

Application Type	Biologics License Application
STN	125546/0
CBER Received Date	July 24, 2014
PDUFA Goal Date	March 24, 2015
Division / Office	DB/OBE
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Review Completion Date / Stamped Date	December 22, 2014
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Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Meningococcal Group B Vaccine
(Proposed) Trade Name	Bexsero®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed) Suspension for intramuscular injection.
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection as a single dose pre-filled syringe.
Dosing Regimen	Two doses (0.5 mL each) by intramuscular injection with an interval of at least 1 month between doses
Proposed Indication(s) and Intended Population(s)	Bexsero® vaccine is indicated for active immunization to prevent invasive meningococcal disease caused by <i>Neisseria meningitidis</i> serogroup B in individuals 10 through 25 years of age.

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GLOSSARY

ABCs	Active Bacterial Core surveillance
AE	Adverse event
BA	Bioavailability
BB-IND	Biological Investigational New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CSR	Clinical study report
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EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FAS	Full analysis set
fHbp	factor H binding protein
GCP	Good Clinical Practice
GMT	Geometric mean titer
hSBA	Serum bactericidal assay using human complement
IMD	Invasive meningococcal disease
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MATS	Meningococcal Antigen Typing System
MedDRA	Medical Dictionary for Regulatory Activities
----(b)(4)-----	------(b)(4)-----
MenACWY	Meningococcal serogroups A, C, W, and Y vaccine
MenB	Serogroup B meningococcus
MeNZB	Outer membrane vesicle vaccine derived from <i>Neisseria meningitidis</i> serogroup B strain NZ98/254
MITT	Modified Intent To Treat
MLST	Multilocus sequence typing
NadA	<i>Neisseria</i> adhesin A
NHBA	<i>Neisseria</i> Heparin Binding Antigen
NNDSS	National Notifiable Diseases Surveillance System
OMV	Outer membrane vesicles
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)-----
PCR	Polymerase chain reaction
PPS	Per protocol set
SAE	Serious adverse events
SBA	Serum bactericidal assay
SD	Standard deviation

SOC	System organ class
UK	United Kingdom
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

Novartis conducted a multinational clinical development program for Bexsero® a Meningitis B vaccine for the prevention of Meningococcal disease. Bexsero® is a vaccine composed of multicomponent Meningococcal group B Vaccine (recombinant, adsorbed) suspension for intramuscular injection.

Bexsero® consists of 0.5 mL suspension for intramuscular injection as a single dose pre-filled syringe. Based on the studies submitted in this Biological License Application (BLA), the proposed administration is two doses (0.5 mL each) by intramuscular injection with an interval of at least 1 month between doses. As per the applicant, this product, Bexsero®, has a proposed label indication “*for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B. BEXSERO® is approved for use in individuals 10 through 25 years of age.*”

Additionally, the applicant indicates that Bexsero® is not expected to provide protection against all circulating meningococcal serogroup B strains.

Overall, approximately 20,574 subjects were exposed to Bexsero® in a variety of different studies and immunization campaigns. A total of 5,223 subjects participated in the Novartis clinical development program of Bexsero®, which consisted of 6 studies sponsored by Novartis. Two additional immunization campaigns, sponsored by the US Centers for Disease Control and Prevention (CDC) under an expanded access IND, examined the rates of Serious Adverse Events (SAEs) in 15,351 subjects in Princeton University and University of California Santa Barbara. Within the Novartis sponsored studies a total of 3,139 subjects 10 years of age or older were exposed to at least one dose of Bexsero®. Specifically, the safety of Bexsero® was evaluated in the following clinical trials from Phase I to Phase III:

