3) Immune response at 1 month after the second dose (primary series) of rMenB+OMV NZ administered to vaccine naïve subjects according to a 0, 1 month schedule. A robust immune response to a 2-dose primary series of rMenB+OMV NZ given 1 month apart was observed in vaccine naïve subjects at 1 month following the first and the second rMenB+OMV NZ dose as indicated by:

- At 1 month after the first dose, the percentages of subjects with hSBA titer of at least 4, ranged from 80% to 88% across strains H44/76, 5/99 and M10713, and was 53% for strain NZ98/254 (Table 11.4.1-8). The hSBA GMT titers increased 16- and 20–fold over baseline for strains H44/76 and 5/99, and 5.07- and 2.56-fold over baseline for strains NZ98/254 and M10713, all respectively (Table 11.4.1-9).

Table 11.4.1-8 Percentages of Vaccine Naïve Subjects With hSBA Titers of at Least 4 at 1 Month After Second Dose of rMenB+OMV NZ – PPS Catch-Up

		Number (%) of Subjects (95% CI)		
Strain (Antigen)		Group B_0_1 (V72_41) (N = 98)	Group B_0_1 (V72P10) (N = 117)	Group B_0_1 (Total) (N = 215)
H44/76 (fHbp)	Day 1[a]	3 (3%) (0.6%-8.7%)	14 (12%) (6.7%-19.3%)	17 (8%) (4.7%-12.4%)
	1 month after first dose	79 (81%) (71.4%-87.9%)	94 (80%) (72%-87.1%)	173 (80%) (74.5%-85.5%)
	1 month after second dose	97 (99%) (94.4%-99.97%)	116 (99%) (95.3%-99.98%)	213 (99%) (96.7%-99.89%)
5/99 (NadA)	Day 1[a]	4 (5%) (1.3%-11.5%) N = 86	20 (21%) (13.4%-30.6%) N = 95	24 (13%) (8.7%-19.1%) N = 181
	1 month after first dose	73 (87%) (77.8%-93.3%) N = 84	83 (84%) (75.1%-90.5%) N = 99	156 (85%) (79.3%-90%) N = 183
	1 month after second dose	91 (100%) (96%-100%) N = 91	101 (97%) (91.8%-99.4%) N = 104	192 (98%) (95.6%-99.68%) N = 195
NZ98/254 (PorA P1.4)	Day 1[a]	0 (0%) (0%-3.7%)	18 (16%) (9.5%-23.6%) N = 115	18 (8%) (5.1%-13%) N = 213
	1 month after first dose	40 (41%) (31.3%-51.7%) N = 97	73 (63%) (53.5%-71.7%) N = 116	113 (53%) (46.1%-59.9%) N = 213
	1 month after second dose	80 (82%) (72.5%-88.7%)	93 (79%) (71%-86.4%)	173 (80%) (74.5%-85.5%)
M10713 (NHBA)	Day 1[a]	59 (60%) (49.8%-70%)	91 (78%) (69.9%-85.5%) N = 116	150 (70%) (63.5%-76.1%) N = 214
	1 month after first dose	79 (81%) (72.3%-88.6%) N = 97	108 (93%) (86.9%-97%) N = 116	187 (88%) (82.6%-91.9%) N = 213
	1 month after second dose	88 (90%) (82%-95%)	111 (96%) (90.2%-98.6%) N = 116	199 (93%) (88.7%-96%) N = 214

Source: Table 14.2.1.1.4, Table 14.2.1.1.4.1.1.
Abbreviations: CI, confidence interval; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A; PPS, per-protocol set.
[a]Baseline = before vaccination.
Note: Results for strains 5/99 and NZ98/254 are computed with a cut-off of hSBA ≥ 1:4; for strains H44/76 and M10713 with a cut-off of hSBA ≥ 1:5.

