

<b>Application Type</b>	Biologics License Application
<b>STN</b>	125546/0
<b>CBER Received Date</b>	24 July 2014
<b>PDUFA Goal Date</b>	24 Mar 2015
<b>Division / Office</b>	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
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<b>Applicant</b>	Novartis Vaccines and Diagnostics, Inc.
<b>Established Name</b>	Meningococcal B Vaccine, rMenB+OMV NZ
<b>(Proposed) Trade Name</b>	Bexsero®
<b>Pharmacologic Class</b>	Vaccine
<b>Formulation(s), including Adjuvants, etc</b>	Composed of three purified recombinant <i>Neisseria meningitidis</i> serogroup B protein antigens, NadA (Neisserial adhesin A), NHBA (Neisseria Heparin Binding Antigen), and fHBP (factor H Binding Protein) as fusion protein and PorA P1.4 as the main antigen of Outer Membrane Vesicles (OMV)
<b>Dosage Form(s) and Route(s) of Administration</b>	The vaccine is to be administered as a two dose (0.5 mL each) series at months 0 and 2, or 0 and 1.
<b>Dosing Regimen</b>	Two doses (0.5 mL each) by intramuscular injection
<b>Indication(s) and Intended Population(s)</b>	For active immunization to prevent invasive disease caused by <i>Neisseria meningitidis</i> serogroup B in individuals aged 10 through 25 years.

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## Glossary

<b>Abbreviation</b>	<b>Definition</b>
ANCOVA	analysis of covariance
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
(b)(4)	------(b)(4)-----
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCT	data collection tool
EDMC	external data monitoring committee
ET	early termination
-(b)(4)	----- ( b ) ( 4 ) -----
FAS	Full analysis set
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GMR	geometric mean ratio
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
LLOQ	lower limit of quantitation
LOD	limit of detection
MCV4	meningococcal conjugate vaccine
---(b)(4)-----	------(b)(4)-----
MenACWY	Meningococcal serogroups A, C, W, and Y vaccine (Menveo®)
MenB	<i>Neisseria meningitidis</i> serogroup B
MeNZB	Outer membrane vesicle vaccine derived from <i>Neisseria meningitidis</i> serogroup B strain NZ98/254
MITT	modified intent-to-treat
ML	maximum likelihood
MMRM	mixed-effects model with repeated measures
OMV	outer membrane vesicle
OMV NZ	Outer membrane vesicle derived from <i>Neisseria meningitidis</i> serogroup B strain NZ98/254 (New Zealand strain)
OMV (b)(4)	Outer membrane vesicle derived from <i>Neisseria meningitidis</i> serogroup B strain ------(b)(4)----- strain)
SAP	statistical analysis plan
SD	standard deviation
ULOQ	upper limit of quantitation
UK	United Kingdom
US; USA	United States; United States of America

## 1. Executive Summary

### 1.1 Introduction

Novartis Vaccines and Diagnostics submitted on June 16, 2014, the original Biologics License Application (BLA) STN BL 125546/0, under the Accelerated Approval licensure pathway for licensing the meningococcal serogroup B (MenB) vaccine BEXSERO®. The applicant is seeking an indication for active immunization of individuals 10 through 25 years of age against invasive disease caused by *Neisseria meningitidis* serogroup B strains.

Need for an accelerated approval is justified by recent local (at Princeton University and at the University of California Santa Barbara) outbreaks of MenB disease. These particular outbreaks at universities in New Jersey and California prompted public health agencies to address the health crisis by utilizing an investigational MenB vaccine being under an Investigational New Drug (IND) application.

The candidate rMenB+OMV NZ vaccine contains four *Neisseria meningitidis* serogroup B antigenic components:

- Three purified protein antigens NadA (Neisserial adhesin A), NHBA (Neisseria Heparin Binding Antigen), and fHbp (factor H Binding Protein), and
- Purified protein antigen of Outer Membrane Vesicles (OMV) composed mainly of the PorA P1.4, which is derived from *Neisseria meningitidis* serogroup B strain NZ 98/254.

The candidate rMenB+OMV NZ vaccine received designation as Breakthrough Therapy on April 1, 2014. The following criteria necessary for Breakthrough Therapy designation were met:

- ✓ The candidate MenB vaccine is intended to prevent a serious and life threatening condition.
- ✓ The available preliminary clinical evidence demonstrates that the vaccine may provide substantial improvement in intervention, as compared to other available disease intervention therapies.

Meningococcal serogroup B disease is a serious and life-threatening disease, and currently there are no available preventative treatments that confer protection against this disease. The BEXSERO® vaccine is intended to prevent some meningococcal serogroup B diseases through active immunization.

### 1.2 Brief Overview of sBLA Submission

License application for use of the rMenB+OMV NZ vaccine for individuals aged 10 to 25 years is based on safety and immunogenicity data obtained/generated from 9 clinical trials. A summary of these Phases 1/2/3 clinical trials can be found in Section 5.3 (Table 2) of this review.

The BLA submission contained immunogenicity and safety data from the pivotal clinical trials V72P10, V72P10E1, V72\_41, V72\_29, and V102\_03, and two supportive studies V72P4 and V72P5. The applicant also submitted data from clinical trials V72P13 and V72P16 in support of lot-to-lot consistency and the proposed dosing regimen, respectively.

Clinical trials V72P10, V72P10E1, V72\_41, V72\_29, V72P5, V72P4, and V72P13 were carried out within the frame of the global clinical development program of rMenB+OMV NZ vaccine, while trial V102\_03 was conducted within the global United States (US) clinical development program (IND (b)(4) of the meningococcal serogroups -----  
----- (b)(4) -----.

All clinical trials contributed to evaluation of safety and immunogenicity of the rMenB+OMV NZ vaccine.

### **1.3 Efficacy Conclusions, Major Statistical Issues, and Recommendations**

The immune response to the candidate rMenB+OMV NZ vaccine was evaluated in 9 clinical trials. A summary of the general information on these clinical studies is provided in Table 2. While all studies evaluated safety and immunogenicity of the rMenB+OMV NZ vaccine, some other issues such as dose selection (trial V72P4) as well as immunogenicity of 2- and 3-dose schedules (e.g., trial V72P10) were also investigated.

The effectiveness of the rMenB+OMV NZ vaccine was measured by serum bactericidal activity against meningococcal serogroup B (MenB) indicator strains using hSBA assays. The MenB indicator strains used for the analyses were NZ98/254, H44/76, and 5/99. They served for assessment of bactericidal antibodies induced by the PorA P1.4 (antigen in the OMV NZ), fHbp, and NadA, respectively. These three MenB indicator strains were selected to reflect the fact that they are reasonably representative of the prevalent strains in the US.

In support of the proposed indication of rMenB+OMV NZ for use in subjects 10 through 25 years of age, the immune response to the rMenB+OMV NZ vaccine was assessed using in analyses primarily the following parameters: the percentages of subjects achieving  $\geq 4$ -fold hSBA response to each of the three strains and the percentages of subjects achieving hSBA titer  $\geq$  the lower limit of quantitation (LLOQ) of the assay for all three indicator strains simultaneously (what the applicant called “composite” response). These parameters were chosen in agreement with CBER. Additionally, Geometric Mean Titers (GMTs) against all 3 indicator strains H44/76, 5/99, and NZ98/254 were evaluated in clinical studies V72P10, V72P10E1, V72\_41, V102\_03, and V72\_29.

It is worth noting that:

- The statistical analyses related to immune responses to the rMenB+OMV NZ vaccine were descriptive; however, hSBA responses were evaluated based on data for an extensive number of participants. Approximately 1800 subjects in the four Phase 2/3 clinical trials (V72P10, V72\_41, V102\_03, and V72\_29) received the rMenB+OMV NZ vaccine at 0, 2, or 0, 1, or 0, 6 months schedule, providing a sizeable evaluable immunogenicity population. The 4-fold rise and composite endpoints were assessed based on evaluable immunogenicity populations.
- Evaluations of immune responses to the rMenB+OMV NZ vaccine based on the immunogenicity data generated by seven Phase 1, Phase 2, and Phase 3 clinical trials submitted in this BLA are not intended to assess the breadth of protection against MnB meningococcal disease the rMenB+OMV NZ might confer. The foremost immunogenicity information regarding the immune responses to the candidate vaccine was generated by analyses related to four (4) immunogenicity endpoints stated in Section 6.0 of this review and to three MenB indicator strains.
- Comparison or interpretation across studies of the immunogenicity data generated by pivotal clinical trials V72P10, V72\_41, V102\_03, and V72\_29 is challenging due to issues such as:
  - These 4 clinical trials were carried out in different countries, namely:
    - in Chile - V72P10
    - in the UK – V72\_29
    - in Canada and Australia – V72\_41, and
    - in the US and Poland – V102\_03.

The baseline titers against three indicator strains were different across these four studies. For instance, percentages of subjects at baseline with hSBA titer  $\geq$  LLOQ against strain H44/76 ranged from 0% (V72\_41) to 44% (V72\_29), against strain 5/9 from 2% to 45%, and against strain NZ98/254 from 1% to 32%. Subjects with, on average, highest baseline titers were in the V72\_29 clinical trial, while the lowest baseline titers were seen in studies V72\_41 and V102\_03.
  - Assays for different studies were performed at different laboratories, namely:
    - For study V72P10, the indicator strains were tested at -----(b)(4)----- laboratory, but -(b)(4)-- strain was tested at Novartis Vaccines --(b)(4)- laboratory.
    - For study V72\_41, the indicator strains were tested at Novartis Vaccines --(b)(4)- laboratory.
    - For study V72\_29, the indicator strains were tested at PHE --(b)(4)---- laboratory.
    - For study V102\_03, all 3 strains were tested at Novartis Vaccines --(b)(4)- laboratory,
    - For study V102\_03, the bactericidal antibody responses were measured using (b)(4)-hSBA ----(b)(4)----- assay for serum

- bactericidal activity using human complement). However, validation of this assay and relationship between this assay and hSBA assay are still not fully adequate and/or understood. Therefore, the interpretation of the immune responses data generated by the (b)(4)-hSBA assay is not sufficiently clear.
- Vaccinations were performed at different schedules such as: Month 0 and Month 1, or Month 0 and Month 2, or Month 0 and Month 6.
- Across studies V72P10, V72\_41, V102\_03, and V72\_29, 1 month after the second rMenB+OMV NZ vaccination administered either at 1, 2, or 6 months after the first vaccination, essential results regarding immunogenicity data are as follows:
- Percentages of subjects achieving 4-fold rise against strains H44/76 and 5/99 ranged from 95% to 100% and from 98% to 100%, respectively. However, the bactericidal response against strain NZ98/25 differed across studies. It ranged from 83% to 90% in study V72P10, while for studies V72\_41, V72\_29, and V102\_03 it was only 39%, 67%, and 61%, respectively.
  - Percentage of subjects achieving hSBA titers  $\geq$  LLOQ against all 3 indicator strains (composite response) ranged from 63% to 94%.
  - Percentages of subjects achieving hSBA titers  $\geq$  LLOQ against strains H44/76 and 5/99 ranged from 79% to 98% and from 94% to 99%, respectively. But the bactericidal response against strain NZ98/25 ranged from 63% to 77% in studies V72\_41 and V102\_03 and from 88% to 97% in studies V72P10 and V72\_29.
  - Significant increases in hSBA GMTs against all indicator strains were consistently observed after the 0, 1-, 0, 2-, or 0, 6-month schedules across studies V72P10 and V72\_41. However, significant increases in hSBA GMTs against H44/76 and 5/99 indicator strains, but not against NZ98/258 strain were observed 1 month after the second dose in study V102\_03. For study V72\_29, increases in hSBA GMTs were lower than across the other 3 studies, against all indicator strains. This effect might be due to the high levels of bactericidal antibodies against the indicator strains already at baseline (GMRs 20-fold for indicator strain H44/76, 66-fold for indicator strain 5/99, and 16-fold for indicator strain NZ98/254).
- Antibody persistence of immunogenicity of rMenB+OMV NZ after a 2-dose primary schedule was evaluated in subjects 11 through 17 years of age (study V72P10E1) and 18 through 24 years of age (study V72\_29). According to data from clinical trial V72\_29, the percentages of subjects with hSBA titer  $\geq$  LLOQ at 11 months after the second vaccination were still high, 93%, 90%, and 69% for H44/76, 5/99, and NZ98/54 strains, respectively. In study V72P10E1, the percentages of subjects with hSBA titer  $\geq$  LLOQ at least 18 months (depending on study group) after the second vaccination were lower than in study V72\_29, but higher than for the control naïve group.

Two studies included in the BLA, but considered by the applicant as supportive studies, are V72P4 (Phase 2) and V72P5 (Phase 1). About 74 subjects (age range 18 to 50 years) received two doses of the rMenB+OMV NZ vaccine in these clinical trials. Results from the supportive studies confirmed that the candidate vaccine elicited immune responses after 2 doses.

Additionally, the applicant submitted in BLA 125546.0 data from clinical trials V72P13 and V72P16 that were carried out in support of testing the lot-to-lot consistency and the dosing regimen, respectively.

- Based on the immunogenicity data of clinical trial V72P13, three investigated lots achieved the pre-defined criteria for lot-to-lot consistency. The criteria required that, for pair-wise comparisons, the 95% CIs of the ratios of post-vaccination GMTs for two lots after the 3<sup>rd</sup> dose and for each indicator strain should be entirely within the interval (0.5, 2.0).
- Based on immunogenicity data from clinical trial V72P16, the applicant selected the final formulation of the candidate rMenB+OMV NZ vaccine, and chose to use the full dose (25µg) of OMV.

### **In summary**

*Overall, based on clinical trials V72\_41, V72\_29, and V72P10, which all generated immunogenicity data in the indicated age range, it appears that two doses of the rMenB+OMV NZ vaccine administered at least 1 month apart elicited immune responses expressed for three MenB indicator strains, H44/76, 5/99, and NZ98/254, in healthy subjects aged 10 through 25 years. In study V102\_03, a different assay (b)(4) hSBA was used in place of hSBA. However, the results in V102\_03 demonstrated a similar pattern of immune responses to those observed in other studies (V72\_41, V72\_20).*

*Results from studies V72P10E1 and V72\_29 suggest persistence of bactericidal antibody responses to the rMenB+OMV NZ vaccine 11-24 months after vaccination, when the vaccine was given as a 2-dose or 3-dose regimen.*

## **2. Clinical and Regulatory Background**

### **2.1 Background**

The applicant has developed a novel investigational vaccine rMenB+OMV NZ, which is to be used to provide protection against meningococcal disease caused by serogroup B. The target populations for this vaccine are adolescents and young adults from 10 through 25 years of age. The current MenB vaccine formulation contains three purified protein antigens, NadA, NHBA, and fHbp, and purified protein antigen of Outer Membrane Vesicles (OMV) composed mainly of the PorA P1.4, which is derived from *Neisseria meningitidis* serogroup B strain NZ 98/254. This final formulation is designated rMenB+OMV NZ. In the initial stages of clinical development, some investigational vaccines were formulated with aluminum hydroxide, and with ---(b)(4)-- OMVs derived

from either the ----(b)(4)----- or the New Zealand strain NZ98/254. Both formulations have been evaluated in preclinical and clinical studies. The decision to continue the clinical program only with rMenB+OMV NZ was based on the experience collected while using the OMV NZ-based vaccine MeNZB, which was shown to be safe and efficacious for controlling the clonal MenB epidemic in New Zealand, and had good immunogenicity results from the adult study V72P5. The final formulation of vaccine was evaluated in clinical trials V72P10, V72P10E1, V72\_41, V102\_03, V72\_29, V72P13, V72P4, V72P5, and V72P16.

## 2.2 Previous Human Experience with the Product

Within the clinical program of the rMenB+OMV NZ vaccine development, many clinical trials were carried out in adolescents, young children, and infant populations. Since January 2013, the vaccine was licensed under the trade name of BEXSERO® for use in the EU, Australia, Canada, and Chile. Following an outbreak of serogroup B meningococcal disease at Princeton University, the Center for Disease Control and Prevention (CDC) approached the applicant and under BB-IND 15810, an expanded access to Investigational New Drug (IND) for treatment use, asked the applicant to make approximately 12,000 doses of the rMenB+OMV NZ vaccine for students and staff of this university (V72\_68TP). The applicant supported this request and approximately 13,440 doses of the rMenB+OMV NZ vaccine were provided under the CDC-sponsored IND during December 2013. Subsequently, due to a separate outbreak of serogroup B meningococcal disease at the University of California Santa Barbara (UCSB), the applicant was again approached by the CDC to make approximately 40,000 doses of rMenB+OMV NZ vaccine available to students and staff of the university under the same expanded access IND (V72\_70TP).

As of May 16, 2014, 5520 individuals at Princeton University received at least one rMenB+OMV NZ vaccine dose starting from December 2013. As of May 20, 2014, 9831 individuals at UCSB received at least 1 vaccine dose starting from February 2014.

The overall total number of individuals exposed to at least 1 dose of rMenB+OMV NZ in clinical trials V72P4, V72P5, V72P10, V72\_29, V72\_41, V102\_03, V72\_68TP, and V72\_70TP was 18,490.

## 2.3 Investigational Vaccine

The investigational vaccine (trade name: BEXSERO®) was the rMenB+OMV NZ vaccine containing the 3 recombinant protein antigens (NHBA, fHbp, and NadA) and OMV NZ derived from *Neisseria meningitidis* serogroup B, strain NZ98/254. The study regimens were 1, or 2, or 3 doses of the investigational vaccine.

Composition of the investigational rMenB+OMV NZ vaccine is given in Table 1.

Table 1: Composition of the rMenB+OMV NZ vaccine

Name of Ingredients	Quantity per dose (0.5mL)
N meningitidis 961c purified antigen	50 µg
<i>N meningitidis</i> 936-741 purified antigen	50 µg
<i>N meningitidis</i> ΔG287-953 purified antigen	50 µg
OMV from <i>N meningitidis</i> Strain NZ 98/254	25 µg
Aluminum hydroxide	1.5 mg
NaCl	---(b)(4)-----
Histidine	10 mM (0.776 mg)
Water for injection	Up to 0.5 mL

Source: The applicant's table (CSR V72P10 page 44)

The rMenB+OMV NZ vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.

## 2.4 Regulatory Activity Related to the Submission

Licensure pathways for MenB vaccines were discussed during the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) meeting, which was held in April 2011. The committee agreed that the use of the SBA assay is a reasonable approach. However, issues regarding the approach/methods of verification of the MenB vaccine effectiveness still existed. Consequently, in an effort to specify criteria for evaluation of immune response to the MenB candidate vaccine and reach agreement on licensing criteria for the vaccine, many discussions and communications took place between the applicant and the Agency.

As the applicant planned to use the combination of -----(b)(4)----- SBA to assess immunogenicity and the breadth of coverage of the candidate MenB vaccine, it was decided that, prior to initiation of pivotal Phase 3 studies, a phase 2 study should be carried out to establish the performance and relevance of the ---(b)(4)----- SBA.

## 3. Submission Quality and Good Clinical Practices

### 3.1 Submission Quality and Completeness

BLA 125546 was accepted as a rolling submission. The first rolling piece was received by CBER on June 16, 2014, and included nonclinical and clinical information supporting licensure of the vaccine for use in individuals 10 through 25 years of age. It contained data for the following clinical trials: V72P10, V72P10E1, V72\_41, V72\_29, and V102\_03, and two supportive clinical trials, V72P4 and V72P5. In support of the lot to lot consistency and dosing regimen, two clinical studies, V72P13 and V72P16,

respectively, were also submitted. The datasets for both these clinical trials were included in the third submission (Amendment 0.2, on July 24, 2014).

Amendment 0.2 also contained the Integrated Summary of Efficacy, the Integrated Summary of Safety, the Clinical Overview, and the labeling documents.

All submissions were adequately organized and integrated and allowed the conduct of a complete statistical review.

### **3.2 Compliance with Good Clinical Practices and Data Integrity**

As per the applicant, data submitted to this BLA were generated by eleven clinical studies conducted in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

## **4. Significant Efficacy/Safety Issues Related to Other Review Disciplines**

This section is not applicable to this statistical review.

## **5. Sources of Clinical Data and Other Information Considered in the Review**

### **5.1 Review Strategy**

Statistical review of this BLA was divided between Dr. Barbara Krasnicka and Dr. Tammy Massie. Issues related to the immune responses were reviewed by Dr. Krasnicka, while safety aspects of vaccinations administered were reviewed by Dr. Massie. The immunogenicity and safety statistical reviews were prepared as two separate documents.

The main focus of this document is evaluation of the immune response to the candidate rMenB+OMV NZ vaccine, as measured by serum bactericidal assay using human complement (hSBA) for strains indicated in the corresponding clinical trial protocols.

### **5.2 BLA Documents that Serve as the Basis for the Statistical Review**

The complete submission that contained clinical study reports (CSRs), SAS datasets, and other related materials was supplied by the applicant mainly in two steps, on June 16 and July 24, 2014, and is located in the EDR under BLA STN 125546/0.0 and 125546/0.2 (Amendment 1). All SAS datasets and programs were placed in Module 5 of Amendments 0.0 and 0.2.

This statistical review of immune responses to the rMenB+OMV NZ vaccine is based on data generated by clinical trials V72P10, V72P10E1, V72\_41, V72\_29, V72P5, V72P4, V102\_3, V72 P13, and V72P16. For verification of the applicant's results, the statistical

reviewer performed several statistical analyses on SAS datasets generated by the above mentioned studies.

For presentation of this statistical review of BLA submission STN125546, mainly the following sources were used:

Amendment 0.0:

- ✓ Module 5: The final protocols, SAPs, and clinical study reports for five studies with adequate datasets and SAS programs.

Amendment 0.2:

- ✓ Module 1: Administrative information and labeling.
- ✓ Module 2: Overviews of clinical efficacy and safety.
- ✓ Module 5: The final protocols, SAPs, and clinical study reports for two studies with adequate datasets and SAS programs.

Amendment 0.17:

- ✓ Efficacy Information Amendment.

Amendment 0.22:

- ✓ Efficacy Information Amendment.

Amendment 0.25:

- ✓ Efficacy Information Amendment.

### 5.3 Overview of Clinical Trial

A summary of the basic information about the studies included in the submission is given in Table 2.

Table 2: General information on the submitted studies

Study (Country)	Phase	Study Objectives	Study Population	Vaccination Schedule	Vaccine Groups	# of Subjects Randomized
V72P10 (Chile)	2b/3	To assess safety and immunogenicity of rMenB+OMV NZ	Adolescents 11 to 17 years old	1 dose, or 2 doses at 0, 1 or 0, 2 months, or 3 doses at 0, 1, 2 months	8 vaccine groups injected with different chronologies of rMenB+OMV NZ or placebo at study month 0,1,2,6	1503 128 (placebo)
V72_41 (Canada, Aus)	3	To assess safety and immunogenicity of rMenB+OMV NZ	Adolescents 11 to 17 years old	2 doses at 0, 1 months	rMenB+OMV NZ Lot1_Rosia  rMenB+OMV NZ Lot2_(b)(4)	170  174
V72_29 (UK)	2	To assess safety and immunogenicity of rMenB+OMV NZ	Young Adults 18 to 24 years old	2 doses at 0, 1 months	rMenB+OMV NZ MenACWY/Placebo  IXIARO (Japanese Encephalitis)	979 988  987
V102_03 (US, Poland)	2	To assess immunogenicity and safety of ----(b)(4)---- (b)(4), ----(b)(4)---- (b)(4), rMenB+OMV NZ	Adolescents and Young Adults 18 to 24 years old	2 doses at 0, 2 months	----(b)(4)----- ----(b)(4)----- rMenB+OMV NZ Placebo/MenACWY	120 121 122 121

Study (Country)	Phase	Study Objectives	Study Population	Vaccination Schedule	Vaccine Groups	# of Subjects Randomized
V72P4 (Italy, Germany)	2	To assess safety and immunogenicity of rMenB+OMV NZ	Adults 18 to 50 years old	3 doses at 0, 2, 6 months	rMenB+OMV NZ (plus MenACWY at 7 months)	54
V72P5 (Switzerland)	1	To assess safety and immune response to rMenB+OMV NZ rMenB+OMV (b)(4) rMenB	Adults 18 to 40 years old	3 doses at 0, 2, 6 months	rMenB+OMV NZ rMenB+OMV (b)(4) rMenB	28 28 14
V72P13 (Italy, Germany, Czech Rep., Finland)	3	To assess safety and immune response to rMenB+OMV NZ with or without routing vaccination	Infants 2 months old	3 doses at 2, 4, 6 months of age	rMenB+OMV NZ + routing vaccination (lot1) rMenB+OMV NZ + routing vaccination (lot 2) rMenB+OMV NZ + routing vaccination (lot 3) Routing vaccination MenC + routing vaccination	833 828 820 659 490
V72P10E1 (Chile)	2b/3	To assess antibody persistence	Adolescents 13 to 19 years old	Consider 1 dose, or 2 doses at 0, 1 or 0, 2 months, or 3 doses at 0, 1, 2 months	9 study groups	666 115 (naive)

Source: Reviewer's compilation based on the individual Clinical Study Reports

All clinical trials contributed to evaluation of safety and immunogenicity of the rMenB+OMV NZ vaccine in different populations spanning ages from 2 months to 50 years (see Table 2). Results from the extension study V72P10E1 (parent clinical trial V72P10) were submitted in this BLA to provide data on antibody persistence in the period 18 to 24 months following the completion of a 2-dose or 3-dose series of the rMenB+OMV NZ vaccine. Data from the additional clinical trial (V72P13), conducted in subjects 2 months of age, were submitted to support consistency of vaccine production lots. Note that study V102\_03 was conducted for clinical development of the ---(b)(4)----- vaccine, but it included an rMenB+OMV NZ arm as well.

For evaluations of immune responses to the candidate rMenB+OMV NZ vaccine, the bactericidal antibody responses against three *N. meningitidis* serogroup B indicator strains, which reasonably represented the prevalent strains in the US and expressed antigens contained in rMenB+OMV NZ, were measured by hSBA. The indicator strains were:

- Strain H44/76, which measured bactericidal antibody primarily directed against fHbp variant 1.1
- Strain 5/99, which measured bactericidal antibody primarily directed against NadA, and
- Strain NZ98/254, which measured bactericidal antibody primarily directed against PorA P1.4 in the OMV NZ vaccine component.

In clinical trials V72P10, V72\_41, V102\_03, and V72\_29, the immune responses to the candidate rMenB+OMV NZ vaccine were assessed against the above mentioned indicator strains.

Recently, 3 additional serogroup B indicator strains were proposed by the applicant and indicated by CBER as additional primary reference strains to be used for the ---(b)(4)--- vaccine development. These strains were --(b)(4)-- for fHbp, ---(b)(4)----- for NadA, and ----(b)(4)----- for NHBA. All these additional strains were also used to measure bactericidal antibodies in subjects in clinical trials V102\_03 and V72\_29. Supportive testing against strains --(b)(4)-- and ----(b)(4)----- was performed on sera from a subset of subjects from study V72P10 (as a *post hoc analysis*).

Table 3 summarizes strains used for evaluation of immune response to the rMenB+OMV NZ vaccine in seven trials.

Table 3: Overview of Used Immunogenicity Indicator and Additional Strains

Study	Indicator strain H44/76 (fHbp)	Indicator strain 5/99 (NadA)	Indicator strain NZ298/254 (PorAP1.4)	Indicator strain ---(b)(4)-- (NHBA)	Additional strain ---(b)(4)--- (fHbp)	Additional strain ---(b)(4)--- (NadA)	Additional strain ----(b)(4)----- (NHBA)
V72P10	+	+	+	+	+	-	+
V72_41	+	+	+	-	-	-	-
V72_29	+	+	+	-	+	+	+
V102_03	+	+	+	-	+	+	+
V72P5	+	+	+	-	-	+ <sup>a</sup>	-
V72P4	+	+	+	+	-	-	-
V72P13	+	+	+	+	+	+	-

a. - In the V72P5 CSR this strain is referred to as strain ---(b)(4)---

Source: Integrated Summary of Efficacy, page 15

## 6. Discussion of Individual Studies/Clinical Trials

### 6.0 General Information

In clinical studies of the rMenB+OMV NZ (BEXSERO®) vaccine, immunogenicity was assessed by measuring antibodies against three *N. meningitidis* serogroup B strains that represented the NadA, fHbp and PorA antigens in the vaccine. Serum Bactericidal Activity assays using human serum as the source of complement (hSBA) were utilized for measurements, and data collected were evaluated by four endpoints related to the main exploratory immunogenicity analyses. Three (3) of these 4 endpoints are vaccine-elicited 4-fold hSBA response to each of the 3 MenB indicator strains, and the fourth endpoint is a composite endpoint defined as hSBA responses  $\geq$  LLOQs for all 3 MenB indicator strains combined.

For the most important descriptive analysis of the immune response to the rMenB+OMV NZ vaccine, the following parameters (proportions) were to be estimated:

- (1)- (3) For each of three indicator strains 44/76-SL, 5/59, and NZ98/254, proportion of subjects achieving at least 4-fold increase in hSBA titer from baseline to one month post second vaccination.
- (4) Proportion of subjects achieving the composite hSBA response, as defined above, at one month after the second vaccination dose.

The four-fold rise was defined as follows:

- the post-vaccination hSBA titer  $\geq 1:16$  for subjects with the pre-vaccination hSBA titer  $< 1:4$ ,
- a post-vaccination titer at least 4-fold the LLOQ for subjects with pre-vaccination hSBA titer  $\geq 1:4$  but  $< \text{LLOQ}$ , and
- a post-vaccination 4-fold rise for subjects with pre-vaccination hSBA titer  $\geq \text{LLOQ}$ .

### **Reviewer's Comment**

*In CSRs for studies included in the BLA, the applicant presented evaluations of the immune responses to the rMenB+OMV NZ vaccine using percentages of subjects achieving hSBA titer  $\geq 1:4$  or  $\geq 1:5$ . As per the applicant, the reason why threshold 1:5 or 1:4 was used in some studies as the threshold for the primary or secondary endpoints was that "Serum bactericidal activity has been proven historically to be the best correlate of protection for all meningococcal serogroups including serogroup B, and its acceptability as a study endpoint has been recommended by health authorities and meningococcal vaccine experts," and using the 1:4 threshold "is regarded as protective" (source: Integrated Summary of Efficacy, pages 15 and 16).*

*Evaluations of the hSBA geometric mean titers (GMTs) and geometric mean ratios (GMRs) were included in all CSRs. For the GMT estimations, the applicant set all titers below the limit of detection to half of that limit, e.g., hSBA titers  $< 2$  were set to 1, and titers  $\geq 2$  and  $< 4$  were set to 2.*

*In this statistical review, if not otherwise indicated, only the applicant's GMT estimates are presented.*

*The protocol pre-defined primary or secondary parameters, "percentages of subjects achieving hSBA titer  $\geq 1:4$  or  $\geq 1:5$ ," stated in each study, were not used by the statistical reviewer to evaluate the immune response to the rMenB+OMV NZ vaccine. Instead, assay parameters such as the lower limits of quantitations (LLOQs) were utilized for evaluations. CBER accepted the use of this method. The applicant provided results of the reanalyzes of the immunogenicity data in the Integrated Summary of Efficacy and additional Amendments 17 and 22.*

*Assessment of the immune responses to the rMenB+OMV NZ vaccine based on the four endpoints -- 4-fold hSBA rise in titer to each of the 3 MenB indicator strains, and a composite endpoint, defined as hSBA responses  $\geq \text{LLOQs}$  for all 3 MenB indicator strains combined -- constituted the main exploratory immunogenicity objective.*

## 6.1 Trial #1: V72P10

**Title of the clinical trial:** “*A Phase 2b/3, Multi-Center, Observer-Blind, Controlled Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine Administered to Healthy Adolescents Aged 11-17 Years According to Different Vaccination Schedules*”

**Study Initiation Date:** June 5, 2008 (the first subject visit)

**Study Completion Date:** December 16, 2010 (the last subject visit)

### 6.1.1 History of Study Protocol

The study protocol was submitted to CBER on November 27, 2007, and was followed by five amendments. Enrollment of subjects was initiated under the original protocol.

Among other modifications, five protocol amendments introduced the following changes:

- An external safety monitoring committee, Data Monitoring Committee (DMC), (Amendment #1, July 23, 2008) was established.
- Inclusion/exclusion criteria, e.g., criteria related to pregnancy, sexual abstinence, and some safety measures (Amendment #2, August 28, 2008) were modified.
- Safety procedure related to the follow-up after a subject’s withdrawal from the study was clarified.
- Classification of study periods from Visit 1 to Visit 4 (i.e., until one month after third injection) and from Visit 4 up to Month 12 (periods used for main and follow-up analyses) was clarified.

After issuing amendments, the applicant also introduced the following changes to the Statistical Analysis Plan (SAP):

- ✓ Baseline blood draw was no longer required for a subject to be included in the MITT population
- ✓ Three per protocol immunogenicity populations were defined. They were named:
  - (1) *Primary Immunogenicity for Main Analysis*,
  - (2) *Per protocol (PP)*, and
  - (3) *Secondary Immunogenicity for Addendum Analysis*populations.
- ✓ Time window for Visit 5 was redefined/extended to be [-21/+32] days.
- ✓ Thirty five subjects from each vaccine group (a total of 280 subjects) were randomly selected for assessment (measured by (b)(4) of immune response against antigen 287-953. The antibody responses were defined by Geometric Mean Concentrations (GMCs) along with their 95% CIs.

### 6.1.2 Objectives

The general objective of clinical trial V72P10 was to assess the antibody responses to and safety of 1, 2, or 3 injections of the rMenB+OMV NZ vaccine administered in healthy adolescents at various vaccination schedules and at various time points.

Primary objectives

- To assess the immunogenicity, safety, and tolerability of one, two (on the 0-, 1- or 0-, 2- month schedule) or three doses (on the 0-, 1-, 2- month schedule) of the rMenB+OMV NZ vaccine in healthy adolescents, as measured by hSBA one month after the last rMenB+OMV NZ dose.

Secondary objectives

- To assess the immunogenicity, safety, and tolerability of an additional dose of Novartis rMenB+OMV NZ given at Month 6, by evaluation of the serum bactericidal activity measured by hSBA at one month after the Month-6 rMenB+OMV NZ dose, for schedules 0,1 and 0,2 months.
- To assess the antibody persistence following one, two (on the 0-, 1-, or 0-, 2-month schedule) or three doses (on the 0-, 1-, 2- month schedule) of the rMenB+OMV NZ vaccine.

**6.1.3 Design Overview**

Study V72P10 was a phase 2b/3, observer-blind, multicenter, randomized, controlled clinical trial conducted in Chile in healthy adolescents 11 through 17 years of age. A total of 1631 enrolled subjects were randomized to 8 groups, and stratified by age (11 through 13 and 14 through 17 years). A total of 4 injections at months 0, 1, 2, and 6 were administered to each subject. For the period between Visit 1 and Visit 4 (corresponding to Day 1 to Month 3), some groups were combined and only 5 groups (see Table 4) were considered for the analysis purpose. This combining was possible because some groups differed in the regimen applied only after Visit 4.

Table 4: Overview of Vaccine Groups in Study V72P10

Vaccine Groups up to Visit 4 (Month 3)	Vaccine Group From Visit 5 (Month 6) through End of Study Visit 7 (Month 12)
rMenB0 (Group 1a + Group 1b)	rMenB06 (Group 1a) rMenB0 (Group 1b)
rMenB01 (Group 2a + Group 2b)	rMenB016 (Group 2a) rMenB01 (Group 2b)
rMenB02 (Group 3a + Group 3b)	rMenB026 (Group 3a) rMenB02 (Group 3b)
rMenB012 (Group 4)	rMenB012 (Group 4)
Placebo (Group 5)	rMenB6 (Group 5)

*Groups 1a - 5 were randomized groups*

*Source: the statistical reviewer’s table based on Clinical Study Report V72P10*

The rMenB+OMV NZ vaccine was administered as:

- 1 dose at Month 0 or Month 6; or
- 2 doses at Months 0 and 1, or at Months 0 and 2, or at Months 0 and 6; or
- 3 doses at Months 0, 1, and 2, or at Months 0, 1, and 6, or at Months 0, 2, and 6.

Placebo was given during visits at which rMenB+OMV NZ was not administered.

At Visit 5, subjects received either an additional dose of rMneB+OMV NZ vaccine (Groups rMen06, rMenB016, rMnenB026, rMenB6) or placebo (Groups rMen0, rMenB01, rMnenB02, rMenB012).

The general study design is presented in Table 5.

Table 5: Study Design

Before Visit 4 (Primary Vaccination Period)

Month #	Month 0	Month 1	Month 2	Month 3
Visit #	Visit 1	Visit 2	Visit 3	Visit 4
<b>rMenB0</b>	rMenB+OMV NZ	Placebo	Placebo	
<b>rMenB01</b>	rMenB+OMV NZ	rMenB+OMV NZ	Placebo	
<b>rMenB02</b>	rMenB+OMV NZ	Placebo	rMenB+OMV NZ	
<b>rMenB012</b>	rMenB+OMV NZ	rMenB+OMV NZ	rMenB+OMV NZ	
Placebo	Placebo	Placebo	Placebo	
Blood draw (all groups)	~15 mL	~15 mL	~15 mL	~15 mL

Source: Statistical reviewer's table based on Clinical Study Report V72P10

After Visit 4 (Secondary Vaccination period)

Month #	Month 6	Month 7	Month 12
Visit #	Visit 5	Visit 6	Visit 7
<b>rMenB06</b>	rMenB+OMV NZ		Phone contact
<b>rMenB0</b>	Placebo		Phone contact
<b>rMenB016</b>	rMenB+OMV NZ		Phone contact
<b>rMenB01</b>	Placebo		Phone contact
<b>rMenB026</b>	rMenB+OMV NZ		Phone contact
<b>rMenB0</b>	Placebo		Phone contact
<b>rMenB012</b>	Placebo		Phone contact
<b>rMenB6</b>	rMenB+OMV NZ		Phone contact
Blood draw (all groups)	~15 mL	~15 mL	~15 mL

Source: Statistical reviewer's table based on Clinical Study Report V72P10

Blood samples (approximately 15 mL) were taken for meningococcal serology from all subjects at the following time points: baseline, Month 1, Month 2, Month 3, Month 6, and Month 7.

Duration of an individual subject participation in the study was approximately 12 months.

#### **6.1.4 Population**

At the time of enrollment (baseline), the study population consisted of 11-17 year-old females and males

- ✓ Who had given their written assent and whose parents or legal guardians had given written informed consent at the time of enrollment, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Anuja Rastogi's clinical review.

#### **6.1.5 Study Treatments or Agents Mandated by the Protocol**

The vaccination groups and the vaccination plan per study group are presented in Table 5 of this review.

##### *Investigational vaccine*

The investigational vaccine was rMenB+OMV NZ. It contained 3 recombinant protein antigens NHBA, fHbp, and NadA, and OMV NZ. The study regimens were 1, 2, or 3 doses of the investigational vaccine and then booster (additional dose of vaccine at Month 6) or placebo.

Composition of the investigational rMenB+OMV NZ vaccine is given in Table 1 in Section 2.3 of this statistical review.

The rMenB+OMV NZ vaccine was administered intramuscularly by injecting vaccine in the deltoid region of the non-dominant arm. Lot number of the investigational product was X38D27N1.

##### *Control vaccine: Placebo*

The clinical trial control was 0.5 mL of placebo injected per various schedules shown in Table 5.

Composition of placebo is presented in Table 6.

Table 6: Composition of Placebo

Name of Ingredients	Quantity per dose (0.5mL)
Aluminum hydroxide	1.5 mg
NaCl	3.12 mg
Sucrose	10 mg
Histidine	10 mM (0.776 mg)
Water for injection	Up to 0.5 mL

Source: The applicant's table (CSR, page 44)

Placebo was also administered intramuscularly in the deltoid region of the non-dominant arm. Lot number of placebo was X38D23N1.

### 6.1.6 Sites and centers

The clinical trial was carried out in 10 study sites and 2 administrative sites in Chile.

### 6.1.7 Surveillance/Monitoring

The clinical trial was administered and monitored by employees or representatives of Novartis Vaccines and Diagnostics. A Medical Monitor was readily available to provide appropriate medical expertise on trial-related medical questions. Novartis's Regulatory Affairs or Pharmacovigilance departments were responsible for the timely reporting of SAEs.

An independent external Data Monitoring Committee (DMC) was established to monitor safety data by performing scheduled assessments. The DMC comprised experienced vaccine clinicians who were not investigators in the trial, and a statistician experienced in the monitoring and evaluation of safety data. In order to make recommendations regarding the protocol and study continuation, the DMC had access, if required, to study-subject treatment assignments, and to results of the scheduled safety analyses.

### 6.1.8 Endpoints and Criteria for Study Success

Blood samples (approximately 15 mL) were collected at baseline and one month after each vaccination for assessing the immune response to the vaccine administered. Immune responses were measured against strains H44/76, 5/99, NZ98/254, and --(b)(4)-- (a *post hoc* analysis performed in a subset of subjects) by hSBA and against antigen 287-953 by (b)(4).

The hSBA assays were performed by the Meningococcal Reference Unit of the -----  
----- (b)(4)----- (all three indicator strains), and whole tests against --(b)(4)-- strain were carried out at Novartis Vaccine --(b)(4)-- laboratories.

### *Study Endpoints and parameters*

Immunogenicity endpoints were:

- ✓ Titers at baseline (before vaccination) and after each vaccination
- ✓ Four-fold response.

Immunogenicity parameters (variables) were

- ✓ For the primary objective, the percentages of subjects with hSBA titers  $\geq 1:4$ , as measured, depending upon different vaccination schedules, at baseline, Month 1, Month 2, and Month 3.
- ✓ For the secondary objective, the percentages of subjects with hSBA titers  $\geq 1:4$ , as measured at Month 6 and Month 7, for each tested MenB strain.
- ✓ Proportions of subjects with hSBA titers equal to or greater than the lower limit of quantitation (LLOQ), 1:4, and 1:8 for each of the available (indicator and additional) strains and at each applicable blood draw time point.
- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to one month after each (i.e., the first, second, and third) vaccination (Visits 2, 3, and 4).
- ✓ hSBA geometric mean titers (GMTs) for each of the available (indicator and additional) strains and at each applicable blood draw time point.

Information on safety outcomes can be found in Dr. Tammy Massie's statistical review of safety and/or in Dr. Anuja Rastogi's clinical review.

### **6.1.9 Statistical Considerations and Statistical Analysis Plan**

#### *Immunogenicity analysis*

No formal hypothesis or study success criteria were defined in the study protocol.

Immunogenicity statistical analyses related to the primary and secondary objectives were pre-defined in the protocol, but all exploratory immunogenicity analyses were performed later as per the Agency request. Most results are descriptive and/or exploratory in nature. The parameters and the associated 95% confidence intervals (CI) were estimated.

#### *Safety analysis*

Safety data collected during the clinical study were summarized utilizing frequencies of events. More information on safety analyses can be found in Dr. Tammy Massie's statistical review.

**Reviewer’s Comments**

*The general objective of study V72P10 was to assess the antibody responses and their short term persistence after one, two, or three doses of rMenB+OMV NZ vaccine, and to find the optimal vaccination schedule for a healthy adolescent population. Per protocol, evaluation of the primary objective was based on the percentages of subjects with hSBA titers  $\geq 1:4$  at Month 1, Month 2, and Month 3 for different vaccination schedules. Based on tests conducted at -----(b)(4)----- and the corresponding hSBA validation reports, the lower limits of quantitation (LLOQ) are listed in Table 7.*

Table 7: The hSBA LLOQs for Four Primary MnB Test Strains

Strain	LLOQ
H44/76	1:16
5/99	1:8
NZ98/54	1:16
--(b)(4)--	1:16

Source: Amendment 0.17, page 5

*Utilizing LLOQ defined in Table7, the essential immunogenicity information regarding the immune response to the rMenB+OMV NZ vaccine was generated by analyses based on data from rMenB02, rMenB01, and combined rMenB01 + rMenB012 groups in which the rMenB+OMV NZ vaccine was administered according to schedules 0 and 2 months, or 0 and 1 month.*

**6.1.10 Study Population**

Demographic Characteristics

The demographic and baseline characteristics were similar for all vaccination groups (combined as well as randomized). The mean age of the cohort across the vaccination groups was about 13.5 years. Females constituted the majority (range 52%-59%) in all groups. Most of the subjects were Hispanic (about 99%). The demographic variables weight (about 55 kg) and height (about 158 cm) were also balanced across the vaccination groups.

Disposition of subjects

A total of 1631 subjects were enrolled into the study and randomized into 8 vaccination groups. Details of the vaccination groups can be found in Section 6.1.3 of this review (Table 5). A summary of the randomized subjects’ disposition is presented in Table 8.