Table 11.4.1-9 Geometric Mean hSBA Titers, Geometric Mean Ratios at 1 Month After Second Dose of rMenB+OMV NZ in Vaccine Naïve Subjects– PPS Catch-Up

Strain (Antigen)		GMT/GMR (95% CI)		
		Group B_0_1 (V72_41) (N = 98)	Group B_0_1 (V72P10) (N = 117)	Group B_0_1 (Total) (N = 215)
H44/76 (fHbp)	GMT Day 1[a]	1.08 (1-1.17)	1.56 (1.29-1.89)	1.32 (1.18-1.47)
	GMT 1 Month after first dose	14 (10-20)	28 (20-39)	20 (16-26)
	GMT 1 month after second dose	57 (47-68)	64 (53-78)	61 (53-70)
	GMR 1 month after first dose/Day 1	13 (9.5-18)	18 (13-24)	16 (12-19)
	GMR 1 month after second dose/Day 1	52 (42-65)	41 (33-51)	46 (39-54)
5/99 (NadA)	GMT Day 1[a]	1.18 (1.03-1.35) N = 86	2.18 (1.58-3) N = 95	1.63 (1.35-1.96) N = 181
	GMT 1 Month after first dose	34 (23-49) N = 84	32 (22-47) N = 99	33 (25-43) N = 183
	GMT 1 month after second dose	239 (200-285) N = 91	274 (207-363) N = 104	257 (217-305) N = 195
	GMR 1 month after first dose/Day 1	28 (19-42) N = 83	15 (9.73-22) N = 92	20 (15-27) N = 175
	GMR 1 month after second dose/Day 1	204 (162-257) N = 86	123 (74-204) N = 95	156 (117-209) N = 181
NZ98/254 (PorA P1.4)	GMT Day 1[a]	1 (1-1)	1.58 (1.3-1.91) N = 115	1.28 (1.15-1.42) N = 213
	GMT 1 Month after first dose	3.64 (2.66-4.97) N = 97	10 (7.06-15) N = 116	6.38 (4.95-8.22) N = 213
	GMT 1 month after second dose	11 (8.41-14)	18 (13-24)	14 (11-17)
	GMR 1 month after first dose/Day 1	3.64 (2.66-4.97) N = 97	6.71 (4.83-9.33) N = 114	5.07 (4.02-6.38) N = 211
	GMR 1 month after second dose/Day 1	11 (8.41-14)	11 (7.94-16) N = 115	11 (8.88-14) N = 213
M10713 (NHBA)	GMT Day 1[a]	10 (7.13-15)	19 (14-26) N = 116	14 (11-18) N = 214
	GMT 1 Month after first dose	25 (18-33) N = 97	50 (38-64) N = 116	36 (30-44) N = 213
	GMT 1 month after second dose	33 (25-44)	60 (48-75) N = 116	46 (38-55) N = 214
	GMR 1 month after first dose/Day 1	2.47 (1.93-3.15) N = 97	2.65 (2.14-3.28) N = 116	2.56 (2.19-3.01) N = 213
	GMR 1 month after second dose/Day 1	3.24 (2.57-4.08)	3.22 (2.60-3.98) N = 116	3.23 (2.76-3.77) N = 214

Source: Table 14.2.1.3.4.

Abbreviations: CI, confidence interval; fHbp, factor H binding protein; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, human serum bactericidal assay; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A; PPS, per-protocol set.

[a]Baseline = before vaccination.

- At 1 month after the second dose, the percentages of subjects with hSBA titer of at least 4, ranged from 93% to 99% across strains H44/76, 5/99 and M10713, and was 80% for strain NZ98/254 (Table 11.4.1-8). The hSBA GMT titers increased 46- and 156–fold over baseline for strains H44/76 and 5/99, and 11- and 3.23-fold over baseline for strains NZ98/254 and M10713, respectively (Table 11.4.1-9). The percentages of subjects with at least a 4-fold hSBA titer increase were 95% and 97% for strains H44/76 and 5/99, and were 67% and 35% for strains NZ98/254 and M10713, all respectively (Table 11.4.1-10).