All the subjects, except subjects 42/0028 and 42/5021, met the inclusion criteria. Subject 42/0028 was 10 years of age, i.e., below the protocol specified age window 11 to 17 years, and subject 42/5021 was enrolled inappropriately due to abnormal weight gain at enrollment.

Table 8: Disposition of Subjects

Disposition of Subjects	rMenB0 n(%)	rMenB01 n(%)	rMenB02 n(%)	rMenB012 n(%)	Placebo n(%)
<b>Enrolled</b>	375	375	380	373	128
Withdrawn during primary vaccination	48 (13)	38 (10)	47 (12)	57 (15)	9 (7)
Withdrawn during primary vaccination: Adverse event	0	0	0	1	0
Withdrawal during primary vaccination: Withdrew consent	35 (9)	32 (9)	37 (10)	44 (12)	8 (6)
Withdrawal during primary vaccination: Lost to follow-up	6 (2)	1 (<1)	6 (2)	8 (2)	0
Withdrawal during primary vaccination: Protocol violation	5 (1)	5 (1)	1 (<1)	2 (<1)	1 (<1)
Withdrawal during primary vaccination: Other	2 (<1)	0	3 (<1)	2 (<1)	1 (<1)
<b>Completed study until Visit 5</b>	<b>327 (87)</b>	<b>337 (90%)</b>	<b>333 (88%)</b>	<b>316 (85%)</b>	<b>119 (93%)</b>
Withdrawal after Visit 5	7 (2)	7 (2)	10 (2.6)	20 (5.4)	2 (1.5)
Withdrawal after Visit 5: Adverse event	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
<b>Completed Study</b>	<b>320 (85)</b>	<b>330 (88)</b>	<b>323 (85)</b>	<b>309 (82.3)</b>	<b>117 (91.4)</b>

Source: Table based on the applicant's tables (CSR V72P10, Pages 62 and 63)

As per the applicant, of the 1631 randomized subjects, 1432 (87.8%) participated in the study up to Month 6 (Visit 5), i.e., completed the primary vaccination phase, while 199 withdrew during this vaccination phase. Until Visit 7 (Month 12, end of the study), 9% to 17% of the subjects were withdrawn across the 8 randomization groups. According to the applicant, a total of 1399 (85.8%) subjects completed Visit 7, i.e., Month 12 safety follow-up.

As per Table 8, the most common reasons for premature withdrawals were “withdrawal of consent” and “lost to follow-up.” Overall, three subjects were terminated from the study due to an AE or death. One subject reported an AE (juvenile arthritis) that was assessed by the investigator to be possibly related to the study vaccination. Two other premature terminations were caused by deaths in a road traffic accident and by suicide.

### Protocol Deviations

Protocol deviations were classified as major or minor. A major deviation was defined as one that could have a significant impact on the subject’s immunogenicity result.

As per the applicant’s report, there were 216 (216/1631 = 13%) major protocol deviations during the primary vaccination course (from baseline until Visit 5). Most reported major protocol deviations in the primary vaccination course were blood draws and vaccinations performed outside the specified time windows.

### Vaccination Compliance

A summary of vaccination compliance by study visit is presented in Table 9.

Table 9: Numbers (%) of Subjects Who Received Study Vaccines

Vaccination Number	Vaccines	rMenB0 N=375 n (%)	rMenB01 N=375 n (%)	rMenB02 N=380 n (%)	rMenB012 N=373 n (%)	Placebo N=128 n (%)
1	rMenB+OMV NZ	375 (100)	375 (100)	380 (100)	373 (100)	0 (0)
	Placebo	0 (0)	0 (0)	0 (0)	0 (0)	128 (100)
2	rMenB+OMV NZ	0 (0)	356 (95)	0 (0)	342 (92)	0 (0)
	Placebo	351 (94)	0 (0)	347 (91)	0 (0)	124 (97)
3	rMenB+OMV NZ	0 (0)	0 (0)	341 (90)	332 (89)	0 (0)
	Placebo	343 (92)	350 (93)	0 (0)	0 (0)	121 (95)

Source: Table based on the applicant's table (CSR V72P10, page 240)

On average, over 90% of the enrolled subjects received the pre-specified vaccinations at Month 0, Month 1, and Month 2.

### 6.1.11 Immunogenicity Analyses

Immune responses to the rMenB+OMV NZ vaccine were evaluated for various vaccination schedules in subjects receiving one, two, or three doses of investigational vaccine in the primary vaccination course. Using hSBA, the immunogenicity was assessed by measuring antibodies against three *N. meningitidis* serogroup B strains that represented the NadA, fHbp, and PorA antigens present in the vaccine. For main assessment of immune response to rMenB+OMV NZ, four immunogenicity exploratory variables -- proportions of subjects with a 4-fold or greater increase in hSBA titer for each of the three strains and the proportion of subjects who achieved titers greater than or equal to LLOQ for all three strains (composite response) -- were evaluated.

#### Datasets analyzed

#### Immunogenicity Modified Intention-to-treat (mITT) Population

The immunogenicity mITT population consisted of 1521 subjects (93% of 1631 enrolled subjects) who received a study vaccination and provided at least one evaluable post-baseline serum sample.

#### Evaluable Immunogenicity Population

The evaluable immunogenicity population consisted of all subjects who received correctly all relevant doses of vaccines, provided evaluable serum samples at the relevant time points, and had no major protocol deviations.

Most often, immunogenicity analyses for different endpoints were based on special subsets of the evaluable immunogenicity population.

Across the individual vaccine groups, the Per Protocol populations (see Table 10) for the primary vaccination course included 81% to 92% and 75% to 79% of enrolled subjects from Month 0 to Month 3 and at Month 6, respectively. An overview of the PP populations in the primary vaccination course is presented in Table 10.

Table 10: Overview of the Populations Analyzed for Immunogenicity in the Primary Vaccination Course (Visits 1 to 5)

Type of Population	Time Point	rMenB0 N(%)	rMenB01 N(%)	rMenB02 N(%)	rMenB012 N(%)	Placebo N(%)
Enrolled	Month 0	375 (100)	375 (100)	380 (100)	373 (100)	128 (100)
MITT	All Time Points	351 (94)	356 (95)	347 (91)	343 (92)	124 (97)
PP	Month 0	335 (89)	344 (92)	342 (90)	334 (90)	116 (91)
PP	Month 1	335 (89)	344 (92)	342 (90)	333 (89)	115 (90)
PP	Month 2	321 (86)	330 (88)	324 (85)	308 (83)	109 (85)
PP	Month 3	316 (84)	320 (85)	320 (84)	303 (81)	108 (84)
PP	Month 6	288 (77)	298 (79)	300 (79)	278 (75)	100 (78)

Source: CSR, V72\_10, page 69

### 6.1.11.1 Analyses related to Primary Endpoints

#### Per Protocol Primary Analyses

As per the protocol, the primary analyses, performed on the vaccination primary course data, were related to the endpoint titer  $\geq 1:4$ , and titers were measured one month after the last dose of the rMenB+OMV NZ vaccine. Almost all subjects who received 2 or 3 doses of rMenB+OMV NZ showed hSBA titers  $\geq 1:4$  (99% to 100% across the groups) for strains H44/76, 5/99, and NZ98/254. In the group that received 1 dose of the vaccine, 92% to 97% of the subjects showed hSBA titers  $\geq 1:4$  across all indicator strains.

When assessed based on a higher hSBA titer cutoff, the percentages of subjects with an hSBA titer  $\geq 1:8$  ranged across groups and strains from 98% to 100%, after 2 or 3 doses of rMenB+OMV NZ, whereas for those receiving only one vaccine dose the results ranged from 83% to 93% across groups and strains.

### 6.1.11.2 Analyses related to Secondary Endpoints

#### Per Protocol Secondary Analyses

As per the protocol, the secondary analyses across the vaccination schedules from Visit 1 to Visit 4 were based on the estimated GMTs one month after the last dose of rMenB+OMV NZ.

Table 11: Estimates of hSBA GMTs for Group rMenB01

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	344	3.32	(2.8, 3.93)
<b>44/76-SL</b>	<b>Month 2</b>	<b>330</b>	<b>184</b>	<b>(157, 216)</b>
5/99	Month 0	344	2.53	(2.18, 2.92)
<b>5/99</b>	<b>Month 2</b>	<b>330</b>	<b>466</b>	<b>(404, 537)</b>
NZ98/254	Month 0	344	3.1	(2.62, 3.68)
<b>NZ98/254</b>	<b>Month 2</b>	<b>330</b>	<b>91</b>	<b>(77, 109)</b>

Source: Based on the applicant's table, CSR V72P10, page 90

Table 12: Estimates of hSBA GMTs for Group rMenB02

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	342	3.76	(3.17, 4.46)
<b>44/76-SL</b>	<b>Month 3</b>	<b>319</b>	<b>212</b>	<b>(182, 246)</b>
5/99	Month 0	342	2.61	(2.25, 3.02)
<b>5/99</b>	<b>Month 3</b>	<b>320</b>	<b>713</b>	<b>(626, 812)</b>
NZ98/254	Month 0	342	3.26	(2.75, 3.87)
<b>NZ98/254</b>	<b>Month 3</b>	<b>319</b>	<b>123</b>	<b>(104, 145)</b>

Source: Based on the applicant's table, CSR V72P10, page 90

Table 13: Estimates of hSBA GMTs for Group rMenB012

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	334	3.84	(3.23, 4.56)
<b>44/76-SL</b>	<b>Month 3</b>	<b>303</b>	<b>238</b>	<b>(204, 278)</b>
5/99	Month 0	334	2.56	(2.21, 2.97)
<b>5/99</b>	<b>Month 3</b>	<b>303</b>	<b>580</b>	<b>(507, 663)</b>
NZ98/254	Month 0	333	2.89	(2.36, 3.34)
<b>NZ98/254</b>	<b>Month 3</b>	<b>302</b>	<b>122</b>	<b>(102, 145)</b>

Source: Based on the applicant's table, CSR V72P10, page 90

**Reviewer’s Comments**

Based on Tables 11-13, there was a trend of slightly higher GMTs across the three strains for the subjects receiving 2 doses two months apart (Group rMen02), or 3 doses one month apart (Group rMen012), than for the subjects receiving 2 doses of vaccine one month apart (Group rMenB01). Additionally, there was no clear or consistent advantage, in terms of greater antibody titers (on average), for using the three-dose schedule (Group rMenB012) as compared to the two-dose groups vaccination regimens.

**6.1.11.3 Analyses related to Exploratory Endpoints**

According to the hSBA validation reports based on tests conducted at ---(b)(4)----, the LLOQs are 1:8 for the NZ98/254 strain, and 1:16 for the H44/76 and 5/99 strains.

The main immune exploratory objectives were to assess immunogenicity response to the rMenB+OMV NZ vaccine using parameters that were defined as follows:

- Proportions of subjects with 4-fold or greater increase in hSBA titer for each of the three indicator strains (NZ98/254, H44/76, and 5/99), and
- Proportion of subjects who achieved a titer greater than or equal to LLOQ for all three strains (composite response),

one month after the second vaccination.

Results of the statistical analyses for the main immunogenicity objectives assessment, i.e., for the PP immunogenicity population, are presented in Table 14.

Table 14: Results for the Main Immunogenicity Objectives - PP Population

A. For rMenB02 group

Variables	Strain	# of subjects	Estimation of endpoint	95% CI
hSBA Titer 4-fold rise	H44/76	319	93%	(89, 95)
hSBA Titer 4-fold rise	5/99	320	98%	(95, 99)
hSBA Titer 4-fold rise	NZ98/54	319	85%	(81, 89)
Composite hSBA response	For three indicator strains	319	94%	

B. For the combined rMenB01 + rMenB012 group

Variables	Strain	# of subjects	Estimation of endpoint	95% CI
hSBA Titer 4-fold rise	H44/76	636	93%	(90, 95)
hSBA Titer 4-fold rise	5/99	637	98%	(97, 99)
hSBA Titer 4-fold rise	NZ98/54	637	83%	(80, 86)
Composite hSBA response	For three indicator strains	637	90%	

Source: The reviewer’s table based on the applicant’s Table Q2-1, Amendment 0.17, page 8

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

Note: The 4-fold increase is defined as follows: a post-vaccination hSBA  $\geq 1:16$  for subjects with pre- vaccination hSBA  $< 1: 4$ , a post-vaccination titer at least 4-fold the LLOQ for subjects with pre-vaccination hSBA  $\geq 1: 4$  but  $< LLOQ$ , and a post-vaccination 4-fold rise for subjects with pre-vaccination hSBA  $\geq LLOQ$ .

Table 14 A demonstrates that, for the rMenB02 group, the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after dose 2 were 93% for H44/76 strain, 98% for 5/99 strain, and 85% for NZ98/54 strain, while 94% of subjects achieved the composite hSBA response, i.e., hSBA  $\geq$  LLOQ for all 3 MenB indicator strains combined.

### 6.1.12 Subgroup Analyses

The applicant performed subgroup analyses utilizing such baseline factors as

- (1) Pre-vaccination hSBA titers  $< 1:4$  or  $\geq 1:4$
- (2) Gender.

Table 15 summarizes results of the statistical analyses performed to investigate possible influence of the categorical factor baseline titer ( $< 4$  or  $\geq 4$ ) on the immune responses, as expressed by GMTs after the 2<sup>nd</sup> dose of the rMenB+OMV NZ vaccine.

Table 15: GMTs in Subjects Sub-grouped by Baseline hSBA Titers  $< 1:4$  or  $\geq 1:4$  in the Primary Vaccination Course - PP Population

For rMenB01 Group

Strain	Groups	Baseline Factor	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	rMenB01	$< 4$	202	135	(112, 162)
<b>44/76-SL</b>	<b>rMenB01</b>	$\geq 4$	<b>128</b>	<b>325</b>	<b>(261, 404)</b>
5/99	rMenB01	$< 4$	230	402	(343, 472)
<b>5/99</b>	<b>rMenB01</b>	$\geq 4$	<b>100</b>	<b>673</b>	<b>(518, 874)</b>
NZ98/254	rMenB01	$< 4$	219	56	(46, 67)
<b>NZ98/254</b>	<b>rMenB01</b>	$\geq 4$	<b>111</b>	<b>242</b>	<b>(192, 305)</b>

For rMenB02 Group

Strain	Groups	Baseline Factor	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	rMenB02	$< 4$	179	161	(135, 192)
<b>44/76-SL</b>	<b>rMenB02</b>	$\geq 4$	<b>140</b>	<b>319</b>	<b>(260, 392)</b>
5/99	rMenB02	$< 4$	211	667	(572, 777)
<b>5/99</b>	<b>rMenB02</b>	$\geq 4$	<b>109</b>	<b>841</b>	<b>(673, 1052)</b>
NZ98/254	rMenB02	$< 4$	208	88	(73, 106)
<b>NZ98/254</b>	<b>rMenB02</b>	$\geq 4$	<b>111</b>	<b>232</b>	<b>(183, 295)</b>

Source: Based on the CSR V72P10, page 103

Across all the vaccine groups, one month after the last dose of the rMenB+OMV NZ vaccine in the primary vaccination course, the subgroup with hSBA titer  $< 1:4$  at baseline showed higher fold increases in GMTs than the subgroup with baseline titers  $\geq 1:4$ .

However, although the fold increases were lower, the post vaccination levels of hSBA titers were higher in subjects with starting baseline titers  $\geq 1:4$ .

Table 16 summarizes results of the statistical analyses performed to investigate possible influence of gender on the immune responses, as expressed by proportions of subjects with hSBA titers  $\geq$  LLOQ after the 2<sup>nd</sup> dose of the MenB+OMV NZ vaccine.

Table 16: Immune Response (% of Subjects with hSBA  $\geq$  LLOQ) to rMenB+OMV NZ After a 2-Dose Schedule, Stratified by Sex - rMenB02 Group and MITT immunogenicity population

Strain	Groups	Factor	Number of Subjects	Estimation of % of subjects with $\geq$ LLOQ	95% CI
44/76-SL	rMenB02	Male	152	99	(96, 100)
<b>44/76-SL</b>	<b>rMenB02</b>	<b>Female</b>	<b>188</b>	<b>98</b>	<b>(95, 99)</b>
5/99	rMenB02	Male	152	99	(96, 100)
<b>5/99</b>	<b>rMenB02</b>	<b>Female</b>	<b>189</b>	<b>99</b>	<b>(97, 100)</b>
NZ98/254	rMenB02	Male	152	97	(93, 99)
<b>NZ98/254</b>	<b>rMenB02</b>	<b>Female</b>	<b>188</b>	<b>93</b>	<b>(88, 96)</b>

Source: Table based on the applicant's Table Q3-1d, Amendment 0.17, page 18

It appears that gender does not have influence on the immune responses, as expressed by proportions of subjects with hSBA responses  $\geq$  LLOQ after the 2<sup>nd</sup> dose of the MenB+OMV NZ vaccine.

**Reviewer's comments and overall conclusions on immunogenicity results**

- *It appears that subjects receiving two doses two months apart (Group rMen02), or three doses one month apart (Group rMen012) of the vaccine had, on average, across the three strains slightly higher titers than the subjects receiving two doses of vaccine one month apart (Group rMenB01). Additionally, there was no clear or consistent advantage in terms of antibody titers, for using the three-dose vaccination (Group rMenB012) as compared to two-dose vaccination regimens.*
- *An exploratory analysis for assessment of the proportions of subjects with 4-fold or greater increase in hSBA titer for each of the three indicator strains, and the proportion of subjects who achieved a titer greater than or equal to LLOQ for all three strains (composite response) showed that the lower limits of the corresponding 95% CIs were greater than or equal to 80%. Thus, results based on these 4 parameters provided evidence that the rMenB+OMV NZ vaccine elicited immune response expressed by the three MenB indicator strains.*
- *Immunogenicity data for about 13% of the subjects are missing. Note that 10% of the subjects were withdrawn from the study during the primary vaccination course period. Reasons for withdrawal are not clear.*

- *The V72P10 clinical trial was carried out in Chile in a population that is 99% of Hispanic ethnic origin and with about 20% of subjects with hSBA titers  $\geq$  LLOQ at baseline before vaccination. Percentages of subjects with hSBA titers  $\geq$  LLOQ before vaccination in the US and Chile populations are different. Regarding these differences, the statistical reviewer defers to the medical reviewers regarding the extrapolation of data from this population to the US population.*
- *Evaluations of immune responses to the vaccine were based only on 3 MenB indicator strains. Therefore, data generated by this study do not provide information on the breadth of protection against MenB meningococcal disease the rMenB+OMV NZ vaccine might confer.*
- *Overall, data generated by study V72P10 provided evidence that the rMenB+OMV NZ vaccine elicits immune responses expressed by the three MenB indicator strains.*

## **6.2 Trial #2: V72\_29**

**Title of the study:** “A Phase 3 Observer blind Randomized, Multi-center, Controlled study to evaluate the effect of Novartis Vaccine’s Meningococcal B recombinant and MenACWY Conjugate vaccines on Pharyngeal Carriage of *N. meningitidis* in Young Adults”

**Study Initiation Date:** September 21, 2010 (the first subject visit)

**Study Completion Date:** January 21, 2012 (the last subject visit)

### **6.2.0 General information**

The V72\_29 clinical trial was conducted in the United Kingdom in healthy young adults 18 through 24 years of age. It was designed to explore the effects of 2 doses of rMenB+OMV NZ given 1 month apart and the effect of a single dose of MenACWY conjugate vaccine on pharyngeal carriage of *N. meningitidis*.

As the statistical endpoints and immunogenicity results of the analyses in this clinical trial are not related to the objective of the submitted BLA, they are not considered in this statistical review. Only data relevant to immunogenicity of rMenB+OMV NZ against serogroup B strains are assessed and reported here.

### **6.2.1 History of Study Protocol**

Clinical trial V72\_29 was not carried out under US IND. The original protocol was issued on June 4, 2010, and was followed by three amendments. Key changes related to the MenB immunogenicity data introduced by the amendments were:

- ✓ The time window for Visit 3 was expanded by -7 and +14 days.

- ✓ Initially, the immunogenicity endpoint against MenB indicator strains was hSBA  $\geq 1:5$ . The hSBA cut-off of 1:5 is used by the Novartis Serology Lab for testing the MenB reference strains. However, later in the CSR V72\_29, the applicant used the hSBA  $\geq 1:4$  cut-off, as per the threshold defined by ---(b)(4)----- laboratories in which the assay was conducted.

### 6.2.2 Objectives

There were two primary objectives:

- (1) To assess carriage prevalence of virulent sequence type 1 (ST1) of *N. meningitidis* group B (genogroupable) at one month (Month 2) following administration of two doses of rMenB+OMV NZ, as compared to the control group receiving the JE (Japanese encephalitis) vaccine.
- (2) To assess carriage prevalence of *N. meningitidis* combined serogroups A, C, W, and Y at one month (Month 1) following administration of a single dose of the MenACWY conjugate vaccine, as compared to the control group receiving JE vaccine.

These objectives and other secondary objectives related to pharyngeal carriage were not evaluated in this statistical review.

The important secondary immunogenicity objectives were:

- (1) To explore the immunogenicity of rMenB+OMV NZ and MenACWY conjugate vaccines administered to healthy young adults, by evaluation of the serum bactericidal activity response, using human complement (hSBA), at one month after two doses of the rMenB+OMV NZ vaccine and two months after a single dose of the MenACWY vaccine.
- (2) To explore the immunogenicity of the MenACWY conjugate vaccine in young adults who received a prior dose of the MenC vaccine.

Note that only the immune responses to rMenB+OMV NZ are assessed in this statistical review.

As per CBER, assessment of the immune responses described by 4-fold rise and composite responses, as measured by hSBA performed against 3 MenB indicator strains, were considered as the immunogenicity exploratory objective in the study. More details on the main immunogenicity objective can be found in Section 6.0 of this review.

### 6.2.3 Design Overview

The V72\_29 clinical trial was a Phase 3, multi-center, observer-blind, randomized trial that enrolled UK university students 18 to 24 years of age. Subjects were randomized to one of three treatment arms – rMenB+OMV, MenACWY (Menveo), or a control group. All subjects received two injections 1 month apart and were followed for a total of 12 months. In particular:

- The MenB group received two doses of the rMenB+OMV NZ vaccine, the first dose on Day 1 and the second dose on Day 31.
- The MenACWY group received one dose of the MenACWY-CRM197 conjugate vaccine (Menveo) on Day 1 and a placebo on Day 31.
- The control group received two doses of Japanese encephalitis (JE) vaccine (IXIARO™ [Intercell, Vienna Austria]), the first dose on Day 1 and the second dose on Day 31.

The study design is presented in Table 17.

Table 17: Study design

Group	Visit 1 Month 0	Visit 2 Month 1	Visit 3 Month 2	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 12
<b>MenB</b>	rMenB+OMV NZ	rMenB+OMV NZ				Menveo
<b>MenACWY</b>	Menveo	Placebo				
<b>JE</b>	IXIARO	IXIARO				Menveo
<b>Blood * draw (all groups)</b>	20 mL		20 mL	20 mL	20 mL	20 mL
<b>Swab (all groups)</b>	yes	yes	yes	yes	yes	yes

\* Blood was collected in subsets of subjects

Source: Based on the Protocol V72\_29, page 17

All subjects had pharyngeal swabs performed at every study visit to determine carriage rates and serogroup of *N. meningitidis* strains occurring in the study population over the trial period. A subset of subjects in each arm also provided blood specimens at baseline and at each visit after the second injection, to assess the immunogenicity of rMenB+OMV NZ and MenACWY (Menveo) vaccines in this young adult population.

The first 600 subjects enrolled at Sheffield University in the UK (Site 1) were included in the immunogenicity subset. This site was the only one that enrolled subjects for the evaluation of the immunogenicity.

## 6.2.4 Population

At the time of enrollment (baseline), the study population consisted of 18-24 year-old females and males

- ✓ who had given written informed consent at the time of enrollment
- ✓ who were available for all the visits scheduled in the study (i.e., had not planned to leave the area before the end of the study period)
- ✓ who were in good health as determined by the outcome of medical history, physical examination, and clinical judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Anuja Rastogi's clinical review.

### **6.2.5 Study Treatments or Agents Mandated by the Protocol**

Vaccination plan per study group is presented in Table 17 of this review.

- The MenB vaccine group received two doses of the investigational vaccine rMenB+OMV NZ. The vaccine contained 3 recombinant protein antigens NHBA, fHbp, and NadA, and OMV NZ. Composition of the rMenB+OMV NZ vaccine is given in Table 1 in Section 2.3 of this statistical review. Lot number of the investigational product was 090101V.
- The MenACWY vaccine group received one dose (0.5 mL) of the MenACWY-CRM197 conjugate vaccine (Menveo; lot number M10076) administered IM in the deltoid area. Each 0.5mL dose consisted of CRM197 conjugated capsular polysaccharides of MenA (10µg), MenC (5µg), MenW (5µg), and MenY (5µg).
- The control group received two doses of IXIARO (Intercell, Vienna Austria; lot number JEV09L38A) supplied as a sterile suspension for IM injection. Each dose of this vaccine contained approximately 6 µg of purified inactivated JEV (Japanese encephalitis virus) proteins and 250 µg of aluminum hydroxide.

### **6.2.6 Sites and centers**

Clinical trial V72\_29 was administered and monitored by employees or representatives of Novartis Vaccines and Diagnostics, and was conducted at 10 study centers in the United Kingdom (UK).

### **6.2.7 Surveillance/Monitoring**

The final protocol, all amendments, and informed consent document (ICD) were reviewed and approved by an Ethics Committee (EC) before study start. A signed and dated statement that the protocol and informed consent were approved by the EC was given to Novartis Vaccines and Diagnostics before study initiation. Prior to study start, the investigator was required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in the protocol.

According to the applicant, the study was designed and implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid out in the Declaration of Helsinki.

### **6.2.8 Endpoints and Criteria for Study Success**

For assessment of the immune response to the rMenB+OMV NZ vaccine, functional antibodies were evaluated for the following 3 MenB indicator strains: (1) H44/76 (to measure bactericidal antibody primarily directed against fHbp variant 1.1 (vaccine

antigen 741)); (2) 5/99 (to measure bactericidal antibody primarily directed against NadA (vaccine antigen 961c)); and (3) NZ98/254 (to measure bactericidal antibody primarily directed against PorA P1.4 (referred to as “PorA”) present in the OMV NZ vaccine component).

### Immunogenicity endpoints and parameters

At each blood sampling time point, immunogenicity endpoints were:

- hSBA titers  $\geq 1:8$  for *N. meningitidis* serogroups A, C, W-135, and Y
- hSBA titers  $\geq 1:4$ ,  $\geq 1:8$ , and  $\geq$  LLOQ for *N. meningitidis* serogroup B indicator strains
- Four-fold response related to *N. meningitidis* serogroup B indicator strains.

Immunogenicity parameters were:

- ✓ hSBA geometric mean titers (GMT) for each of the MenB 3 indicator strains at each blood sampling time point
- ✓ Proportion of subjects who achieved a titer greater than or equal to LLOQ for all three indicator strains at baseline, one month, and 11 months after second vaccination
- ✓ Proportion of subjects with hSBA titer  $\geq$  LLOQ for each of the 3 primary strains at each blood sampling time point
- ✓ Proportion of subjects with hSBA titers  $\geq 1:4$  and  $\geq 1:8$  at each blood sampling time point.

Definitions of the endpoints related to the main immunogenicity exploratory objective can be found in Section 6.0 of this review.

### **6.2.9 Statistical Considerations and Statistical Analysis Plan**

The primary objectives of the study were: (1) to investigate carriage of virulent STs of *N. meningitidis* (genogroupable) group B at 1 month (Month 2) following administration of two doses of rMenB+OMV NZ, and compare to the control group receiving the JE vaccine, and (2) to investigate carriage of *N. meningitidis* combined serogroups A, C, W, and Y at 1 month (Month 1) following administration of a single dose of MenACWY conjugate vaccine, and to compare to the control group receiving JE vaccine. The pre-defined hypotheses were related to the primary objectives which were not interrelated to the objective of the current BLA. Therefore, these hypotheses were not evaluated in this review.

Only descriptive analyses of immunogenicity against serogroup B indicator strains are presented in this review.

## 6.2.10 Study Population and Disposition

### Demographic characteristics

At baseline, demographic characteristics of the enrolled subjects were balanced across the three vaccination study groups. Gender ratios were similar across the vaccine groups. Males constituted about 46% of subjects. The majority of subjects were Caucasian (89%). The mean age ( $\pm$  SD) at the first vaccination was 19.9 ( $\pm$ 1.6) years, while the total age range was 18 to 24 years. Other baseline characteristics such as mean weight and height were also balanced across vaccine groups. Overall, 14 enrolled subjects did not meet the study entry criteria.

The demographic and baseline characteristics of the immunogenicity population were similar to the enrolled population.

### Disposition of subjects

Overall, 2968 subjects were enrolled into the V72\_29 study, but only 592 subjects (approximately 20% of the enrolled population) were included in the immunogenicity subset.

A summary of the randomized subject disposition is presented in Table 18.

Table 18: Randomized Subjects Disposition

Disposition of Subjects	MenB n(%)	MenACWY n(%)	Control n(%)
<b>Randomized</b>	979	988	987
Withdrawal due to Adverse Event	11 (1%)	8 (<1%)	3 (<1%)
Withdrawal due to Protocol violation	5 (<1%)	5 (<1%)	6 (1%)
Withdrawal due to Withdrawn consent	38 (4%)	31 (3%)	28 (3%)
Withdrawal due to Lost to follow-up	124 (13%)	98 (10%)	123 (12%)
Withdrawal due to Other	5 (<1%)	2 (<1%)	1 (<1%)
<b>Study Completed</b>	<b>796 (81%)</b>	<b>844 (85%)</b>	<b>826 (84%)</b>

Source: Based on Clinical Study Report, page 89

Across vaccine groups, 81% to 85% of subjects completed the protocol-specified study visits. About 16% to 20% of subjects across the vaccine groups withdrew prematurely. Most of the premature withdrawals were due to being lost to follow-up (10% to 13% across vaccine groups), while 3% to 4% of subjects across the vaccine groups withdrew consent. Premature withdrawals due to AEs were reported for 22 subjects. Please refer to Dr. Anuja Rastogi's clinical review and/or Dr. Tammy Massie's statistical review of safety for further details.

### Protocol Deviations

As only the immunogenicity subset is relevant to this review, protocol deviations only related to this subset are discussed in what follows.

Protocol deviations were classified as major or minor. Major deviation was defined as one that could have a significant impact on the subject's immunogenicity results. All subjects with major deviations were excluded from the PP set for immunogenicity analysis.

Across the vaccine groups, 33% to 38% of subjects from the immunogenicity subset (592 subjects) showed major protocol deviations with a possible impact on the immune response to the vaccine administered. The most commonly reported deviations were vaccinations administered outside the protocol specified window, blood samples drawn outside the visit window, and no blood drawn at the scheduled visits.

### **6.2.11 Immunogenicity Analyses**

#### Immunogenicity Population

As per the applicant, immunogenicity was assessed on the MITT population of the immunogenicity subset, i.e., on data from the rMenB+OMV group. The MITT population included subjects who received a study vaccination and provided at least one evaluable serum sample after baseline and whose assay results were available for at least one serogroup.

Overall, 585 subjects (about 20% of the enrolled population) from 3 groups were included in the MITT population. Exclusions from this population were mainly limited to subjects who did not receive any study vaccination or did not have a blood draw at Visit 3.

An overview (limited only to the MenB group) of populations for which immunogenicity analysis should be performed is presented in Table 19.

Table 19: Number (%) of Subjects Used for Immune Response Analyses

Populations	MenB n(%)
Randomized	196 (100)
MITT	<b>193 (98)</b>
Reason for Out-of-MITT Population – no vaccination at All	3 (<1)
PP population for 1 month post 1 <sup>st</sup> vaccination	161 (82)
PP population for 1 month post 2 <sup>nd</sup> vaccination	<b>151 (77)</b>
# of subjects who had at least one major protocol deviation	74 (38)

Source: CSR V72\_29, pages: 143, 398, 399

As per Table 19, 193 subjects were included in the immunogenicity analysis performed on the MITT population. The PP population included all subjects from the MITT population who correctly received the study vaccinations, provided evaluable serum samples within the protocol-specified visit windows, and had no major protocol deviations.

#### 6.2.11.1 Analyses of Primary Endpoint(s)

Analyses related to the primary endpoints of this study are not the subject of this review. However, it is worth noting that “the data generated by the V72\_29 clinical trials study showed no significant difference in the carriage rates between groups receiving meningococcal vaccines and non-meningococcal control vaccine at 1 month after vaccination” but for “carriage at any time point from 3 months after second vaccination, the rMenB+OMV vaccine showed significant differences in carriage of any *N meningitidis*, genogroups (b)(4)--, genogroups ACWY, serogroups ACWY, genogroup Y and serogroup Y.”

#### 6.2.11.2 Analyses Related to MenB Immunogenicity Endpoints

The main exploratory immunogenicity objective was to assess the immune responses to the rMenB+OMV NZ vaccine using the following parameters:

- (1) to (3) For each of 3 MenB indicator strains H79/76, 5/99, and NZ98/254, proportion of subjects in rMenB+OMV group achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the second vaccination.
- (4) Proportion of subjects in rMenB+OMV group achieving the composite hSBA response, i.e., achieving hSBA titer  $\geq$  LLOQ for all 3 MenB indicator strains combined, one month after the second vaccination.

Detailed information on this objective can be found in Sections 6.0 of this review.

Validation of the hSBA assay used in this study was conducted at ---(b)(4)----, and the LLOQs were established as follows: 1:8 for the 5/99 strain, and 1:16 for the H44/76, and NZ98/54 strains.

Results of the exploratory statistical analyses for the main immunogenicity objective, i.e., for proportions of subjects achieving at least 4-fold hSBA titer rise separately for each of the 3 MenB indicator strains and for the proportion of subjects achieving the composite response, carried out for the MITT population are presented in Table 20.

Table 20: Results for the Main Immunogenicity Objective - MITT Population

Variables	Strain	# of subjects	Estimation of endpoint (%)	95% CI
hSBA Titer 4-fold rise	H44/76	189	79%	(73, 85)
hSBA Titer 4-fold rise	5/99	189	94%	(90, 97)
hSBA Titer 4-fold rise	NZ98/254	188	67%	(60, 74)
Composite hSBA response	For three indicator strains	188	88%	(82, 92)

Source: The reviewer's table based on the applicant's Table Q2-1, Amendment 0.17, page 8

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254. Note: The 4-fold increase is defined as follows: a post-vaccination hSBA  $\geq 1:16$  for subjects with pre-vaccination hSBA  $< 1:4$ , a post-vaccination titer at least 4-fold the LLOQ for subjects with pre-vaccination hSBA  $\geq 1:4$  but  $< LLOQ$ , and a post-vaccination 4-fold rise for subjects with pre-vaccination hSBA  $\geq LLOQ$ .

Table 20 demonstrates that the proportions of subjects from the MenB group achieving 4-fold rise of hSBA titer from baseline to one month after dose 2 were 79% for the H44/76 strain, 94% for the 5/99 strain, and 67% for the NZ98/54 strain, while 88% of subjects achieved the composite hSBA response, i.e., hSBA  $\geq LLOQ$  for all 3 MenB indicator strains combined.

Percentages of adolescents and young adults with hSBA titer  $\geq LLOQ$ , as assessed at baseline and one month after the second dose of rMenB+OMV NZ, are summarized in Table 21.

Table 21: Percentages of Subjects with hSBA titer  $\geq LLOQ$  for MenB Group at Baseline and 1 Month after the Second Dose - MITT Population

Strain	Sampling Time Point	Number of Subjects	% of Subjects with $\geq LLOQ$	95% CI
44/76-SL	Month 0	193	44	(37, 51)
<b>44/76-SL</b>	<b>Month 2</b>	<b>189</b>	<b>100</b>	<b>(98, 100)</b>
5/99	Month 0	193	45	(38, 52)
<b>5/99</b>	<b>Month 2</b>	<b>189</b>	<b>99</b>	<b>(97, 100)</b>
NZ98/254	Month 0	193	32	(25, 39)
<b>NZ98/254</b>	<b>Month 2</b>	<b>189</b>	<b>88</b>	<b>(82, 92)</b>

Source: The reviewer's table based on the applicant's Table Q3-16, Amendment 0.17, page 15

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

**Reviewer’s comments**

Based on Table 21, it appears that the study population in the V72\_29 clinical trial carried out in the UK had at baseline very high percentages (over 23%) of subjects who achieved hSBA titer  $\geq$  LLOQ across indicator strains. However, the corresponding percentages of subjects in the US population were usually lower, i.e., about 4% (see Section 6.4). The statistical reviewer defers to the medical reviewers regarding the clinical or public health relevance of this finding.

Results of analyses for the estimated GMTs one month and eleven months after the last dose of rMenB+OMV NZ are presented in Table 22.

Table 22: Estimates of hSBA GMTs for rMenB+OMV Group - MITT Population and at 3 Time Points

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	193	11	(8.7, 14)
<b>44/76-SL</b>	<b>Month 2</b>	<b>189</b>	<b>229</b>	<b>(192, 274)</b>
<b>44/76-SL</b>	<b>Month 11</b>	<b>177</b>	<b>68</b>	<b>(54, 84)</b>
5/99	Month 0	193	6.44	(5.1, 8.1)
<b>5/99</b>	<b>Month 2</b>	<b>189</b>	<b>424</b>	<b>(355, 507)</b>
<b>5/99</b>	<b>Month 11</b>	<b>177</b>	<b>55</b>	<b>(45, 67)</b>
NZ98/254	Month 0	193	6.15	(4.8, 7.8)
<b>NZ98/254</b>	<b>Month 2</b>	<b>189</b>	<b>99</b>	<b>(80, 122)</b>
<b>NZ98/254</b>	<b>Month 11</b>	<b>177</b>	<b>34</b>	<b>(26, 45)</b>

Source: Based on the applicant’s table, CSR V72\_29, page 147

Table 22 demonstrates significant increases (16-fold to 66-fold) in the rMenB+OMV group in the GMTs against all strains at 1 month after the second dose of the rMenB+OMV NZ vaccine. At the subsequent time-point, i.e., 11 months post second vaccination, the hSBA GMTs were lower but still significantly higher than at baseline. The percentages of subjects who achieved hSBA titer  $\geq$  LLOQ 11 months after the second vaccination were still high, i.e., 90%, 93%, and 69% for H44/76, 5/99, and NZ98/54 strains, respectively (see Table 23).

Table 23: Subjects (%) with hSBA titer  $\geq$  LLOQ for Three MenB Indicator Strains at 11 Months after the 2-dose Regimen – MITT population, rMenB+OMV Group

Variables	Sampling Time Point	Strain	# of subjects	Estimation of endpoint (# of subjects)	95% CI
% of subjects with $\geq$ LLOQ	Month 11	H44/76	177	90% (159)	(84, 94)
% of subjects with $\geq$ LLOQ	Month 11	5/99	177	93% (165)	(88, 96)
% of subjects with $\geq$ LLOQ	Month 11	NZ98/54	177	69% (122)	(62, 76)
Composite hSBA response	Month 11	For three indicator strains	176	65% (115)	(58, 72)

Source: The reviewer’s table based on the Integrated Efficacy Summary Table 6.7, and Amendment 0.25, page 3

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

### **Reviewer's comments**

*One hundred seventy seven (177) subjects provided information on antibody persistence following the two doses of the rMenB+OMV NZ vaccine. The immunogenicity subset of the rMenB+OMV study group (subset of MITT population) is representative of the whole immunogenicity study group at baseline. An assessment of the representativeness, based on a descriptive analysis, was carried out by the statistical reviewer using demographic and immunogenicity factors at Month 12 of the study. This assessment revealed that characteristics of the two sets of subjects were statistically similar.*

*Based on the GMTs and percentages of subjects with hSBA titers  $\geq$  LLOQ (see Table 23), antibody persistence was observed for each indicator strain at 11 months after two-dose vaccination.*

### **6.2.13 Subgroup Analyses**

In Amendment 0.17, the applicant presented results of statistical analyses related to possible influence of gender on immune responses to the rMenB+OMV NZ vaccine at one month after the second vaccination. No substantial differences in the proportions of subjects with hSBA titer  $\geq$  LLOQ between male and female subjects were revealed. However, across indicator strains, the percentages of males with hSBA titer  $\geq$  LLOQ were higher at baseline than for females.

According to the applicant, a tendency towards slightly higher titers in male vs. female subjects against 2 (H44/76 and 5/99) of the 3 indicator strains was observed in the analyses of hSBA GMT. However, due to a small sample size and the overlapping of 2-sided 95% CIs around the point estimates, these differences did not appear to be statistically meaningful.

### **Reviewer's comments and overall conclusions on immunogenicity results related to study V72\_29**

- ✓ *As per the applicant, data generated by the V72\_29 clinical trial showed no significant difference in the carriage rates between groups receiving meningococcal vaccines and non-meningococcal control vaccine at 1 month after vaccination, but for “carriage at any time point from 3 months after second vaccination, the rMenB+OMV vaccine showed significant differences in carriage of any N meningitidis, genogroups (b)(4)--, genogroups ACWY, serogroups ACWY, genogroup Y and serogroup Y.”*
- ✓ *Based on the GMTs and percentages of subjects with hSBA titers  $\geq$  LLOQ, antibody persistence for each indicator strain at 11 months after the two-dose regimen was observed in subjects vaccinated with rMenB+OMV NZ.*
- ✓ *Evaluation of immune responses to the vaccine was based only on 3 MenB indicator strains and descriptive analyses. Therefore, data generated by this study*

*do not appear to provide information on the breath of protection against MenB meningococcal disease the rMenB+OMV NZ vaccine might confer.*

- ✓ *Based on the results related to the main exploratory immunogenicity endpoints and estimations of GMTs, data generated by study V72\_29 indicate that the rMenB+OMV NZ vaccine elicited immune responses expressed for the three MenB indicator strains.*

### **6.3 Trial #3: V72\_41**

**Title of the study:** “A Phase 3, Randomized, Comparative, Multicenter, Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with OMV Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years”

**Study Initiation Date:** August 30, 2011 (first subject enrolled)

**Study Completion Date:** December 1, 2011 (last subject completed participation)

#### **6.3.1 Changes in the Study Conduct or Planned Analyses**

It was planned to enroll about 320 subjects into this study. Subject enrollment took place in multiple sites in Canada and Australia. Sites were informed of the study status when the target enrollment number was close to being reached. However, to ensure that the target enrollment was really achieved, sites were permitted to proceed with all pre-scheduled screening and enrollment visits, which led to a slight over-enrollment (about 8%). Finally, a total of 344 subjects were enrolled into the study.

Several additional exploratory analyses not specified in the statistical analysis plan were performed. For example, impact of gender, country, and center on the immune responses to the rMenB+OMV NZ vaccine, as measured by the percentage of subjects with hSBA titers  $\geq 1:5$  at one month after second dose, was examined.

#### **6.3.2 Objectives**

The main study objective was to evaluate the consistency of the immune responses to the MenB+OMV NZ vaccine originating from two lots manufactured at two different sites ((b)(4) and Rosia, Italy).

##### Primary objective

- To demonstrate the equivalence of rMenB+OMV NZ Lot 1 to rMenB+OMV NZ Lot 2 when vaccine was administered to adolescents, as measured by hSBA GMTs against three *N. meningitidis* serogroup B indicator strains H44/76, 5/99, and NZ98/254 and as measured by -----(b)(4)-----

GMCs against vaccine antigen 287-953, approximately 30 days after the primary vaccination course of two doses administered one month apart.

Important secondary objectives

- To assess the immune response at one month after the primary vaccination course of two rMenB+OMV NZ doses administered one month apart, as measured by the percentage of subjects with hSBA  $\geq 1:5$  and as measured by the ratio of post-vaccination to pre-vaccination hSBA GMTs [GMR] against three *N. meningitidis* serogroup B indicator strains, H44/76, 5/99, and NZ98/254.
- To evaluate the immune response at two weeks after the primary vaccination course of two rMenB+OMV NZ doses administered one month apart, as measured by hSBA GMTs, the ratio of post-vaccination to pre-vaccination hSBA GMTs [GMR], and the percentage of subjects with hSBA  $\geq 1:5$  against three *N. meningitidis* serogroup B indicator strains, H44/76, 5/99, and NZ98/254.

Detailed information on other secondary objectives can be found in Dr. Anuja Rastogi's clinical review. Endpoints considered in this study are discussed in Section 6.3.8 of this review.