Table 11.4.1-10 Percentages of Vaccine Naïve Subjects With at Least 4-fold Increase[a] in hSBA Titers after First and Second Dose of rMenB+OMV NZ Over Day 1[b] – PPS Catch-Up

Strain (Antigen)		Number (%) of Subjects (95% CI) Group B_0_1 (V72_41) (N = 98)	Group B_0_1 (V72P10) (N = 117)	Group B_0_1 (Total) (N = 215)
H44/76 (fHbp)	1 Month after first dose	66 (67%) (57.1%-76.5%)	86 (74%) (64.5%-81.2%)	152 (71%) (64.1%-76.7%)
	1 Month after second dose	95 (97%) (91.3%-99.4%)	110 (94%) (88.1%-97.6%)	205 (95%) (91.6%-97.7%)
5/99 (NadA)	1 Month after first dose	66 (80%) (69.2%-87.6%) N = 83	67 (73%) (62.6%-81.6%) N = 92	133 (76%) (69%-82.1%) N = 175
	1 Month after second dose	86 (100%) (95.8%-100%) N = 86	89 (94%) (86.8%-97.6%) N = 95	175 (97%) (92.9%-98.8%) N = 181
NZ98/254 (PorA P1.4)	1 Month after first dose	28 (29%) (20.1%-39%) N = 97	62 (54%) (44.8%-63.7%) N = 114	90 (43%) (35.9%-49.6%) N = 211
	1 Month after second dose	63 (64%) (54%-73.7%)	79 (69%) (59.4%-77%) N = 115	142 (67%) (59.9%-73%) N = 213
M10713 (NHBA)	1 Month after first dose	24 (25%) (16.5%-34.5%) N = 97	30 (26%) (18.2%-34.8%) N = 116	54 (25%) (19.7%-31.7%) N = 213
	1 Month after second dose	36 (37%) (27.2%-47.1%)	38 (33%) (24.3%-42.1%) N = 116	74 (35%) (28.2%-41.4%) N = 214

Source: Table 14.2.1.2.3.
Abbreviations: CI, confidence interval; fHbp, factor H binding protein; hSBA, human serum bactericidal assay; LOD, limit of detection; NadA, Neisserial adhesin A; NHBA, Neisseria heparin binding antigen; PorA, Porin A; PPS, per-protocol set.
[a] The percentage of subjects with 4-fold increase in hSBA titers relative to baseline defined as: for a prevaccination titer < 2 (LOD), a postvaccination titer of at least 8; for a prevaccination titer ≥ 2 a postvaccination titer of at least 4 x prevaccination titer.
[b] Baseline = before vaccination.

Thus, 2 doses of rMenB+OMV NZ vaccine administered 1 month apart to vaccine naïve subjects 15 through 21 years of age induced an overall robust antibody response against all strains with evidence of an early response observed already at one month after the first dose.

Assessor's comment:

Overall, strong immune responses were observed for all 4 strains after the second dose and after booster vaccination as reflected in high rates of individuals showing hSBA titers of ≥ 4 in both cases. Of note, rates of individuals showing hSBA titers ≥ 4 latest 30 days after the second vaccination remained clearly lower for the strains NZ98/254 (79-82%) and M10713 (90-96%) compared to the other two strains and the outcome observed after booster vaccination. The lower response of NZ98/254 and M10713 after the second vaccination is also reflected in a lower rate of individuals reaching an at least 4 fold increase in hSBA titers after the second vaccination compared to the other two strains.

In general, higher GMTs were reached by booster vaccination compared to the second vaccination dose for all four strains. This observation is especially pronounced for strain 5/99 as reflected in both very high GMTs and GMRs after the booster vaccination and weakest for strain M10713.

Safety results

- A total of 530 (>99%) subjects out of enrolled 531 subjects were exposed to the study vaccine and were included in the overall safety set (Table 12.1-1).

Table 12.1-1 Number (%) of Subjects Analyzed in the Exposed and Safety Sets – All Enrolled Set

Analysis Set	Group 3B N = 276	Group B_0_1 N = 255
Enrolled Set	**276 (100%)**	**255 (100%)**
Exposed Set		
Any dose	275 (>99%)	255 (100%)
Booster/First dose	275 (>99%)	255 (100%)
Second dose	0	250 (98%)
Solicited Safety Set		
Any Dose	266 (96%)	254 (>99%)
Booster/First Dose	266 (96%)	253 (99%)
Second Dose	0	248 (97%)
Unsolicited Safety Set		
Any dose	275 (>99%)	255 (100%)
Booster/First Dose	275 (>99%)	255 (100%)
Second Dose	0	250 (98%)
Overall Safety Set	275 (>99%)[a]	255 (100%)

Source: Table 14.1.1.1; Table 14.1.1.1.2.

[a] In one subject, study vaccine was not administered at all but subject number was allocated; the subject was excluded from all safety sets.

Note: The percentages presented for each analysis set are relative to the number of subjects enrolled.

- Any solicited AEs were reported in 263 (99%) follow-on subjects after a single booster dose and in 251 (99%) vaccine naïve subjects after 2 doses (Table 2-5).

Table 2-5 Numbers (%) of Subjects With At Least One Solicited Local and Systemic AE From 6 Hours Through 7 Days After Any and Each Vaccination – Solicited Safety Set

AE	Number (%) of Subjects			
	Group 3B (Total)	Group B_0_1 (Total)		
	N = 266	N = 254	N = 253	N = 248
	Booster	Any Vaccination	First Vaccination	Second Vaccination
Any	263 (99%)	251 (99%)	248 (98%)	232 (94%)
Local	258 (97%)	250 (98%)	247 (98%)	226 (91%)
Systemic	203 (76%)	191 (75%)	163 (64%)	140 (56%)

Source: Table 14.3.1.1; Table 14.3.1.1.5.

Abbreviation: AE, adverse event.

- Solicited local AEs were reported in 258 (97%) follow-on subjects and 247 (98%) vaccine naïve subjects after the first dose and 226 (91%) vaccine naïve subjects after the second dose (Table 2-5). Pain was the most common solicited local AE reported after each dose in both groups (Table 12.2.3-1). Most of the reported solicited local AEs after either dose of vaccine were mild to moderate in intensity with onset 6 hours to day 3 after vaccination, that resolved within 7 days.

Table 12.2.3-1 Number (%) of Subjects with Solicited Local AEs from 6 Hours Through Day 7 After Any and Each Dose – Solicited Safety Set

AE	Grade	Number (%) of Subjects			
		Group 3B	Group B_0_1		
		Booster	Any Dose	First Dose	Second Dose
Pain		N = 264	N = 254	N = 252	N = 247
	Any	258 (98%)	250 (98%)	247 (98%)	226 (91%)
	Severe	71 (27%)	63 (25%)	48 (19%)	31 (13%)
Erythema (mm)		N = 261	N = 253	N = 248	N = 247
	Any	54 (21%)	29 (11%)	18 (7%)	21 (9%)
	Severe (> 100 mm)	7 (3%)	2 (1%)	0	2 (1%)
Induration (mm)		N = 261	N = 253	N = 248	N = 247
	Any	54 (21%)	43 (17%)	26 (10%)	31 (13%)
	Severe (> 100 mm)	1 (<1%)	1 (<1%)	1 (<1%)	0
Swelling (mm)		N = 261	N = 254	N = 249	N = 248
	Any	60 (23%)	43 (17%)	34 (14%)	32 (13%)
	Severe (> 100 mm)	1 (<1%)	0	0	0

Source: Table 14.3.1.2.
Abbreviation: AE, adverse event.

- Solicited systemic AEs were reported in 203 (76%) follow-on subjects after the booster dose and 163 (64%) vaccine naïve subjects after the first dose and 140 (56%) vaccine naïve subjects after the second dose (Table 2-5). The most common solicited systemic AEs reported in both groups were fatigue (after each dose) and headache (after the second dose; Table 12.2.3-2).