Reviewer's comments

*Data generated by -----(b)(4)----- measurements were not relevant to the BLA submission. Therefore, only hSBA data related to the objective of the BLA submission were considered in this review.*

*Additionally, the main exploratory immunogenicity objective related to immune response to the MenB+OMV NZ, as described by four immunogenicity endpoints (4-fold rise for each indicator strain and composite endpoint against 3 indicator strains), was not pre-defined in the protocol; however, results related to this objective played a key role in evaluation of immune response to the rMenB+OMV NZ vaccine. More information on the main immunogenicity objective can be found in Section 6.0 of this statistical review.*

**6.3.3 Design Overview**

Study V72\_41 was a Phase 3, multicenter, observer-blind, randomized trial in adolescents (11-17 years, inclusive). All subjects were to receive two rMenB+OMV NZ vaccinations one month apart and be followed for a total of 2 months. At Visit 1, subjects were randomized in a ratio 1:1 to one of two treatment arms to receive either two doses of rMenB+OMV NZ vaccine from Lot 1 or 2 doses of rMenB+OMV NZ from Lot 2. Lot 1 and Lot 2 were manufactured in Novartis Rosia and (b)(4) facilities, respectively. The study design is presented in Table 24.

Table 24: Study Design

Group	Visit 1 Month 0	Visit 2 Month 1	Visit 2b* Month 1.5	Visit 3 Month 2
MenB - Lot 1 (Rosia)	rMenB+OMV – Lot 1	rMenB+OMV – Lot 1		
MenB – Lot 2 (b)(4)	rMenB+OMV – Lot 2	rMenB+OMV – Lot 2		
Blood draw (all groups)	20 mL		20 mL	20 mL

\*At Visit 2b (Month 1.5): blood draw was collected in a subset of approximately 160 subjects (approximately 80 subjects from each group). Some pre-selected sites enrolled the subset of subjects who required an additional blood draw at two weeks after the second vaccination.

Source: CSR V72\_41, page 45

The signed informed consent and complete medical history documents, as well as complete physical examinations, were collected/performed at Visit 1 before randomization and administration of the first study vaccination.

The study staff dispensing and administering vaccines were unblinded, but all other study personnel, particularly individuals who evaluated subjects' safety, the principal investigator, and subjects were blinded.

**Reviewer's comments**

*The study was designed to evaluate the consistency of 2 lots of rMenB+OMV NZ, formulated with OMV manufactured at sites Rosia and (b)(4) for Lot 1 and Lot 2, respectively, from the safety and immunogenicity points of view. Because there was no information available about the early immune responses after vaccination with the rMenB+OMV NZ in the healthy adolescents 11 through 17 years of age at the beginning of the trial, additional blood draws took place in a subset of subjects at two weeks after the second dose of vaccination.*

**6.3.4 Population**

Individuals eligible for enrollment into this study were males and females 11-17 years of age (inclusive) who:

- ✓ Provided a personally signed and dated informed consent document (ICD) indicating that the subject and a legally authorized representative were informed of all pertinent aspects of the study,
- ✓ Were available for all visits scheduled in the study, i.e., did not plan to leave the area before the end of the study period, and
- ✓ Were healthy, as determined by medical history, physical examination, and judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Anuja Rastogi's clinical review.

### **6.3.5 Study Treatments or Agents Mandated by the Protocol**

The vaccination groups and the vaccination plan per study group are presented in Table 23 of this review.

#### *Investigational vaccine*

The investigational vaccine was rMenB+OMV NZ. It contained three recombinant protein antigens, NHBA, fHbp, and NadA, and OMV NZ. The study regimen was to administer 2 doses of the investigational vaccine.

Two lots of the Investigational Vaccine rMenB+OMV NZ of composition described in Table 1 in Section 2.3 of this statistical review, but formulated with OMV manufactured at sites Rosia or (b)(4), respectively, were utilized in the study.

Lot numbers of the investigational product were (1) rMenB+OMV NZ 101601 (release date: 28 JUL 11), and (2) rMenB+OMV NZ 090101 (release date: 27 JUL 11).

The rMenB+OMV NZ vaccine was administered intramuscularly (IM) by injecting vaccine into the deltoid region. This vaccine was supplied as single-dose syringes.

### **6.3.6 Sites and Centers**

The study was conducted in Canada and Australia at 13 different sites.

### **6.3.7 Surveillance/Monitoring**

As per the Applicant, study progress was monitored by Novartis Vaccines and Diagnostics as frequently as necessary to ensure that the rights and well-being of study subjects are protected, to verify adequate, accurate, and complete data collection, protocol compliance, and to determine that the study was conducted in conformance with the applicable regulatory requirements. The study was conducted according to the principles of Good Clinical Practice.

According to the study compliance rules, the investigator was responsible for adequate and accurate accounting of vaccine usage. The investigator or designee administered the study vaccines only to individuals included in the study, following procedures set out in the study protocol. The date, dosage, and time of the vaccinations were recorded. The investigator kept track of vaccines received.

### **6.3.8 Endpoints and Criteria for Study Success**

In order to demonstrate equivalence of the two lots and assess the immune responses to rMenB+OMV NZ Lot 1 and Lot 2 vaccines, the hSBA and (b)(4) measures were used.

### *Study endpoints and parameters*

Immunogenicity endpoints were:

- ✓ Titers at baseline, 0.5 Month and 1 Month after the second vaccination
- ✓ -----(b)(4)----- measurements
- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ Ratios of the Lot 1 to Lot 2 hSBA GMTs for each of the three serogroup B indicator strains (H44/76, 5/99, and NZ98/254) at one month after the second vaccination.
- ✓ The ratio of the (b)(4) GMCs (Lot 1 vs. Lot 2) for the 287-953 vaccine antigen at one month after the second vaccination.
- ✓ The hSBA GMTs (for each MenB indicator strain) and --(b)(4)- GMC estimated for each study group at baseline, two weeks, and one month after the second vaccination.
- ✓ Proportions of subjects with hSBA titers equal to or greater than the lower limit of quantitation (LLOQ), and  $\geq 1:5$ , for each MenB indicator strain at each applicable blood draw time point.
- ✓ hSBA geometric mean titers (GMTs) for each of the indicator strains at each applicable blood sampling time point.
- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the second vaccinations (Visit 3).

For the main immunogenicity exploratory objective, the following parameters were defined:

- (1) - (3) For each of the indicator strains 44/76 SL, 5/99, and NZ98/254, proportions of subjects in the combined Lot 1 + Lot 2 group achieving at least 4-fold increase in hSBA titer from baseline to one month post second vaccination.
- (4) Proportions of subjects in the combined Lot 1 + Lot 2 group achieving a composite hSBA response defined as hSBA titer  $\geq$  LLOQ for all three indicator strains combined at one month after the second vaccination.

### **6.3.9 Statistical Considerations and Statistical Analysis Plan**

#### *Hypotheses*

The primary objective was to demonstrate the equivalence of rMenB+OMV NZ Lot 1 to rMenB+OMV NZ Lot 2 when administered to adolescents, as measured by hSBA GMTs against three *N. meningitidis* serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and as measured by (b)(4)- GMCs against the 287-953 vaccine antigen at one month (Visit 3) after the second vaccination with rMenB+OMV NZ.

The following formal lot-to-lot hypotheses were to be considered:

$H_0: \phi_{ij} \leq 0.5, \text{ or } \phi_{ij} \geq 2.0$

$H_a: 0.5 < \phi_{ij} < 2.0$  for all combinations of  $i \neq j$  and for all indicator strains and 287-953 vaccine antigen,

where  $\phi_{ij} = \mu_i/\mu_j$ , and  $\mu_i, \mu_j$  are GMT or GMC values (for Visit 3) for the  $i^{\text{th}}$  and  $j^{\text{th}}$  lots, respectively.

### *Study success and statistical analysis*

The V72\_41 study success would take place when consistency of immune responses between the two lots was demonstrated for each of the three serogroup B indicator strains and vaccine antigen 287-953. Consistency could be concluded if, at one month following the second vaccination, the two-sided 95% CIs of the ratios of the hSBA GMTs in Lot 1 and Lot 2 for each of 3 serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and the two-sided 95% CI of the ratio of the (b)(4) GMCs against vaccine antigen 287-953 for Lot 1 and Lot 2 are contained within the interval (0.5, 2.0).

The above hypotheses were tested by checking whether the difference in means of log10 transformed hSBA titers for Lot 1 and Lot 2 was within the equivalence range (-0.301 to 0.301) for each of the three serogroup B indicator strains (H44/67, 5/99, and NZ98/254), and whether the two-sided 95% CI of the difference in means of log10 transformed (b)(4) concentrations for Lot 1 and Lot 2 were within the equivalence range (-0.301 to 0.301) for vaccine antigen 287-953.

All immunogenicity analyses related to the rMenB+OMV NZ vaccine data for this study are summarized in this review descriptively.

Note that the immune response to the candidate vaccine was assessed additionally at two weeks after the second vaccination. For this purpose, blood samples were collected at 2 weeks after the primary vaccination course (Month 1.5) for a subset of approximately 160 subjects. For each lot and each reference strain or vaccine antigen 287-953, the GMT (or GMC) and the corresponding two-sided 95% CI was estimated utilizing a two-way Analysis of Variance (ANOVA) with vaccine lot and study center as factors. No between-group statistical comparisons were performed, because such analysis would be underpowered to demonstrate equivalence.

### **6.3.10 Study Population and Disposition**

#### *Demographic characteristics*

At baseline, demographic and other characteristics of the enrolled subjects, except for gender, were balanced across the two vaccination study groups. Within each lot group the percentages of males were higher compared to females. Between Lot 1 (Rosia) and Lot 2 (b)(4), there was 5% difference in percentages of males (58% and 53%, respectively). The majority of subjects were white (about 80%). The median age at first vaccination was 14 years, while the age range was 11 to 17 years.

Disposition of subjects

A summary of the enrolled subject disposition is presented in Table 25.

Table 25: Subject Disposition

Disposition of Subjects	Lot 1 (Rosia) n(%)	Lot 2 (b)(4) n(%)	Total n(%)
<b>Enrolled</b>	170	174	344
Withdrawal due to Adverse Event or Death	0 (0)	1 (<1)	1 (<1)
Withdrawal due to Withdrew Consent	2 (1)	3 (2)	5 (1.5)
<b>Study Completed</b>	<b>168 (99)</b>	<b>170 (98)</b>	<b>338 (98)</b>

Source: CSR V72\_41, page 69

Overall, 344 subjects were enrolled in the study. During the course of the study, six subjects were prematurely withdrawn from the study.

Protocol deviations

A summary of protocol deviations is presented in Table 26.

Table 26: Summary of Major Protocol Deviations

	Lot 1 (Rosia) n(%)	Lot 2 (b)(4) n(%)	Total n(%)
<b>Enrolled</b>	170	174	344
Subjects with any Deviation	66 (39)	63 (36)	129 (38)
Subjects with any Major Deviation	23 (14)	26 (15)	49 (14)
Subject did not receive the 2 <sup>nd</sup> Vaccination	1 (<1)	3 (2)	4 (1)
Subject with 2 <sup>nd</sup> Vaccination outside Allowed Window	14 (8)	10 (6)	24 (7)

Source: CSR V72\_41, page 72

Major protocol deviations were noted for a total of 49 (14%) subjects. The most common reasons for major protocol deviations were: 2<sup>nd</sup> vaccination outside allowed window (range 6% to 8% of subjects) and receiving excluded concomitant medication (3% to 4% of subjects).

**6.3.11 Immunogenicity Analyses**

Immunogenicity Population

Immunogenicity populations considered in this review are presented in Table 27.

Table 27: Immunogenicity Populations

Population	Lot 1 (Rosia) # of subjects(%)	Lot 2 (b)(4) # of subjects (%)
Enrolled	170	174
Vaccinated	169 (99)	173 (99)
MITT	168 (99)	171 (99)
PP immunogenicity population	147 (86)	152 (87)

Source: CSR V72\_41, page 75

A total of 299 (87.0% of 344) subjects were included in the post-Vaccination 2 evaluable immunogenicity population.

Thirty six subjects were excluded from the immunogenicity PP population due to vaccination non-compliance:

- Two subjects (52/023/Lot 2 and 59/001/Lot 1) did not receive vaccination at all.
- Four subjects (51/061 Lot 1; 06/003, 51/013, and 55/027 from Lot 2) did not receive the second vaccination.
- Six subjects (3 from Lot 1 and 3 from Lot 2) received the wrong treatment.
- Twenty four subjects received the second vaccination administered outside the allowed window.

### 6.3.11.1 Analyses Related to Primary Endpoints

#### Primary immunogenicity hypothesis

The primary immunogenicity hypotheses are related to clinical lot-to-lot consistency. To support the hypotheses, the applicant was to demonstrate that vaccines drawn from two vaccine lots -- Lot 1 (Rosia) and Lot 2 ---(b)(4)-- elicited equivalent immune responses. For pair-wise comparisons, the 95% CIs of the ratios of post-vaccination GMTs against each of the indicator strains, and the 95% CIs of the ratios of post-vaccination GMCs against vaccine antigens measured one month after the second vaccination should be entirely within the interval (0.5, 2). A summary of results for lot-to-lot consistency is presented in Tables 28 and 29.

Table 28: Lot-to-Lot Consistency Results based on GMTs – Per Protocol Population

Strain	Lot 1 (Rosia) # of subjects	Lot 1 (Rosia) GMT (95%CI)	Lot 2 (b)(4) # of subjects	Lot 2 (b)(4) GMT (95%CI)	Lot 1 vs. Lot 2 GMTs ratio (95%CI)
H44/76	147	111 (96, 129)	152	111 (96, 1129)	1.0 (0.82, 1.23)
5/99	147	183 (160, 209)	152	199 (174, 227)	0.92 (0.77, 1.1)
NZ98/254	147	9.27 (7.44, 12)	152	11 (9.22, 14)	0.81 (0.6, 1.09)

Source: CSR V72\_41, page 80

Table 29: Lot-to-Lot Consistency Results based on GMCs – Per Protocol Population

Vaccine Antigen	Lot 1 (Rosia) # of subjects	Lot 1 (Rosia) GMC (95%CI)	Lot 2 (b)(4) # of subjects	Lot 2 (b)(4) GMC (95%CI)	Lot 1 vs. Lot 2 GMCs ratio (95%CI)
287-953	147	2729 (2338, 3186)	152	3291 (2829, 3828)	0.83 (0.67, 1.02)

Source: Erratum to Final Clinical Study Report V72\_41, page 8

**Reviewer’s comments**

*The null hypotheses can be rejected because the two-sided 95% CI of the Lot 1 vs. Lot 2 ratio of the hSBA GMTs for each of the three serogroup B indicator strains H44/76, 5/99, and NZ98/254 and the two-sided 95% CI of the ratio of the (b)(4) GMCs against vaccine antigen 287-953 were within the interval (0.5, 2.0).*

*Therefore, the primary objective to demonstrate equivalence of rMenB+OMV NZ Lot 1 (Rosia) to rMenB+OMV NZ Lot 2 (b)(4) at one month after second vaccination was met for the three indicator strains and the 287-953 vaccine antigen.*

As per the applicant, results of testing the primary hypothesis based on the MITT population were similar to the results for the PP immunogenicity population.

**6.3.11.2 Analyses Related to Secondary Endpoints**

One of the secondary parameters is related to the immune response to the rMenB+OMV NZ vaccine measured by GMTs against three indicator strains at two weeks after the second vaccination. Results regarding this secondary objective are presented in Table 30.

Table 30: hSBA GMTs Two Weeks after the Second Vaccination

Strain	Lot 1 (Rosia) # of subjects	Lot 1 (Rosia) GMT (95%CI)	Lot 2 (b)(4) # of subjects	Lot 2 (b)(4) GMT (95%CI)	Lot 1 + Lot 2 # of subjects	Lot 1 + Lot 2 GMT (95%CI)
H44/76	76	187 (152, 229)	71	171 (139, 210)	147	175 (153, 199)
5/99	76	254 (206, 314)	71	339 (273, 420)	147	294 (257, 336)
NZ98/254	76	14 (10, 18)	71	20 (15, 27)	147	18 (15, 21)

Source: CSR V72\_41, page 88

**Reviewer’s comments**

*Results shown in Tables 28 and 30 indicate a notable decline in hSBA GMT levels measured at one month after the second vaccination as compared to the respective titer GMT levels measured at two weeks after the second vaccination, for all three indicator strains and for both Lot 1 and Lot 2.*

GMT estimates based on three different analysis methods are presented below.

- (1) For the purpose of the first method, all titers below the limit of detection were set to half of that limit (e.g., an hSBA titer < 2 was set to 1). Estimates of GMTs at

baseline and one month after the second vaccination received with the use of this method are presented in Table 31.

Table 31: Estimates of hSBA GMTs for Combined Lot 1 + Lot 2 Group - PP Population and Method 1

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	299	1.07	(1.02, 1.11)
<b>44/76-SL</b>	<b>Month 2</b>	<b>298</b>	<b>117</b>	<b>(105, 130)</b>
5/99	Month 0	299	1.23	(1.13, 1.33)
<b>5/99</b>	<b>Month 2</b>	<b>298</b>	<b>179</b>	<b>(163, 197)</b>
NZ98/254	Month 0	299	1.06	(1.01, 1.11)
<b>NZ98/254</b>	<b>Month 2</b>	<b>299</b>	<b>10</b>	<b>(8.8, 12)</b>

Source: Based on the applicant's table, CSR V72\_41, page 80

- (2) Based on validation of the hSBA assay conducted at ---(b)(4)----, the LLOQs were established to be 1:8 for the NZ98/254 strain, and 1:16 for the H44/76 and 5/99 strains. In the second method, estimates of hSBA GMTs were assessed by setting titers below the LLOQ to ½ LLOQ. Results of these calculations are presented in Table 32.

Table 32: Estimates of hSBA GMTs utilizing LLOQ Information for Combined Lot 1 + Lot 2 Group - PP Population and Method 2

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	299	8.05	(7.9, 8.14)
<b>44/76-SL</b>	<b>Month 2</b>	<b>298</b>	<b>118</b>	<b>(106, 130)</b>
5/99	Month 0	299	8.25	(8.05, 8.45)
<b>5/99</b>	<b>Month 2</b>	<b>298</b>	<b>179</b>	<b>(163, 197)</b>
NZ98/254	Month 0	299	4.11	(3.9, 4.23)
<b>NZ98/254</b>	<b>Month 2</b>	<b>299</b>	<b>12</b>	<b>(11, 14)</b>

Source: The reviewer's table based on the applicant's Table Q6-1, Amendment 0.17, page 27

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

- (3) In the case of the third scenario, the applicant was asked to perform a sensitivity analysis of hSBA GMTs using maximum likelihood estimation, based on left censoring. The applicant showed that using maximum likelihood estimation method for estimation of hSBA GMTs did not have impact on the results related to the primary hypothesis.

### **Reviewer's Comments**

*Based on three methods of GMT estimation for all indicator strains at baseline and one month after the second vaccination, it appears that there were differences in GMTs at baseline, while no meaningful differences were observed one month after the second vaccination.*

### 6.3.11.3 Analyses Related to Exploratory Endpoints

The main immunogenicity exploratory objective was to assess immune response to the rMenB+OMV NZ vaccine using the following parameters:

- For each of three MenB indicator strains, H44/76, 5/99, and NZ98/254, proportion of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the second vaccination, in the combined Lot 1 + Lot2 group.
- Proportion of subjects achieving the composite hSBA response defined as hSBA titer  $\geq$  LLOQ for all three MenB indicator strains in the combined Lot 1 + Lot 2 group one month after the second vaccination.

Detailed information on this objective can be found in Section 6.0 of this review.

As mentioned previously, validation of the hSBA assay used in this study was conducted at ---(b)(4)-----, and the LLOQs were established to be 1:8 for the NZ98/254 strain, and 1:16 for the H44/76 and 5/99 strains. Results of the statistical analyses carried out for the PP population for the main immunogenicity exploratory objective, i.e., for proportions of subjects achieving at least 4-fold hSBA titer rise separately for each of the three MenB indicator strains and for the proportion of subjects achieving the composite response, are presented in Table 33.

Table 33: Results for the Main Immunogenicity Exploratory Objective - PP Population

Variables	Strain	# of subjects	Estimation of endpoint	95% CI
hSBA Titer 4-fold rise	H44/76	298	98%	(95, 99)
hSBA Titer 4-fold rise	5/99	299	99%	(98, 100)
hSBA Titer 4-fold rise	NZ98/254	298	39%	(33, 44)
Composite hSBA response	For three indicator strains	298	63%	(57, 68)

Source: The reviewer's table based on the applicant's Table Q2-1, Amendment 0.17, page 8

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

Note: The 4-fold increase is defined as: a post-vaccination hSBA  $\geq$  1:16 for subjects with pre-vaccination hSBA < 1:4, a post-vaccination titer at least 4-fold the LLOQ for subjects with pre-vaccination hSBA  $\geq$  1:4 but < LLOQ, and a post-vaccination 4-fold rise for subjects with pre-vaccination hSBA  $\geq$  LLOQ.

Table 33 demonstrates that, for the PP population, the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after dose 2 were 98%, 99%, and 39% for H44/76, 5/99, and NZ98/54 strains, respectively, while 63% of subjects achieved the composite hSBA response, i.e., hSBA  $\geq$  LLOQ for all 3 MenB indicator strains combined.

### 6.3.12 Subgroup Analyses

Utilizing pooled data (Group Lot 1 + Group Lot 2), the applicant performed statistical analyses to investigate possible influence of gender and country on the immune responses. Tables 34 and 35 display results of statistical analyses related to the possible influence of country and gender on immune responses measured by the hSBA GMTs for *N. meningitidis* serogroup B test (indicator) strains, and the pre- to post-vaccination geometric mean titer ratios (GMRs) after the 2<sup>nd</sup> dose of the rMenB+OMV NZ vaccine.

Table 34: hSBA GMTs and GMRs with corresponding 95% CIs after the Second Dose of rMenB+OMV NZ – PP Population (Lot 1 +Lot 2) and by Country

Strain	Factor Country	Number of Subjects	Estimation of GMT	GMT 95% CI	Estimation of GMR	GMR 95% CI
44/76-SL	Australia	70	91	(76, 110)	87	(71, 106)
<b>44/76-SL</b>	<b>Canada</b>	<b>228</b>	<b>126</b>	<b>(111, 143)</b>	<b>118</b>	<b>(104, 134)</b>
5/99	Australia	70	163	(136, 196)	134	(111, 162)
<b>5/99</b>	<b>Canada</b>	<b>229</b>	<b>184</b>	<b>(165, 206)</b>	<b>150</b>	<b>(130, 172)</b>
NZ98/254	Australia	70	11	(8.5, 15)	11	(8.5, 15)
<b>NZ98/254</b>	<b>Canada</b>	<b>229</b>	<b>9.9</b>	<b>(8.3, 12)</b>	<b>9.2</b>	<b>(7.8, 11)</b>

Source: The reviewer's table based on CSR V72\_41, pages 579-584

Table 35: hSBA GMTs and GMRs with Corresponding 95% CIs after the Second Dose of rMenB+OMV NZ dose – PP Population (Lot 1+Lot 2) and by Gender

Strain	Factor Gender	Number of Subjects	Estimation of GMT	GMT 95% CI	Estimation of GMR	GMR 95% CI
44/76-SL	Female	134	103	(87, 119)	95	(81, 113)
<b>44/76-SL</b>	<b>Male</b>	<b>165</b>	<b>131</b>	<b>(114, 151)</b>	<b>123</b>	<b>(107, 142)</b>
5/99	Female	134	182	(155, 214)	150	(124, 182)
<b>5/99</b>	<b>Male</b>	<b>165</b>	<b>177</b>	<b>(157, 199)</b>	<b>143</b>	<b>(124, 164)</b>
NZ98/254	Female	134	8.6	(6.7, 11)	7.97	(6.3, 10)
<b>NZ98/254</b>	<b>Male</b>	<b>165</b>	<b>12</b>	<b>(9.8, 14)</b>	<b>11</b>	<b>(9.4, 13)</b>

Source: The reviewer's table based on CSR V72\_41, pages 824-829

As results for Canada are greater, it can be concluded based on Table 34, that country may have influenced the immune response to rMenB+OMV NZ vaccine against both 44/76-SL and 5/99 indicator strains.

However, Table 35 indicates no influence of gender on immune responses to the rMenB+OMV NZ vaccine at one month after the second vaccination. Additionally, based on the applicant's analysis, the percentages of subjects with  $\geq$  LLOQ in male and female subjects did not exhibit any systematic trends.

Note that the statistical analyses evaluating possible influence of such factors as country and gender on the immune responses to the rMenB+OMV NZ vaccine after the 2<sup>nd</sup> dose were *post-hoc* in nature. Therefore, the results should be interpreted appropriately.

**Reviewer's comments and overall conclusions on immunogenicity results related to study V72\_41**

- *The primary objective to demonstrate equivalence of rMenB+OMV NZ Lot 1 (Rosia) to rMenB+OMV NZ Lot 2 (b)(4) at one month after the second vaccination was met for the three indicator strains and the 287-953 vaccine antigen. The two-sided 95% CI for the ratio of the hSBA GMTs in Lot 1 and Lot 2*

*for each of the three MenB indicator strains H44/76, 5/99, and NZ98/254, and the two-sided 95% CI for the ratio of the (b)(4) GMCs for Lot 1 and Lot 2 against vaccine antigen 287-953 were within the pre-defined interval (0.5, 2.0).*

- *A notable decline in hSBA GMT levels measured one month after the second vaccination as compared to the respective GMT levels measured two weeks after the second vaccination, for all three indicator strains and for both Lot 1 and Lot 2, was observed.*
- *The applicant estimated GMTs using three different methods and showed that these assessment methods did not have impact on the results and conclusion regarding the primary objective, i.e., lot-to-lot consistency. Based on the three types of estimates of GMTs for all indicator strains at baseline and at one month after the second vaccination, it appears that there were differences in GMTs at baseline, but there were no notable differences one month after the second vaccination.*
- *Results of statistical analyses related to possible influence of gender on immune responses to the rMenB+OMV NZ vaccine at one month after the second vaccination, as measured by the percentages of subjects with  $\geq$  LLOQ, showed no meaningful differences between the male and female subjects at one month after the second vaccination. However, country may have influenced the immune response to rMenB+OMV NZ vaccine against both 44/76-SL and 5/99 indicator strains as measured by hSBA GMTs.*
- *Based on the results related to the main immunogenicity exploratory endpoints and estimations of GMTs and GMRs, data generated by study V72\_41 indicated that the rMenB+OMV NZ vaccine elicited immunogenicity responses expressed for the three MenB indicator strains.*

#### **6.4 Trial #4: V102\_03**

**Title of the study:** “Phase 2, Observer Blinded, Controlled, Randomized, Multi-Center Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of Two Different rMenB with OMV + MenACWY Combination Vaccination Formulations”

**Study Initiation Date:** August 08, 2011 (the first subject visit)

**Study Completion Date:** September 11, 2012 (the last subject visit)

##### General information

The main objective of the V102\_03 clinical trial was to explore safety and immunogenicity of 2 different formulations of the ---(b)(4)----- vaccine.

#### **6.4.1 Changes in the Study Conduct or Planned Analyses**

The study protocol was submitted to CBER in December 2010, and was followed by three amendments. Enrollment of subjects was initiated under the first amendment.

Among other modifications, three protocol amendments introduced the following essential changes to the original protocol:

- The vaccine study formulation -----  
------(b)(4)-----  
-----.
- Vaccine rMenB+OMV (MenB+OMV NZ) was added as a reference vaccine, and thus the fourth study group was introduced and the sample size was increased from 360 to 480 subjects.
- The third secondary objective (comparison with rMenB+OMV NZ vaccine) was added.
- Subjects' age range was broadened from 11 through 18 years to 10 through 25 years.
- Additional safety measures, such as guidelines for evaluation of rash as an indicator of hypersensitivity and rules for pausing/stopping the study or individual subject participation, were introduced.
- A Data Monitoring Committee (DMC) to evaluate subject safety throughout the study was established.
- Secondary immunogenicity endpoints were changed by inclusion of hSBA titers  $\geq 1:8$  and 4-fold increase in hSBA titer for serogroup B strains.
- An exclusion criterion related to concomitant vaccination was clarified.
- Safety data collection instructions prohibiting verbal recall of solicited AEs at study visits, and clarifying that the primary source for each reported AE was to be recorded (details below) were updated.
- Additional information to be collected for any rash episode reported during the 7 days following vaccination was specified.
- Statistical analyses regarding inter-group comparisons and sample size were clarified.
- The second primary immunogenicity objective, i.e., evaluation of optimal ---(b)(4)--- formulation -----(b)(4)----- in comparison with a single dose of MenACWY and with 2 doses of rMenB+OMV NZ, using a desirability model based on both immunogenicity and safety parameters (and definition of the analysis sets and statistical methods to be used for this), was added
- The serogroup B test strains to be used for assays, including test strains for exploratory analyses, were specified.

The original Statistical Analysis Plan (SAP) was issued on Jan 10, 2011, and was later modified 4 times. The first SAP amendment included revisions of the objectives and analyses to reflect changes introduced by protocol Amendment 2.0, and also added separate summaries of safety and key immunogenicity data for Poland and the US, and gender, age, center, and country as factors in analyses of GMTs. The second and third SAP amendments incorporated changes necessitated by other changes to the protocol. An addendum to the SAP was issued after completion of the protocol-specified analyses and it incorporated additional analyses for exploratory study endpoints for serogroup B test (indicator) strains.

## 6.4.2 Objectives

### Primary objectives

- To demonstrate immunogenicity non-inferiority of 2 doses of 2 different formulations of ---(b)(4)----- as compared to a single dose of MenACWY (Menveo), as measured by the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W-135, and Y at 30 days after the second vaccination, in healthy adolescents and young adults aged 10 through 25 years.
- To identify, based on the overall desirability index, the optimal formulation of ---(b)(4)----- vaccine by comparing with
  - a single dose of Menveo (MenACWY), and
  - 2 doses of rMenB+OMV NZ
 in healthy adolescents and young adults aged 10 through 25 years.

The overall desirability index (which converts a multivariate optimization problem into a univariate one) is based on immunogenicity parameters, i.e., GMT ratios against *N. meningitidis* serogroups A, C, W-135, and Y and serogroup B test strains at 30 days after the second vaccination, and reactogenicity parameters, i.e., percentages of doses associated with severe local and severe systemic solicited AEs following any vaccination.

The primary and secondary objectives of this study, which are related to immune response to (b)(4) formulations of the ---(b)(4)----- vaccine, are not evaluated in this statistical review as they are irrelevant to this BLA. However, brief general information on the results related to the primary objectives is mentioned later.

## 6.4.3 Design Overview

The V102\_03 clinical trial was a Phase 2, multi-center, observer-blind, randomized trial in healthy adolescents and young adults aged 10 to 25 years at time of enrollment. This clinical trial was conducted in the US and Poland. Study subjects were randomized in a 1:1:1:1 ratio to one of four vaccination groups to receive vaccines listed in Table 36.

Table 36: Treatments by study group

Study group	Study Vaccine
Group I	------(b)(4)-----
Group II	------(b)(4)-----
Group III	rMenB +OMV NZ
Group IV	Saline Placebo at Month 0/Menveo at Month 2

Source: CSR V102\_03, page 39

An overview of the study design is presented in Table 37.

Table 37: Study design

Month #	Month 0	Month 2	Month 3	Month 8
Visit #	Visit 1	Visit 2	Visit 3	Visit 4
Group I	------(b)(4)-----	------(b)(4)-----		Phone contact
Group II	------(b)(4)-----	------(b)(4)-----		Phone contact
Group III	rMenB+OMV NZ	rMenB+OMV NZ		Phone contact
Group IV	Saline	MenACWY (Menveo)		Phone contact
Blood draw (all groups)	~20 mL		~20 mL	

Source: CSR V102\_03, page 39

Study subjects and personnel assessing the safety and eligibility of subjects' enrollment into Groups I - IV remained blinded to the treatment assigned. However, study personnel who prepared and administered study vaccinations were unblinded to the treatment assignment.

**Reviewer's comments**

*Clinical trial V102\_03 was not primarily designed for assessments of safety and immunogenicity of the rMenB+OMV NZ vaccine. Despite that, data generated by study Group III was utilized to evaluate in an exploratory way the functional immune responses to the rMenB+OMV NZ vaccine for three MenB indicator strains.*

*More details on the main immunogenicity exploratory objective can be found in Section 6.0 of this review.*

**6.4.4 Population**

At the time of enrollment (baseline), the study population consisted of 10-25 year-old females and males

- ✓ who had given their written informed consent at the time of enrollment, and, if the subject was under age 18 at the time of enrollment, the legal parents/guardians of the subject had given their written consent on behalf of the subject
- ✓ who were available for all visits scheduled in the study (i.e., had not planned to leave the area before the end of the study period)
- ✓ who were in good health as determined by the outcome of medical history, physical examination, and clinical judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Anuja Rastogi's clinical review.

### 6.4.5 Study Treatments or Agents Mandated by the Protocol

The vaccination plan per study group is presented in Table 37 of this review.

#### *Investigational Vaccines*

- -----  
-----  
-----  
----- (b)(4) -----  
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-----:
- ✓ -----  
----- (b)(4) -----  
-----  
-----
- ✓ -----  
----- (b)(4) -----  
-----  
-----  
-----

#### *Reference Vaccines*

- (Group III) The rMenB+OMV NZ vaccine containing 3 recombinant protein antigens, NHBA, fHbp, and NadA, and OMV NZ. Composition of the rMenB+OMV NZ vaccine is given in Table 1 in Section 2.3 of this statistical review.
- (Group IV) MenACWY vaccine (0.5mL dose) consisting of CRM197 conjugated capsular polysaccharides of MenA (10µg), MenC (5µg), MenW (5µg), and MenY (5µg). The saline placebo was a clear, colorless liquid presented in ampoules.

Enrolled subjects received 2 doses (0.5 mL each) of study vaccine, the first on Day 1 and the second on Day 61. Vaccines were administered intramuscularly (IM) in the deltoid muscle of (preferably) the non-dominant arm. Vaccine lot numbers are presented in Table 38.

Table 38: Lot Numbers of Investigational and Reference Vaccines

Study Vaccine	Lot Numbers
----- (b)(4) -----	090101B3 / 090101B6
----- (b)(4) -----	A38P18N1H / A38P18N1F
rMenB +OMV NZ	090101B4 / 090101B5
Menveo (MenACWY)	US: A10154 / X10154 Poland: A10153 / X10153

Source: CSR V201\_03, page 43

#### 6.4.6 Sites and Centers

Multiple sites (8) in the US and 5 sites in Poland participated in the study.

#### 6.4.7 Surveillance/Monitoring

According to the applicant, the V102\_03 clinical trial was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid out in the Declaration of Helsinki.

Study progress was monitored by Novartis Vaccines and Diagnostics to ensure that the rights and well-being of study subjects were protected, to verify adequate, accurate, and complete data collection, protocol compliance, and to determine that the study was conducted in conformance with the applicable regulatory requirements. The coordinating investigators were Dr. Stanley Block (US) and Prof. Leszek Szenborn (Poland).

Additionally, an external data monitoring committee (DMC) was appointed for this study to evaluate safety data throughout the study, particularly for a pilot group of the first 10% of subjects.

#### 6.4.8 Endpoints and Criteria for Study Success

In order to assess the primary objectives and the immune responses to ---(b)(4)-----, MenACWY (Menveo), and rMenB+OMV NZ vaccines using (b)(4)-hSBA -----(b)(4)-- ----- assay for human Serum Bactericidal Activity), blood samples (approximately 20 mL each) were drawn from each subject immediately before Visit 1, about 61 days after the first vaccination, and about 30 days after the second vaccination.

##### *Study endpoints and parameters*

Immunogenicity endpoints were:

- Titers at baseline and 1 Month after the second vaccination
- Seroresponse
- Four-fold response.

For serogroups A, C, W-135, and Y, by definition, seroresponse to the vaccine took place if:

- ✓ a post-vaccination hSBA titer was  $\geq 1:8$ , for subjects with a pre-vaccination hSBA titer  $< 1:4$

or

- ✓ hSBA increased at least four times in comparison to the pre-vaccination titer, for subjects with a pre-vaccination hSBA titer  $\geq 1:4$ .

Definition of four-fold response related to the main immunogenicity exploratory objective can be found in Section 6.0 of this review.

Immunogenicity parameters were:

- ✓ Proportion of subjects with seroresponse in Groups I, II, and IV, and in serogroups A, C, W-135, and Y at each applicable blood draw time point.
- ✓ hSBA GMT against each MenB test strain and serogroups A, C, W, and Y at each applicable blood draw time point.
- ✓ Proportion of subjects with hSBA titers equal to or greater than the lower limit of quantitation (LLOQ) and  $\geq 1:5$ , for each MenB indicator strain at each applicable blood draw time point and for Groups I, II, and III.

For the main immunogenicity objective, the following parameters were considered:

- (1) - (3) For each of the indicator strains, 44/76 SL, 5/99, and NZ98/254, proportion of subjects in Group III achieving at least 4-fold increase in (b)(4)-hSBA titer from baseline to one month after the second vaccination.
- (4) Proportion of subjects in Group III achieving a composite (b)(4)-hSBA response defined as hSBA titer  $\geq$  LLOQ, for all three indicator strains combined at one month after the second vaccination.

More information on immunogenicity endpoints and parameters can be found in the Dr. Anuja Rastogi’s clinical review.

### 6.4.9 Statistical Considerations and Statistical Analysis Plan

#### Primary objective

For each formulation of ---(b)(4)---- vaccine, the hypotheses were defined as follows:

$$\begin{aligned} (b)(4): & \text{-----} (b)(4) \text{-----}, \\ (b)(4) & \text{-----} (b)(4) \text{-----}, \end{aligned}$$

where --(b)(4)--- denotes the percentage of subjects with seroresponse after administration of two doses of ---(b)(4)----- at one month after the second vaccination, and  $p_{\text{MenACWY}}$  is the percentage of subjects with seroresponse one month after administration of one dose of MenACWY.

#### The second primary objective

The second primary objective was related to the identification of the optimal formulation of the ---(b)(4)---- vaccine. No formal hypothesis was associated with this objective. According to the applicant, justification of the optimal formulation was to be based on the ranks obtained from the estimation of the overall desirability index according to the predefined weights (for different estimates) for both formulations.

Note that the overall desirability index (multi-criteria optimization) was based on the immunogenicity parameters (GMT ratios against *N. meningitidis* serogroups A, C, W-135, and Y, and serogroup B test strains at 30 days after the second vaccination) and reactogenicity parameters (related to an association of vaccine formulation with severe local and severe systemic solicited adverse events [AEs] following any vaccination).

#### *Method of hypothesis testing*

According to the applicant, the non-inferiority hypotheses underlying the co-primary objectives were to be tested by a stepwise approach. First, the non-inferiority of -----(b)(4)----- vaccine with respect to MenACWY would be assessed (4 hypotheses). Following confirmation of this non-inferiority, the next 4 hypotheses of non-inferiority of -----(b)(4)----- would be tested.

The pre-defined hypotheses were related to the primary objectives, which are not related to the objective of the current BLA. Therefore, these hypotheses were not evaluated in this review, but very short information on the results is reported later in this review. Descriptive analyses of immunogenicity against serogroup B indicator strains are, however, presented in this review.

#### **6.4.10 Study Population and Disposition**

##### *Demographic characteristics*

At baseline, demographic and other characteristics of the enrolled subjects were balanced across the four vaccination study groups. Gender ratios were similar across the vaccine groups. Males constituted about 48% of subjects. The majority of subjects were Caucasian (61%), 32% were Hispanic, 5% were Black, and the remainder were Asian or other ethnicities. The median age was 13 years; the minimum age in each group was 10 years; and the maximum was 24 or 25 years. Note that 50% of subjects were below 13 years of age. The younger age group (10 to < 18 years old) constituted 70% of the subjects. Other baseline characteristics such as mean weight and height were balanced across the vaccine groups.

##### *Disposition of subjects*

The actual number of subjects enrolled was 484. Of these, a total of 480 subjects received at least one vaccination and were analyzed.

A summary of the randomized subject disposition is presented in Table 39.

Table 39: Randomized Subject Disposition

Disposition of Subjects	Group I n(%)	Group II n(%)	Group III (rMen+OMV NZ) n(%)	Group IV n(%)
<b>Randomized</b>	120	121	<b>122</b>	121
Withdrawal due to adverse event	0 (0%)	0 (0%)	<b>1 (&lt;1%)</b>	3 (<1%)
Withdrawal due to protocol violation	0 (0%)	1 (<1%)	<b>0 (0%)</b>	0 (0%)
Withdrawal due to withdrawn consent	2 (2%)	6 (5%)	<b>2 (2%)</b>	2 (2%)
Withdrawal due to lost to follow-up	15 (13%)	14 (12%)	<b>15 (13%)</b>	10 (8%)
Withdrawal due to Other	0 (0%)	0 (0%)	<b>1 (&lt;1%)</b>	1 (<1%)
<b>Study Completed Visit 3</b>	<b>108 (90%)</b>	<b>110 (91%)</b>	<b>116 (95%)</b>	<b>110 (91%)</b>
<b>Study Completed Study</b>	<b>103 (86%)</b>	<b>100 (83%)</b>	<b>109 (89%)</b>	<b>107 (88%)</b>

Source: Based on Clinical Study Report, page 89

Forty subjects (8%) were withdrawn prematurely up to Visit 3 (day 91) inclusive, while 65 subjects (13%) were withdrawn before Day 241. The most common reasons for withdrawal were loss to follow-up (54 subjects (11%)) and withdrawal of consent (12 subjects (3%)). Two subjects in Group III (rMenB+OMV NZ) reported unsolicited AEs that led to premature withdrawal from the study. One subject developed convulsion on Day 60 after the first vaccination and was hospitalized. The AE was assessed as not related to the study vaccination. The subject withdrew from the study due to this SAE as the primary reason. Another subject developed generalized lymphadenopathy on Day 6 after the first vaccination. The AE was assessed as possibly related to vaccination. The subject was prematurely terminated from the study due to withdrawal of consent (primary reason) and due to the AE.

### Protocol Deviations

A major protocol deviation was defined as a deviation that was considered capable of having a significant impact on the immunogenicity data of a subject. All subjects with a major protocol deviation were excluded from the per-protocol sets (PPS) used for immunogenicity and desirability analyses. A summary of some protocol deviations is presented in Table 40.

Table 40: Summary of some Major Protocol Deviations

	Group I n(%)	Group II n(%)	Group III (rMen+OMV NZ) n(%)	Group IV n(%)
<b>Randomized</b>	120	121	<b>122</b>	121
Subjects with any Major Deviation	30 (25%)	36 (30%)	<b>30 (25%)</b>	45 (37%)
Subjects did not received the 1 <sup>st</sup> vaccine	0 (0%)	1 (<1%)	<b>2 (2%)</b>	1 (<1%)
Subjects did not received the 2 <sup>nd</sup> vaccine	11 (9%)	11 (9%)	<b>9 (7%)</b>	11 (9%)
Subject with Vaccination outside Window	5 (4%)	11 (9%)	<b>11 (9%)</b>	12 (10%)
Subject received forbidden vaccine	6 (5%)	4 (3%)	<b>1 (&lt;1%)</b>	4 (3%)
Subject did not comply blood draw schedule	6 (5%)	10 (8%)	<b>8 (7%)</b>	5 (4%)

Source: Clinical Study Report V102\_03, page 77

Of 484 enrolled subjects, 141 subjects (29% overall) had at least one major protocol deviation during the course of the study. The most common major deviations were noncompliance with protocol-specified time windows for vaccination (8% of enrolled subjects) or for blood draw (6% of enrolled subjects). In addition, 7% of enrolled subjects did not provide a completed diary card for assessment of solicited AEs after either the first or the second vaccination. Study groups differed in frequency of subjects with randomization failure, defined as receiving a wrong vaccination course. A higher frequency of this deviation in Group IV (Placebo/MenACWY) was caused by a reversal in order of vaccinations in 11 subjects at a single site (i.e., MenACWY was incorrectly administered as the first vaccination and placebo incorrectly administered as the second vaccination).

### 6.4.11 Immunogenicity Analyses

#### Immunogenicity Population

Immunogenicity populations considered in this review are presented in Table 41.