Table 12.2.3-2 Number (%) of Subjects with Solicited Systemic AEs from 6 Hours Through Day 7 After Any and Each Dose – Solicited Safety Set

AE	Grade	Number (%) of Subjects			
		Group 3B	Group B_0_1		
		Booster	Any	First	Second
Nausea		N = 264	N = 254	N = 252	N = 248
	Any	56 (21%)	51 (20%)	30 (12%)	33 (13%)
	Severe	4 (2%)	5 (2%)	2 (1%)	3 (1%)
Generalized Myalgia		N = 265	N = 254	N = 252	N = 248
	Any	120 (45%)	98 (39%)	71 (28%)	64 (26%)
	Severe	21 (8%)	12 (5%)	8 (3%)	7 (3%)
Generalized Arthralgia		N = 265	N = 254	N = 252	N = 248
	Any	84 (32%)	63 (25%)	47 (19%)	36 (15%)
	Severe	13 (5%)	10 (4%)	8 (3%)	4 (2%)
Headache		N = 266	N = 254	N = 253	N = 248
	Any	146 (55%)	125 (49%)	94 (37%)	84 (34%)
	Severe	18 (7%)	19 (7%)	10 (4%)	13 (5%)
Fatigue		N = 266	N = 254	N = 252	N = 248
	Any	155 (58%)	140 (55%)	110 (44%)	92 (37%)
	Severe	26 (10%)	23 (9%)	13 (5%)	14 (6%)
Fever (≥ 38°C)		N = 265	N = 254	N = 253	N = 248
	Fever (≥ 38°C)	16 (6%)	9 (4%)	4 (2%)	5 (2%)
	High Fever (≥ 39.5°C)	0	0	0	0
Other Indicators					
Analgesic/Antipyretic Medication Used		N = 266	N = 254	N = 253	N = 247
	Prophylaxis	43 (16%)	56 (22%)	37 (15%)	30 (12%)
		N = 265	N = 254	N = 253	N = 247
	Treatment	108 (41%)	100 (39%)	69 (27%)	70 (28%)

Source: Table 14.3.1.2.
Abbreviation: AE, adverse event.

Assessor's comment:

The majority of individuals experienced solicited AEs in the included study arms, which were mainly of mild to moderate intensity, and resolving within a week. AE frequencies were comparable between individuals obtaining 2 doses of vaccination and individuals obtaining the booster dose. The majority of AEs observed in both groups of individuals were typical as described for meningococcal vaccines including local (pain, erythema, induration and swelling) and systemic reactions such as fever, headache, arthralgias and myalgias.

Thus, no new safety concern is detected here.

- Unsolicited AEs were reported by 87 (32%) follow-on subjects after the booster dose, 96 (38%) vaccine naïve subjects after the first dose and 73 (29%) vaccine naïve subjects after the second dose, with 45 (16%), 58 (23%), and 43 (17%) subjects in respective groups having at least possibly related unsolicited AEs (Table 2-6).

Table 2-6 Overview of Unsolicited Adverse Events After Any Vaccinationa from Day 1 to Study Termination - Unsolicited Safety Set

	Number (%) of Subjects			
	Group 3B	Group B_0_1		
	Booster N = 275	Any Vaccination N = 255	First Vaccination N = 255	Second Vaccination N = 250
Any AEs	87 (32%)	131 (51%)	96 (38%)	73 (29%)
At least possibly related AEs	45 (16%)	80 (31%)	58 (23%)	43 (17%)
Serious AEs	0	1 (<1%)	1 (<1%)	0
At least possibly related SAEs	0	0	0	0
Medically-attended AEs	17 (6%)	34 (13%)	13 (5%)	21 (8%)
AEs leading to withdrawal	0	1 (<1%)	1 (<1%)	0
AEs leading to death	0	0	0	0

Source: Table 14.3.1.13; Table 14.3.1.13.8; Table 14.3.1.18; Table 14.3.1.18.7; Table 14.3.2.1; Table 14.3.2.2; Table 14.3.2.2.2; Table 14.3.2.3; Table 14.3.2.4; Table 14.3.2.4.1; Table 14.3.2.8; Table 14.3.2.8.1.