Table 41: Immunogenicity Populations

Population	Group I n(%)	Group II n(%)	Group III (rMen+OMV NZ) n(%)	Group IV n(%)
Enrolled	120	121	<b>122</b>	121
Vaccinated	120 (100)	120 (99)	<b>120 (98)</b>	120 (99)
Full Analysis Set for Immunogenicity (FASi)	104 (87)	105 (87)	<b>110 (90)</b>	105 (87)
Per Protocol set for Immunogenicity (PPSi)	90 (75)	85 (70)	<b>92 (75)</b>	76 (63)

Source: Clinical Study Report V102\_03, page 80

Four enrolled subjects (< 1%) did not receive the first vaccination. Thirty eight (8%) subjects received the first but not the second vaccination. As per the protocol, the second vaccination should be given in the time window 54 to 74 days after the first vaccination, and 403 (83%) subjects received the second vaccination within that time window. One subject received the second vaccination less than 54 days after the first vaccination, while 38 subjects (8%) received the second vaccination more than 74 days after the first vaccination.

#### 6.4.11.1 Analyses Related to Primary Endpoints

In this study, bactericidal antibody responses to each of the major vaccine antigens in rMenB+OMV NZ were measured using (b)(4)-hSBA (the ---(b)(4)----- assays for serum bactericidal activity using human complement). However, validation of this assay and relationship between this assay and hSBA assay are still unknown. Therefore, the interpretation of the immune responses data generated by the (b)(4)-hSBA assay is not completely univocal.

The following serogroup B test strains were used in this study, each selected to test the antibody response to a single antigen: --(b)(4)-- (fHbp), ---(b)(4)----- (NHBA), ----(b)(4)---- (NadA), and NZ98/254 (PorA). Two additional serogroup B test strains, 44/76-SL (fHbp) and 5/99 (NadA), were also used. But for evaluation of the immune response to the candidate vaccine, only three strains were taken into account, NZ98/254 (PorA), 44/76-SL (fHbp), and 5/99 (NadA), as these strains were evaluated in other studies as well.

Primary immunogenicity hypothesis

The null hypotheses associated with the study’s first primary immunogenicity objective were to demonstrate the non-inferiority of the immune responses to 2 doses of 2 different formulations of ---(b)(4)----- vaccine as compared to immune response to a single dose of MenACWY (Menveo), as measured by the percentage of subjects with (b)(4)-hSBA seroresponse against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after the second vaccination. Two doses of -----(b)(4)----- vaccine were considered non-inferior to a single dose of MenACWY if the lower limit of the 2-sided 95% CI for the difference of the percentages of subjects with a seroresponse for two study groups --(b)(4)-- and Placebo/ACWY, was greater than -10% for each serogroup. Results of the hypotheses testing related to the non-inferiority of 2 doses of (b)(4) different formulations of ---(b)(4)----- vaccine to a single dose of MenACWY (Menveo) are presented in Table 42.

Table 42: Results of Testing the Primary Hypothesis Related to Non-inferiority - PP Population

Non-inferiority of -----(b)(4)----- to MenACWY

Serogroup	Group I ----(b)(4)----- Seroresponse	Group I ----(b)(4)----- 95% CI	Group IV ACWY Seroresponse	Group IV ACWY 95% CI	Diff. Group I – Group IV	Diff. 95% CI
MenA	90%	(81%, 95%)	73%	(62%, 83%)	16%	(5%, 29%)
MenC	95%	(89%, 99%)	63%	(51%, 74%)	32%	(21%, 44%)
MenW-135	80%	(69%, 88%)	65%	(52%, 77%)	15%	(0%, 30%)
MenY	92%	(83%, 97%)	75%	(62%, 85%)	18%	(5%, 31%)

Source: Based on the applicant’s table, CSR V102\_03, page 87

Non-inferiority of ----(b)(4)----- to MenACWY

Serogroup	Group 1 ----(b)(4)----- Seroresponse	Group 1 ----(b)(4)----- 95% CI	Group IV ACWY Seroresponse	Group IV ACWY 95% CI	Diff. Group I – Group IV	Diff. 95% CI
MenA	92%	(83%, 97%)	73%	(62%, 83%)	18%	(7%, 30%)
MenC	93%	(85%, 97%)	63%	(51%, 74%)	30%	(18%, 42%)
MenW-135	84%	(73%, 91%)	65%	(52%, 77%)	19%	(4%, 33%)
MenY	90%	(80%, 96%)	75%	(62%, 85%)	15%	(3%, 29%)

Source: Based on the applicant’s table, CSR V102\_03, page 87

**Reviewer’s Comments**

*The non-inferiority criteria for two vaccine formulation comparisons were met; all 8 comparisons of the null hypothesis were rejected. Moreover, the immune responses against serogroups A, C, W-135, and Y were statistically higher after 2 doses of each of the ---(b)(4)----- formulations than after a single dose of the MenACWY (Menveo) vaccine, as the lower limits of the 2-sided 95% CIs for the difference between study groups were greater than 0%.*

*Based on Table 42, no notable differences between seroresponse rates of 2 different formulations of ---(b)(4)----- vaccine were observed.*

The second primary objective concerned identification of the optimal vaccine formulation. The desirability approach was used for selection of the optimal formulation of the ---(b)(4)----- vaccine. Eight immunogenicity parameters (GMT ratios for each ---(b)(4)-- group and the appropriate comparator group) and 2 reactogenicity parameters (percentages of doses associated with severe local and systemic solicited AEs after any vaccination) were selected as parameters for the desirability model. It appears that the differences between the overall desirability indexes for different weighting schemes of the ---(b)(4)----- formulations were small.

**Reviewer’s Comments**

*Desirability analysis, based on combined immunogenicity and reactogenicity parameters, did not differentiate between the -----(b)(4)-----formulations. However, there was a trend of higher GMT responses against the serogroup B NHBA, NadA, and PorA test strains for the ---(b)(4)----- formulation.*

**6.4.11.2 Analyses related to Secondary Endpoints**

Results of analyses for the estimated GMTs one month after the second dose of rMenB+OMV NZ vaccine are presented in Table 43.

Table 43: Estimates of hSBA GMTs for rMenB+OMV Group and Per Protocol Set

Strain	Sampling Time Point	Number of Subjects	Estimation of GMT	95% CI
44/76-SL	Month 0	92	1.25	(1.02, 1.53)
<b>44/76-SL</b>	<b>Month 3</b>	<b>92</b>	<b>102</b>	<b>(77, 134)</b>
5/99	Month 0	92	2	(1.49, 2.7)
<b>5/99</b>	<b>Month 3</b>	<b>92</b>	<b>352</b>	<b>(266, 466)</b>
NZ98/254	Month 0	92	1.21	(1.04, 1.42)
<b>NZ98/254</b>	<b>Month 3</b>	<b>92</b>	<b>19</b>	<b>(13, 27)</b>

Source: Based on the applicant’s table, CSR V102\_03, page 277

Table 43 demonstrates that increases in the GMTs against all indicator strains (82-fold for H44/76, 179-fold for 5/99, and 16-fold for NZ98/254) were observed in the rMenB+OMV group at 1 month after the second dose of the rMenB+OMV NZ vaccine.

Table 44 presents percentages of subjects achieving hSBA titer  $\geq$  LLOQ (as defined by the Agency) at baseline and 1 month after the second vaccination with rMenB+OMV NZ.

Table 44: Immune Responses (% of Subjects with hSBA  $\geq$  LLOQ) to rMenB+OMV NZ at Baseline and after the Second Dose - PP Set

Strain	Sampling Time Point	Number of Subjects	% of Subjects with hSBA $\geq$ 1:LLOQ	95% CI
44/76-SL	Month 0	92	4	(1, 11)
<b>44/76-SL</b>	<b>Month 3</b>	<b>92</b>	<b>95</b>	<b>(88, 98)</b>
5/99	Month 0	92	7	(2, 14)
<b>5/99</b>	<b>Month 3</b>	<b>92</b>	<b>98</b>	<b>(92, 100)</b>
NZ98/254	Month 0	92	3	(1, 9)
<b>NZ98/254</b>	<b>Month 3</b>	<b>92</b>	<b>77</b>	<b>(67, 85)</b>

Source: The reviewer's table based on Amendment 0.17, page 15

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

### 6.4.11.3 Analyses related to Exploratory Endpoints

According to the (b)(4)-hSBA validation reports, based on tests conducted at ---(b)(4)---, the LLOQs are 1:8 for the NZ98/254 strain, and 1:16 for the H44/76 and 5/99 strains.

The main exploratory immunogenicity objectives were to assess immune response to the rMenB+OMV NZ vaccine using the following parameters:

- Proportion of subjects with 4-fold or greater increase in (b)(4)-hSBA titer for each of the three indicator strains (NZ98/254, H44/76, and 5/99) at one month after the second vaccination, and
- Proportion of subjects who achieved a titer greater than or equal to LLOQ for all three strains (composite response) at one month after the second vaccination.

Results of statistical assessments for the main exploratory immunogenicity objectives, performed for the PP immunogenicity population, are presented in Table 45.

Table 45: Results for the Main Immunogenicity Exploratory Objectives - PP Set

Variables	Strain	# of subjects	Estimation of endpoint	95% CI
hSBA Titer 4-fold rise	H44/76	92	79%	(85, 97)
hSBA Titer 4-fold rise	5/99	92	94%	(92, 100)
hSBA Titer 4-fold rise	NZ98/54	92	67%	(50, 71)
Composite hSBA response	For three indicator strains	92	75%	(65, 83)

Source: The reviewer's table based on Amendment 0.17, page 8 and Amendment 25, page 20

Note: LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.

Note: The 4-fold increase is defined as: a post-vaccination hSBA  $\geq 1:16$  for subjects with pre-vaccination hSBA  $< 1:4$ , a post-vaccination titer at least 4-fold the LLOQ for subjects with pre-vaccination hSBA  $\geq 1:4$  but  $< LLOQ$ , and a post-vaccination 4-fold rise for subjects with pre-vaccination hSBA  $\geq LLOQ$ .

Note that the proportion of subjects achieving a titer greater than or equal to LLOQ for all three strains (composite response) one month after the second vaccination, assessed based on the FASi, is similar to the proportion assessed based on the PP set.

#### 6.4.12 Subgroup Analyses

The applicant performed some statistical analyses to investigate possible influence of the categorical factor age (10-18, 19-25), and gender on the immune responses.

Tables 46 and 47 display results of statistical analyses related to the possible influence of age and gender on immune responses measured by hSBA GMTs for *N. meningitidis* serogroup B test (indicator) strains, and the pre- to post-vaccination GMT ratios after the 2<sup>nd</sup> dose of the rMenB+OMV NZ vaccine.

Table 46: hSBA GMTs and GMRs with Corresponding 95% CIs after the Second Dose of rMenB+OMV NZ - PP Set and by Age Group

Strain	Factor Age Group	Number of Subjects	Estimation of GMT	GMT 95% CI	Estimation of GMR	GMR 95% CI
44/76-SL	10-18	79	124	(96, 159)	119	(93, 100)
<b>44/76-SL</b>	<b>19-25</b>	<b>31</b>	<b>75</b>	<b>(51, 110)</b>	<b>34</b>	<b>(20, 54)</b>
5/99	10-18	79	344	(275, 430)	191	(137, 265)
<b>5/99</b>	<b>19-25</b>	<b>31</b>	<b>267</b>	<b>(197, 362)</b>	<b>118</b>	<b>(73, 191)</b>
NZ98/254	10-18	79	19	(14, 24)	18	(13, 23)
<b>NZ98/254</b>	<b>19-25</b>	<b>31</b>	<b>23</b>	<b>(12, 44)</b>	<b>12</b>	<b>(7, 22)</b>

Source: The reviewer's table based on CSR V102\_03, pages 3847-3852

Table 47: hSBA GMTs and GMRs) with Corresponding 95% CIs after the Second Dose of rMenB+OMV NZ – PP Set and by Gender

Strain	Factor Gender	Number of Subjects	Estimation of GMT	GMT 95% CI	Estimation of GMR	GMR 95% CI
44/76-SL	Female	57	103	(76, 140)	76	(53, 109)
<b>44/76-SL</b>	<b>Male</b>	<b>53</b>	<b>112</b>	<b>(84, 151)</b>	<b>93</b>	<b>(67, 130)</b>
5/99	Female	57	304	(233, 397)	133	(88, 201)
<b>5/99</b>	<b>Male</b>	<b>53</b>	<b>339</b>	<b>(263, 436)</b>	<b>213</b>	<b>(151, 300)</b>
NZ98/254	Female	57	21	(15, 31)	17	(12, 25)
<b>NZ98/254</b>	<b>Male</b>	<b>53</b>	<b>18</b>	<b>(13, 27)</b>	<b>15</b>	<b>(10, 21)</b>

Source: The reviewer's table based on CSR V102\_03, pages 3935-3940

Based on Tables 46 and 47, it can be concluded that, due to higher GMTs for males and for the younger age group, gender and age may have influence on the immune response to the rMenB+OMV NZ vaccine against the 44/76-SL and 5/99 indicator strains. However, the statistical analyses evaluating the possible influence of gender and age on the immune responses (GMTs, GMRs) after the 2<sup>nd</sup> dose of the rMenB+OMV NZ vaccine were *post-hoc* in nature. Therefore, differences observed (if any) should be considered accordingly.

Moreover, in Amendment 0.17, the applicant showed that percentages of subjects with hSBA titer  $\geq$  LLOQ across the three strains for male and female subjects were similar at one month after the second vaccination.

**Reviewer's comments and overall conclusions on immunogenicity results related to study V102\_03**

- *Analyses for the study's first primary objectives showed that the immune responses to 2 doses of (b)(4) formulations of the ---(b)(4)---- vaccines were non-inferior to responses to a single dose of the MenACWY vaccine, as measured by percentages of subjects with seroresponse against all 4 serogroups at Day 30 after the second study vaccination.*
- *“Desirability analysis,” based on combined immunogenicity and reactogenicity parameters, did not differentiate between the ---(b)(4)----- formulations. However, there was a trend of higher GMT responses against the serogroup B NHBA, NadA, and PorA test strains for the -----(b)(4)-----formulation compared to -----(b)(4)-----*
- *Assessments of the immune response to the rMenB+OMV NZ vaccine based on GMTs showed apparent increases in the GMTs against all indicator strains at one month after the second vaccination.*
- *Results of statistical analyses related to possible influence of gender on immune responses to the rMenB+OMV NZ vaccine at one month after the second*

*vaccination, as measured by the percentages of subjects with hSBA titer  $\geq$  LLOQ, showed no notable differences (across three strains) between the male and female subjects at one month after the second vaccination.*

- *Bactericidal antibody responses to each of the major vaccine antigens in rMenB+OMV NZ were measured, in this study, using (b)(4)-hSBA (the -----(b)(4)----- assay for serum bactericidal activity using human complement). However, validation of this assay and relationship between this assay and the hSBA assay are still not fully known. Therefore, interpretation of the data generated by the (b)(4)-hSBA assay is not completely univocal.*
- *The assessment of the immune responses to the rMenB+OMV NZ vaccine was based only on 3 MenB indicator strains. Therefore, data generated by this study were not anticipated to assess the breath of protection against MenB meningococcal disease.*
- *Based on data generated by study V102\_03 and related to the main immunogenicity exploratory endpoints, the rMenB+OMV NZ vaccine elicited immune responses expressed for the three MenB indicator strains.*

## **6.5 Trial #5: V72P10E1**

Note: Only a brief treatment of study V72P10E1 is presented in this review, because this study was the extension of study V72P10 to evaluate persistence of immune response. However, the persistence of the immune response in rMenB01 and rMen02 groups, as measured by percentage of subjects with hSBA  $\geq$  LLOQ, is relevant to the objective of this BLA.

***Title of Study:** “A Phase 2b/3, Multi-Center, Extension Study of V72P10 to Assess Antibody Persistence at Eighteen Months after the Completion of the Vaccination Course in Study V72P10”*

**Date of first enrollment:** August 5, 2010

**Study Completion Date:** January 17, 2012 (the last subject visit)

### *Study design*

Study V72P10E1 was a Phase 2b/3, multi-center, extension of study V72P10. Subjects who participated and completed the vaccination course of study V72P10 and who met all other enrollment criteria for this extension study were eligible for enrollment. An additional group of vaccine-naïve subjects of similar age were recruited from the same study sites. No investigational vaccine was administered in this extension study. The study groups and populations analyzed are presented in Table 48.

Table 48: Overview of Populations Analyzed

Group	# of subjects in V72P10 Enrolled Population	# of subjects in V72P10E1 Enrolled Population	# of subjects in V72P10E1 MITT Population	# of subjects in V72P10E1 PP Population
rMenB06	128	49	49	47
rMenB0	247	95	95	88
rMenB016	128	53	53	53
rMenB01	247	102	102	92
rMenB026	127	57	57	53
rMenB02	253	106	106	100
rMenB012	373	153	153	148
rMenB6	128	51	51	47
Naïve	NA	151	151	151

Source: CSR V72P10E1, page 49

Overall, 817 subjects (about 50% of the V72P10 enrolled population) who participated and completed the vaccination course of study V72P10 met all enrollment criteria and were enrolled into the extension study. The additional group of vaccine-naïve subjects consisted of 151 enrollees.

### Objectives

#### Immunogenicity Objective:

- ✓ To explore antibody persistence at eighteen months after the completion of the vaccination course in subjects enrolled in the V72P10 study.

#### Safety Objective:

- ✓ There was no safety objective in this study, as only a blood draw took place.

### Study Endpoints and parameters

Immunogenicity of the rMenB+OMV NZ vaccine was assessed at least 18 months after the last vaccination by performing measurements against strains H44/76, 5/99, NZ98/254, and ---(b)(4)--- by hSBA and against antigen 287-953 by (b)(4). The hSBA assays for all three indicator strains were performed by the Meningococcal Reference Unit of the -----(b)(4)-----, and tests against the ---(b)(4)-- strain were carried out at the Novartis Vaccines ---(b)(4)-- laboratories.

Immunogenicity endpoint was:

- ✓ Titers at least 18 months after completion of vaccination in the parent study.

Immunogenicity parameters (variables) were:

- ✓ Proportions of subjects with hSBA titers equal to or greater than the lower limit of quantitation (LLOQ), 1:4, and 1:8 for each of the available (indicator and additional) strains and at the blood draw time point, and
- ✓ hSBA geometric mean titers (GMTs) for each of the available (indicator and additional) strains and at the blood draw time point.

### *Demographic Characteristics*

As per the applicant, demographic and baseline age, ethnicity, weight, and height characteristics were balanced across all MenB vaccinated groups and the vaccine-naive group. The mean age of the enrolled subjects was  $15.9 \pm 1.9$  years. The percentage of female subjects was higher in the “follow-on” from study V72P10 groups, while a higher percentage (60%) of male subjects were enrolled into the vaccine-naive group.

### *Immunogenicity Results*

The antibody persistence after at least 18 months from the completion of vaccination in the parent study was assessed in 8 “follow-on” from study V72P10 vaccine groups that consisted of subjects who previously obtained 1, 2, or 3 doses of rMenB+OMV NZ administered on different schedules. The persistence of bactericidal response was compared with immunogenicity data for vaccine-naive subjects of similar ages (approximately 13 through 19 years of age).

**Note:** Due to different vaccination schedules in parent study V72P10, the persistence interval after the last rMenB+OMV NZ vaccination in the parent study varied for each vaccine group. For groups rMenB016, rMenB026, rMenB06, and rMenB6 which received the rMenB+OMV NZ vaccine at Month 6 in the V72P10 study, the persistence interval was 18 months. For groups rMenB02 and rMenB012, which received the last rMenB+OMV NZ dose at Month 2, the persistence interval was about 22 months, while for rMenB01 (the last dose at Month 1) and rMenB0 (only one vaccine dose at Month 0) groups, the persistence intervals were about 23 and 24 months, respectively.

As per the protocol, the primary analyses performed on the antibody persistence data were related to the endpoint titer  $\geq 1:4$ , at 18 months from the completion of vaccination in the parent V72P10 study. For subjects who received 2 or 3 doses of rMenB+OMV NZ, hSBA titers  $\geq 1:4$  persisted in 73% to 92% of subjects against the H44/76-SL strain, in 65% to 100% of subjects against the 5/99 strain, and in 61% to 96% of subjects against the NZ98/254 strain. In the vaccine-naive group, subjects showing hSBA  $\geq 1:4$  were 50%, 25%, and 40% against the H44/76-SL, 5/99, and NZ98/254 strains, respectively.

The results on persistence of immune response in the rMenB01 and rMen02 groups are presented in Table 49.

Table 49: Persistence of the Immune Response as Measured by Percentages (95% CI) of Subjects with hSBA Titer  $\geq$  LLOQ after a 2-Dose Regimen of rMenB+OMV NZ – MITT population

For rMenB02 group

Variables	Blood Drawing Time Point	Strain	# of subjects	Estimation of endpoint	95% CI
% of subjects with $\geq$ LLOQ	Month 22	H44/76	106	68%	(58, 77)
% of subjects with $\geq$ LLOQ	Month 22	5/99	106	87%	(79, 93)
% of subjects with $\geq$ LLOQ	Month 22	NZ98/254	106	50%	(40, 60)

Source: The reviewer's table based on the applicant's Table 5-3, Integrated Summary of Efficacy, page 87

Note: LLOQ = 1:16 for H44/76; for 1:8 5/99; 1:16 for NZ98/254.

For rMenB01 group

Variables	Blood Drawing Time Point	Strain	# of subjects	Estimation of endpoint	95% CI
% of subjects with $\geq$ LLOQ	Month 23	H44/76	102	61%	(51, 70)
% of subjects with $\geq$ LLOQ	Month 23	5/99	102	87%	(79, 93)
% of subjects with $\geq$ LLOQ	Month 23	NZ98/254	102	49%	(39, 59)

Source: The reviewer's table based on the applicant's Table 5-3, Integrated Summary of Efficacy, page 87

Note: LLOQ = 1:16 for H44/76; for 1:8 5/99; 1:16 for NZ98/254.

In the vaccine-naive group (at the baseline), percentages of subjects showing hSBA titer  $\geq$  LLOQ were 23%, 19%, and 17% against the H44/76-SL, 5/99, and NZ98/254 strains, respectively.

**Reviewer's comments and overall conclusions on immunogenicity results related to study V72P10E1**

- Study V72P10E1 demonstrated existence of immunogenicity persistence against the 3 indicator antigenic strains H44/76, 5/99, and NZ98/254 of *N. meningitidis* in subjects at 18 to 24 months after the last rMenB+OMV NZ vaccine dose in study V72P10, irrespective of the vaccination schedule, when compared with the vaccine-naive subjects.
- The applicant did not demonstrate that the persistence cohort of study V72P10E1 was statistically similar to the enrolled population in the parent study V72P10. An appropriate assessment of the representativeness of the persistence cohort for study V72P10E1 would need to be carried out with respect to not only demographic characteristics, but also immunogenicity factors and occurrence of safety events as well. The results of study V72P10E1 related to persistence should be considered accordingly.

## 6.6 Supportive Studies

### General information

The applicant submitted in BLA 125546.0 data from clinical trials V72P13 and V72P16 in support of the lot-to-lot consistency and the dosing regimen, respectively.

Two other supportive clinical trials V72P4 (Phase 2) and V72P5 (Phase 1) were also included in the BLA. Overall, only 124 subjects were vaccinated in these 2 supportive studies.

### 6.6.1 Study V72P13

*Title: “A Phase 3, Partially Blinded, Randomized, Multi-Center, Controlled Study to Evaluate Immunogenicity, Safety, and Lot to Lot Consistency of Novartis Meningococcal B Recombinant Vaccine When Administered with Routine Infant Vaccinations to Healthy Infants”*

This clinical trial was conducted at many sites: 16 in Finland, 28 in the Czech Republic, 13 in Germany, 6 in Austria, and 7 in Italy.

#### *Main Study Objectives*

- ✓ To show the consistency of immune responses to the rMen+OMV NZ vaccine originated from 3 different lots, as measured by hSBA GMTs at 1 month after the third vaccination, when administered to healthy infants at 2, 4, and 6 months of age.
- ✓ For 3 lots combined, to assess the immunogenicity of 3 doses of rMenB+OMV NZ given to healthy infants at 2, 4, and 6 months of age concomitantly with routine infant vaccines, by evaluation of the serum bactericidal activity (hSBA) at 1 month after the third vaccination.

#### *Study design*

Study V72P13 was a Phase 3, partially blinded, multi-center, randomized, controlled study in healthy infants in Europe (Italy, Germany, Austria, Finland, and the Czech Republic). Subjects meeting the enrollment criteria were assigned to one of five vaccination groups at a ratio 4:4:4:3:3. Subjects in rMenB Lot 1, rMenB Lot 2, and rMenB Lot 3 groups received one dose of rMenB+OMV NZ from Lot 1, Lot 2, and Lot 3, respectively, at 2, 4, and 6 months of age concomitantly with the routinely administered infant vaccines (Infanrix Hexa® and Prevenar®). The Routine group received only the routinely administered infant vaccines at 2, 4, and 6 months of age. The MenC+Routine group received the routinely administered infant vaccines plus Menjugate® at 2, 4, and 6 months of age.

A total of 3630 subjects were enrolled and 3499 completed the study. Overall, 131 subjects withdrew from the study due to AEs, consent withdrawal, loss to follow up, and protocol deviations. No deaths were reported in this study.

Caucasians constituted 99% of the subjects. Gender, age, height, and weight distributions were similar across the vaccination groups.

Subjects for the open-label immunogenicity subset (N=1282) of this study were enrolled in the Czech Republic and Finland. They were randomized in a 1:1:1:1 ratio to the rMenB+OMV NZ Lot 1, rMenB+OMV NZ Lot 2, rMenB+OMV NZ Lot3 groups, or to the routine vaccinations only group. Blood samples were obtained from these subjects for serology testing at baseline and 1 month after the third vaccination visit.

For testing the primary hypotheses, the applicant randomly selected a subset of about 400 subjects in each rMenB (Lot 1, Lot2, Lot3) group, for whom immunogenicity hSBA tests were performed against indicator strains H44/76, 5/99, and NZ98/254. A randomly selected subset of 120 subjects in the routine group had immunogenicity hSBA tests performed for all three MenB indicator strains to assess the presence of maternal antibodies.

Lot-to-lot consistency

The primary immunogenicity hypotheses are related to the clinical lot-to-lot consistency. To support the hypotheses, the applicant was to demonstrate that vaccines drawn from three vaccine lots -- Lot 1 (X38D27N1), Lot 2 (X38D28N1), and Lot 3 (X38D29N1) -- elicited equivalent immune responses. For pair-wise comparisons, the 95% CIs of the ratios of post-vaccination GMTs for two groups, after the 3<sup>rd</sup> dose vaccination and for each indicator strain, should be entirely within the interval (0.50, 2.00). A summary of the results for the lot-to-lot consistency is presented in Table 50.

Table 50: Lot-to-Lot Consistency Results

Estimates of GMTs (95% CIs) per Lot and Strain

Strain	Lot 1 # of subjects	Lot 1 GMT (95%CI)	Lot 2 # of subjects	Lot 2 GMT (95%CI)	Lot 3 # of subjects	Lot 3 GMT (95%CI)
H44/76	384	87 (80, 95)	379	98 (90, 106)	394	85 (78, 93)
5/99	385	598 (550, 651)	380	681 (626, 741)	390	607 (558, 661)
NZ98/54	386	15 (13, 17)	380	14 (12, 16)	394	15 (14, 17)

Source: CSR V72P13, page 94

Estimates of GMTs Ratios (95% CI) per Strain

Strain	Lot 1 vs. Lot 2 GMTs ratio (95%CI)	Lot 1 vs. Lot3 GMTs ratio (95%CI)	Lot 2 vs. Lot 3 GMTs ratio (95%CI)
H44/76	0.9 (0.81, 0.99)	1.02 (0.93, 1.13)	1.14 (1.03, 1.27)
5/99	0.88 (0.78, 0.98)	1.01 (0.92, 1.1)	1.12 (1.0, 1.26)
NZ98/54	1.04 (0.88, 1.23)	0.96 (0.81, 1.13)	0.92 (0.78, 1.08)

Source: CSR V72P13, page 94

**Reviewer’s conclusion**

Three investigated lots in clinical trial V72P13 achieved the pre-defined criteria for lot-to-lot consistency, *which* required that the 95% CI of the ratio of post-vaccination GMTs for two lots, after the 3<sup>rd</sup> dose and for each indicator strain, be entirely within the interval (0.5, 2.0).

**6.6.2 Study V72P16**

**Title of Study:** “A Phase 2 Partially Observer-Blind Randomized Controlled Multicenter Dose-Ranging and Formulation-Finding Study of a new Novartis Meningococcal B Recombinant Vaccine evaluating the safety and immunogenicity when given concomitantly with routine vaccines in 2-month-old infants”

*Study Centers*

The clinical trial was carried out in 79 sites in the Czech Republic (subjects were enrolled only in 71 sites, while 8 sites had a coordinating role only), in 8 sites in Hungary, in 6 sites in Italy, and in 1 site each in Argentina and Chile.

*Main Primary Objective*

To assess if any of the seven different formulations of rMenB+OMV NZ or rMenB (without OMV) vaccines induced sufficient immune response when given to healthy infants at 2, 3, and 4 months of age, as measured by the percentage of subjects with serum bactericidal activity (SBA) titer  $\geq 1:5$  at 1 month after the third vaccination.

*Study design*

A total of 1507 infants were enrolled into the clinical trial and were randomized in 1:1:1:1:1:1:1:1 ratio into one of eight study groups as shown in Table 51.

Table 51: Study Groups with Different Vaccine Formulations

Group	Vaccine Type	Formulation
rMenB+ OMV	rMenB+OMV NZ	150µg of rMenB proteins, 25µg of OMV
rMenB (+¼OMV)	rMenB+OMV NZ	150µg of rMenB proteins, 12.5µg of OMV
rMenB+½ OMV	rMenB+OMV NZ	150µg of rMenB proteins, 6.25µg of OMV
rMenB no OMV	rMenB	150µg of rMenB proteins
½ dose rMenB+½ OMV	rMenB+OMV NZ	75µg of rMenB proteins, 12.5µg of OMV
rMenB+OMV	rMenB+OMV NZ	150µg of rMenB proteins, 25µg of OMV (manufactured according to Phase 2 process)
Meningococcal C Conjugate Vaccine	Menjugate®	
rMenB+OMV with Prophylactic Paracetamol	rMenB+OMV NZ	150µg of rMenB proteins, 25µg of OMV

Source: Table based on the study protocol V72P16

Randomization of eligible subjects was performed after the parent(s) or legal guardian(s) had given their written informed consent. Subjects received either three doses of one of the investigational vaccines containing meningococcal B antigens in B+OMV, B+½OMV, B+¼OMV, and B groups or three doses of meningococcal C vaccine as primary vaccination in the control MenC group. Subjects in all groups received routine infant vaccines (InfanrixHexa and Prevenar) at the same time they received the study vaccination.

### *Immunogenicity Result*

As per the applicant, one month after the three-dose infant series, 99%-100% of the subjects treated with the seven different formulations of rMenB with or without OMV achieved sufficient immune responses in terms of the percentage of subjects with hSBA  $\geq$  1:5 against the reference strains 44/76-SL and 5/99. However, only the vaccine groups in which a formulation containing a full dose of OMV (25µg of OMV) was given demonstrated a sufficient (per the applicant) primary immune response (95%LCL  $\geq$ 65%) against the NZ98/254 strain, as measured by the percentage of subjects with hSBA titer  $\geq$  1:5.

The following is worth noting about the immunogenicity one month after the primary vaccination course:

- The hSBA GMTs against reference strains 44/76-SL and 5/99 appear to have increased from baseline for all seven different formulations.
- There was a trend of lower GMT responses for groups rMenB and ½(rMenB+OMV) against strain 44/76-SL, and for group ½(rMenB+OMV) against strain 5/99, as compared to other formulations.
- The antibody response against the NZ98/254 strain was relatively low and was dependent on the OMV dose. The vaccine groups receiving formulations containing the full OMV content showed generally higher antibody responses (GMR 8.69 to 10) than the vaccine groups receiving formulations with the reduced doses of OMV.

### **Reviewer's conclusion**

*Based on immunogenicity data from clinical trial V72P16, the applicant selected the final formulation of the candidate rMenB+OMV NZ vaccine, and decided to use the full dose (25µg) of OMV.*

### **6.6.3 Study V72P4**

***Title of Study:*** “A Phase 2, Multi-Center, Open-label Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered at a 0, 2, 6-Month Schedule and of a Single dose of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy At-risk Adults 18-50 Years of Age”

### *Study Centers*

The clinical trial was carried out at one site in Italy and one site in Germany.

### *The Main Immunogenicity Objectives*

- To explore the immunogenicity of three doses of rMenB + OMV NZ in healthy at-risk adults, by evaluation of the breadth of serum bactericidal activity using human complement response against a panel of genetically distinct meningococcal strains, at one month after administration of the first, second, and third dose, and immediately before administration of the third dose.

### *Study Design*

The V72P4 clinical trial was a Phase 2, open-label, multi-center study in healthy at-risk adults routinely exposed to *N. meningitidis*, and was designed to explore the immunogenicity and safety of three doses of rMenB + OMV given on a 0, 2, and 6 months schedule, and a single dose of MenACWY conjugate vaccine given at study Month 7.

A total of 54 subjects were enrolled, while 53 were vaccinated and 48 completed the study. The immunogenicity analysis was performed on the per protocol (PP) population, which included 46 (85%) subjects.

### *Summary of Immunogenicity Results*

The results demonstrated that the rMenB+OMV NZ vaccine induced bactericidal antibodies in adults following 2 doses, given at 0 and 2 months, as measured by hSBA GMT against the 3 MenB indicator strains, H44/76, 5/99, and NZ98/254. It appears that the third dose at 6 months may not provide added benefit. For strains H44/76 and NZ98/254, the GMTs were similar following the second and third doses of rMenB+OMV NZ (93 and 95 for H44/76, 32 and 30 for NZ98/254). For strain 5/99, the GMTs were high following the second dose (144) and increased further after the third dose (269).

### **Reviewer's conclusion**

*It is difficult to draw a definitive conclusion from results of study V72P4 due to a small number (46) of evaluable subjects and the open-label, non-randomized study design.*

### **6.6.4 Study V72P5**

***Title of the Study:*** “A Phase 1, Observer Blind, Single-center, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine +/- OMV When Administered at a 0, 1, 2-Month Schedule in Healthy Adults 18-40 Years of Age”

### *Study Center*

Clinical trial V72P5 was carried out in one center, namely, the Institute for Pharmacokinetic and Analytical Studies, Ligornetto, Switzerland.

### *Main immunogenicity objective*

“To explore the immunogenicity of three dose of Meningococcal B Recombinant vaccine +/- OMV in healthy adults at 30 days after the third dose, by evaluation of the breadth of bactericidal activity (BCA) response against a panel of genetically distinct meningococcal strains.”

### *Study Design*

Clinical trial V72P5 was a Phase I, observer-blind, single-center, randomized study conducted in Switzerland in healthy adults. This was the first study to explore the safety and immunogenicity of rMenB formulation with OMV purified from *N. meningitidis* serogroup B strain NZ98/254 in healthy adults. A cohort of healthy adults 18 through 40 years of age was randomized in a 2:2:1 ratio to one of the following three groups:

**Group I – rMenB+OMV NZ** (Novartis Meningococcal B Recombinant Vaccine + OMV New Zealand (NZ)), 26 subjects

**Group II - rMenB + OMV (b)(4)** (Novartis Meningococcal B Recombinant Vaccine + OMV ----(b)(4)-----, 26 subjects

**Group III – rMenB** (Novartis Meningococcal B Recombinant Vaccine without OMV), 13 subjects.

A total of 70 adults were enrolled and received 3 doses of rMenB+OMV NZ, or rMenB+OMV (b)(4), or rMenB administered on a 0, 1, and 2-month schedule.

As per the study protocol, blood samples were collected for meningococcal serology (bactericidal activity and immunoglobulin G [IgG] antibody levels), and some clinical laboratory tests from all subjects at baseline and to assess any significant changes from the screening values, during the study. Additionally, blood samples were collected in a subset of 10 subjects per vaccination group at baseline and at 6 months after the third dose, to explore the ability of Novartis Meningococcal B Recombinant Vaccine +/- OMV to elicit long-term B cell memory responses.

### *Immunogenicity Results*

In this clinical trial, to assess serum bactericidal activity of the investigational vaccines, the applicant selected a panel of 15 MenB strains. According to the applicant, the criteria for selection of this panel included genetic diversity, clonal complexity, geographic distribution, PorA/B assortment, and year of isolation.

### *Summary of the main results of study V72P5*

Measurements of hSBA GMTs performed in study V72P5 showed increases in titers one month after the third vaccination, but GMTs of the same magnitude were observed already at 1 month after the second vaccination.

Memory B cells were measured for antigens 287-953, 936-741, and 961C for a subset of 10 subjects per vaccination group at baseline and 6 months after the third dose. The results indicate an increased frequency of B cells after 6 months, as compared to baseline, for antigens 936-741 and 961C.

### **Reviewer's conclusion**

*It appears that all three vaccines were immunogenic. However, the sample size in study V72P5 was too small, and the variation of measurement results was too large to permit drawing definitive conclusions.*

## **7. Integrated Overview of Efficacy**

### **7.1 Background**

The immunogenicity of the candidate rMenB+OMV NZ vaccine was evaluated in 9 clinical trials. A summary of the general information on these clinical studies is provided in Table 2. While all studies evaluated safety and immunogenicity of the rMenB+OMV NZ vaccine, some other issues such as dose selection (trial V72P4) as well as immunogenicity of 2- and 3-dose schedules were also investigated (e.g., trial V72P10). The applicant also submitted data from clinical trials V72P13 and V72P16 in support of the lot-to-lot consistency and the dosing regimen, respectively.

### **7.2 Demographic and Baseline Characteristics**

Across the studies, demographic and other baseline characteristics, such as gender, age, and country, of the evaluable immunogenicity populations were generally balanced between the rMenB+OMV NZ and control groups within each study (e.g., in trial V72P10). The ethnicity spectra of the subjects reflected the demographics of the countries where the studies were conducted.

The pooled analyses of the pivotal studies, V72P10, V72\_29, V72\_41, and V102\_03, provided limited information, because:

- (1) These clinical trials were carried out in different countries, namely:
  - a. in Chile - V72P10
  - b. in the UK – V72\_29
  - c. in Canada and Australia – V72\_41, and
  - d. in the US and Poland – V102\_03.

- The baseline titers against three indicator strains were different across these four studies.
- (2) Assays for different studies were performed at different laboratories. Additionally, for study V102\_03, the bactericidal antibody responses were measured using (b)(4)-hSBA, not hSBA.
  - (3) Vaccinations were administered on different schedules, such as Month 0 and Month 1, or Month 0 and Month 2, or Month 0 and Month 6.

### 7.3 Analyses

The effectiveness of the rMenB+OMV NZ vaccine was measured by serum bactericidal activity against meningococcal serogroup B (MenB) indicator strains using hSBA assays. The MenB indicator strains used for the analyses were NZ98/254, H44/76, and 5/99.

The immune response to the rMenB+OMV NZ vaccine was analyzed using primarily the following parameters: the percentages of subjects achieving  $\geq 4$ -fold hSBA response to each of the three strains and the percentage of subjects achieving the hSBA titer greater than or equal to the assay LLOQ for all three indicator strains simultaneously (composite response). Additionally, Geometric Mean Titers (GMTs) against all 3 indicator strains, H44/76, 5/99, and NZ98/254, were evaluated in clinical studies V72P10, V72P10E1, V72\_41, V102\_03, and V72\_29.

Across studies V72P10, V72\_41, and V72\_29, one month after the second rMenB+OMV NZ vaccination administered at 1, 2, or 6 months after the first vaccination, a high percentage of subjects achieved hSBA titer  $\geq$  LLOQ against strains H44/76 (97%-100%) and 5/99 (98%-100%). The bactericidal response against strain NZ98/254 differed across studies. In studies V72P10 and V72\_29, this parameter was in the range of 88% to 97%, but it was 63% in study V72\_41. Differences in immune response rates or in GMTs were observed across populations from different studies.

In the CSRs for some studies, the applicant included information on immune responses to the rMenB+OMV NZ vaccine utilizing additional serogroup B strains, namely, strains -----(b)(4)-----, and ----(b)(4)-----. These strains were chosen, as agreed upon by CBER, as reference strains for the ---(b)(4)----- vaccine development. Strains -----(b)(4)-----, and ----(b)(4)----- are used to measure bactericidal activity against the fHbp variant 1.1 protein, the NHBA protein, and the NadA protein, respectively.

The Clinical Study Report of Study V102\_03 provided information on the immune response to the rMenB+OMV NZ vaccine measured by (b)(4)-hSBA (the ---(b)(4)----- assay for serum bactericidal activity using human complement) against the above mentioned 3 strains, in addition to the previously reported results for strains H44/76, 5-99, and NZ98/254. A post hoc analysis against ---(b)(4)-- and ---(b)(4)-----, strains was also performed utilizing hSBA assay in a subset of subjects who received the rMenB+OMV NZ vaccine on a month 0, 6 or 0, 2, 6 schedule in study V72P10. A

notable immune response to the rMenB+OMV NZ vaccine, following a 2-dose schedule, for the additional serogroup B indicator strains was observed in both V102\_03 and V72P10 studies.

Evaluation of immunogenicity data from all clinical trials can be found in Section 6 (Clinical Studies) of this review.

#### **7.4 Efficacy Conclusions**

The clinical data submitted in the BLA in support of accelerated approval of the rMenB+OMV NZ vaccine support the immunogenicity as well as existence of persistent immune responses, in adolescents and young adults 10 through 25 years of age.

### **8. Integrated Overview of Safety**

Information about safety of the candidate vaccine can be found in Dr. Tammy Massie's statistical review of the safety and Dr. Anuja Rastogi's clinical review.

### **9. Additional Statistical Issues**

None.

### **10. Efficacy Conclusions**

The clinical immunogenicity data included in the BLA support accelerated approval of the rMenB+OMV NZ vaccine. Effectiveness of vaccine was demonstrated based on the ability of the rMenB+OMV NZ vaccine to induce bactericidal antibodies measured by hSBA assays using three meningococcal group B indicator strains.

(1) The indicator strains were:

- ✓ Strain H44/76, which measured bactericidal antibody primarily directed against fHbp variant 1.1
- ✓ Strain 5/99, which measured bactericidal antibody primarily directed against NadA, and
- ✓ Strain NZ98/254, which measured bactericidal antibody primarily directed against PorA P1.4 (the OMV NZ vaccine component).

The indicator strains were chosen to represent prevalent MenB strains in the United States.

(2) The immunogenicity parameters evaluated in support of US licensure under accelerated approval were:

- ✓ For each of three indicator strains, H44/76, 5/99, and NZ98/254, the proportion of subjects achieving at least 4-fold increase in hSBA titer from baseline to one month post second vaccination.
- ✓ Proportion of subjects achieving the composite hSBA response defined as hSBA titers  $\geq$  LLOQs for all 3 MenB indicator strains combined, at one month after the second vaccination dose.

- ✓ Proportion of subjects with hSBA titer greater than or equal to the assay LLOQ for each indicator strain at one month after the second vaccination dose.
- (3) In three phase 2/3 studies, the hSBA responses following vaccination at some two-dose schedules, as assessed by the immunogenicity parameters described above, appeared to be adequate. For more details please see Section 6 of this review.
- (4) Antibody persistence of immunogenicity of the rMenB+OMV NZ vaccine after a 2-dose primary schedule was evaluated in two studies and subjects 11 through 17 years of age (study V72P10E1) and 18 through 24 years of age (study V72\_29). Results from studies V72P10E1 and V72\_29 appear to demonstrate persistence of bactericidal antibody responses to the rMenB+OMV NZ vaccine 11-24 months after vaccination, when the vaccine was given as a 2-dose or 3-dose regimen.

Extended discussion of major statistical issues, related to vaccine efficacy and encountered in the BLA, can be found in Section 1.3 of this review.

### **Final Conclusions**

Data generated by 6 clinical trials and submitted in the BLA provided preliminary evidence supporting the immunogenicity of the rMen+OMV NZ vaccine administered in individuals 10 through 25 years of age. Despite differences in immune responses to the rMenB+OMV NZ vaccine among the clinical trials, multiple analyses that utilized such parameters as proportions of subjects achieving hSBA titer  $\geq$  LLOQ for all indicator strains, proportions of subjects achieving 4-fold response for each MenB indicator strain and hSBA GMTs, showed that the vaccine elicited immune responses in healthy subjects aged 10 through 25 years. In US study V102\_03, despite using the (b)(4)-hSBA assay, i.e., an assay different from the one used in all other studies, the analyses performed confirmed a pattern of immune responses to the candidate vaccine similar to the responses observed in other studies (V72\_41, V72\_29). Additionally, persistence of bactericidal antibody responses to the rMenB+OMV NZ vaccine 11-24 months after vaccination was demonstrated.