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a] Single dose in follow-on subjects and two doses in vaccine-naïve subjects.

The most commonly affected system organ classes (SOCs) were 'general disorders and administration site conditions' and 'infections and infestations' while the most common unsolicited AE by preferred term were injection site pain and viral upper respiratory tract infection (Table 12.2.3-3; Table 12.2.3-4). Most of the unsolicited AEs were mild to moderate in intensity, and most of them resolved before study termination.

Table 12.2.3-3 Number (%) of Subjects with All and At Least Possibly Related Unsolicited Adverse Events from Day 1 to Study Termination[a] Presented by System Organ Class – Unsolicited Safety Set

System Organ Class	Number (%) of Subjects			
	All		At Least Possibly Related	
	Group 3B N = 275	Group B_0_1 N = 255	Group 3B N = 275	Group B_0_1 N = 255
Any AE	87 (32%)	131 (51%)	45 (16%)	80 (31%)
Blood and lymphatic system disorders	1 (<1%)	2 (1%)	1 (<1%)	2 (1%)
Ear and labyrinth disorders	0	1 (< 1%)	0	0
Gastrointestinal disorders	2 (1%)	13 (5%)	1 (<1%)	4 (2%)
General disorders and administration site conditions	40 (15%)	61 (24%)	36 (13%)	59 (23%)
Immune system disorders	2 (1%)	2 (1%)	0	1 (<1%)
Infections and infestations	30 (11%)	62 (24%)	2 (1%)	7 (3%)
Injury, poisoning and procedural complications	6 (2%)	9 (4%)	0	1 (<1%)
Metabolism and nutrition disorders	0	2 (1%)	0	1 (<1%)
Musculoskeletal and connective tissue disorders	9 (3%)	7 (3%)	5 (2%)	5 (2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (<1%)	1 (<1%)	0	0
Nervous system disorders	9 (3%)	24 (9%)	5 (2%)	16 (6%)
Psychiatric disorders	3 (1%)	1 (<1%)	1 (<1%)	0
Renal and urinary disorders	1 (<1%)	1 (<1%)	0	0
Reproductive system and breast disorders	3 (1%)	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (1%)	3 (1%)	1 (<1%)	0
Skin and subcutaneous tissue disorders	6 (2%)	5 (2%)	3 (1%)	4 (2%)
Surgical and medical procedures	1 (<1%)	0	0	0
Vascular disorders	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

Source: Table 14.3.1.13; Table 14.3.1.18.

Abbreviation: AE, adverse event.

[a] After a single dose in follow-on subjects and two doses in vaccine-naïve subjects.

Table 12.2.3-4 Number (%) of Subjects with Unsolicited Adverse Events Reported by ≥ 5% of Subjects from Day 1 to Study Termination[a] Presented by Preferred Term - Unsolicited Safety Set

Preferred Term	Number (%) of Subjects			
	All		At Least Possibly Related	
	Group 3B N = 275	Group B_0_1 N = 255	Group 3B N = 275	Group B_0_1 N = 255
Injection site pain	9 (3%)	32 (13%)	9 (3%)	32 (13%)
Viral upper respiratory tract infection	13 (5%)	23 (9%)	2 (1%)	3 (1%)
Injection site induration	7 (3%)	22 (9%)	7 (3%)	22 (9%)
Headache	5 (2%)	15 (6%)	1 (<1%)	10 (4%)
Injection site swelling	3 (1%)	15 (6%)	3 (1%)	15 (6%)

Source: Table 14.3.1.12, Table 14.3.1.18.

[a] Single dose in follow-on subjects and two doses in vaccine-naïve subjects.

- One vaccine-naïve subject, after the first dose had AEs (lymphadenopathy and herpangina) leading to premature withdrawal from the study. One vaccine naïve subject had an SAE (severe appendicitis) after the first dose that was considered as unrelated to the study vaccine by the investigator.

No death was reported in the study (Table 2-6).

Assessor's comment:

32% and 38% of individuals reported unsolicited AEs after the booster dose and after the second vaccination, respectively, with 'general disorders and administration site conditions' and 'infections and infestations' as most commonly affected system organ classes (SOCs) and "injection site pain" and "viral upper respiratory tract infection" as most common preferred terms.

Scrutinization of the AE related original data submitted for the SOCs 'Nervous system disorders' and 'Immune system disorders' revealed diagnoses/PTs of more general character including dizziness, headache, paresthesia, involuntary muscle contraction and allergy.

No deaths were reported.

In summary no new safety concern arose from the reported unsolicited AEs.

2.3.3. Discussion on clinical aspects

Although clearly falling over time, immune persistence was observed for all 4 strains 4-7.5 years after vaccination with 2 doses of rMenB+OMV NZ as demonstrated by GMT ratios (hSBA) > 1 when comparing vaccinated and vaccine naïve subjects. Highest persistence of immunogenic response was reached for strain 5/99 followed by H44/76, and NZ98/254. Immune persistence for strain M10713 is likely a result of high abundant basal GMTs as shown in the vaccine naïve population.

Strong booster induced immune responses were observed in individuals treated with the third vaccine dose 4-7.5 years after dose 1 and 2. This is reflected in a high proportion of subjects showing hSBA titer $\geqslant$ 4 one month after the booster vaccination compared to vaccine naïve individuals treated for the first time with the vaccine. Strongest effects were reached for strain 5/99 and H44/76, lower immunogenicity was observed for NZ98/254 and M10713.

Strong immune responses were also observed after the second dose of vaccination as reflected in high rates of individuals showing hSBA titers of $\geqslant$ 4 latest after 30 days. Of note, rates of individuals showing hSBA titers $\geqslant$ 4 latest 30 days after the second vaccination remained clearly lower for the strains NZ98/254 (79-82%) and M10713 (90-95%) compared to the other two strains and to the outcome observed after booster vaccination. In congruence to this observation, lower rates of individuals reaching an at least 4 fold increase in hSBA titers after the second vaccination as especially seen for NZ98/254 and M10713 after the second vaccination.

In general, higher GMTs were reached by booster vaccination compared to the second vaccination dose for all four strains. This observation is especially pronounced for strain 5/99 as reflected in both very high GMTs and GMRs after the booster vaccination and weakest for strain M10713.

No significant differences in the principle antibody kinetics 1 to 30 days after vaccination were observed when comparing the behaviour of antibody titers after the second vaccine dose and after the booster dose. A greater increase in GMT and response rates were seen after the booster dose compared to the priming doses.

Reported AEs reflected the known side effect profile of the vaccine. Thus, no new safety concern was observed with regard to the solicited and unsolicited AEs reported in the frame of the study.

In summary a strong booster effect is observed by the application of the third dose on all 4 strains. The booster effect appears to be especially valuable for the immunogenicity against the strains NZ98/254 and M10713, which appear to show the lowest immunogenic response to the vaccine after the second dose and the strongest decrease of immune persistence.

3. Rapporteur's overall conclusion and recommendation

With the submission of the current report the commitment is considered fulfilled. The MAH should further discuss to what extent these data should be implemented in the SmPC.

☒ **Fulfilled:**

Based on the data submitted, the MAH should provide a further discussion to what extent the observations made with regard to long persistence and effect of late booster vaccination should be reflected in the SmPC as part of this procedure. (see section "Additional clarification requested")

The response of the MAH to the question posed as documented in section 4 is endorsed and the commitment, thus, completely fulfilled.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The MAH is requested to discuss to what extent the observations made with regard to long persistence and effect of late booster vaccination should be reflected in the SmPC.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

The Company acknowledges the Assessor's request and would like to inform the Agency that an internal evaluation of the data generated with the paediatric study V72_75 is still on-going. We are defining how the data should be adequately reflected in the Summary of Product Characteristics and the current plan is to submit a type II variation for Bexsero later this year.