1. Study V72P10 was a phase 2b/3 study conducted in Chile, which compared rMenB+OMV NZ (Bexsero®) vaccine to placebo in various schedule combinations in subjects 11 through 17 years of age. The 0, 1-, 0, 2-, and 0, 6-month schedules evaluated in the study provide the main safety data for the proposed 2-dose indication in adolescents. Further support is provided by the safety data from the first 2 doses of a 3-dose study of the 0, 1, 2-month schedule, the 0, 1, 6-month schedule, and the 0, 2, 6-month schedule in V72P10.
2. Study V72_41 was a phase 3 study conducted in Canada and Australia, which compared the safety and tolerability of 2 lots of rMenB+OMV NZ (Bexsero®) formulated with OMV manufactured at 2 different sites, in healthy adolescents 11 through 17 years of age, according to a 0, 1-month vaccination schedule.
3. Study V72_29 was a phase 3 study conducted in the United Kingdom (UK) that enrolled university students 18 through 24 years of age. One group of subjects received 2 injections of rMenB+OMV NZ (Bexsero®) 1 month apart. Two other groups received control vaccines (2 injections of the Japanese encephalitis

- vaccine (Ixiaro®), or 1 injection of placebo followed 1 month later by one injection of MenACWY conjugate vaccine (Menveo®).
4. Study V102_03 was a phase 2 study conducted in the US and Poland and was primarily designed to evaluate the safety and immunogenicity of 2 different combined meningococcal -----(b)(4)----- vaccine formulations in healthy adolescents and young adults (10 through 25 years of age). This study had an additional study group of participants given 2 doses of rMenB+OMV NZ (Bexsero®) 2 months apart.
 5. V72P5 was a Phase I/II study conducted in Switzerland, which collected safety data for 2-doses of a variety of MenB products, including Bexsero® administered at least 1 month apart (with no active control or placebo arm). Within this study, only 6 subjects were less than 25 years of age.
 6. V72P4 was a Phase I/II study conducted in Italy and Germany, which collected safety data for a 2-dose schedule of BEXSERO®, administered at least 1 month apart (with no active control or placebo arm). Within this study, only 9 subjects were less than 25 years of age.

Two uncontrolled CDC immunization campaigns provided additional safety data in individuals 17-65 years of age, with the majority being college aged. Study V72_68TP administered Bexsero® to Princeton University students, and Study V72_70TP administered Bexsero® to the University of California Santa Barbara students and staff.

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials for the specific country or geographic location where the studies were performed. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time and the location in which the trials were performed.

A summary of the 8 clinical studies sponsored by Novartis, including the purpose of the study, number of patients exposed to the doses of Novartis rMenB+OMV NZ (Bexsero®) is provided in Tables 1 a-b) below.

Table 1a) Summary of Safety Studies Submitted to the BLA-Novartis Clinical Studies

Study	V72 P10 (*)	V102_03 (*)	V72_41
Vaccinated with Bexsero®	1503 (within 6 months) 1622 ^{*a} overall	120	342
Vaccinated with Comparator	128-Placebo	109- Placebo/MenACWY	None
Phase	Phase 2b/3	Phase 2	Phase 3
Safety Follow-up/ Timing			
Location	Chile	Poland/ USA	Canada/ AUS
Age	11-17 years old	10-25 years old	11-17 years old
Study Design	Observer-blind, multi-center, randomized, controlled, safety, and immunogenicity study in healthy adolescents with various schedules	Observer-blind, multi-center randomized, controlled study to evaluate safety and immunogenicity of two different rMenB with OMV + MenACWY combination vaccination formulations. rMenB+OMV NZ was administered to a control group	Observer-blind multi-center randomized, controlled study to evaluate safety and immunogenicity of rMenB+OMV NZ formulated with OMV manufactured at two different sites

Source: Table created by reviewing statistician utilizing data provided in CSRs within the BLA submission----- (b)(4)-----

NOTE: *a) 1503 were administered MenB vaccine during the initial phase of the study. Then after 6 months, 119 of the placebo subjects (of the 128 randomized and 120 receiving placebo treatment with any follow-up) were ultimately administered Novartis's MenB, Bexsero® vaccine

Table 1a) cont. Summary of Safety Studies Submitted to the BLA-Novartis Clinical Studies

Study	V72_29 (*)	V72_P5	V72_P4
Vaccinated with Bexsero®	974	28	53
Vaccinated with Comparator	984-MenACWY/ Placebo 985- Ixiaro	None	None
Phase	Phase 3	Phase 1	Phase 2
Safety Follow-up/ Timing			
Location	UK	Switzerland	Switzerland
Age	18-24 years old	18-50 years old	18-40 years old
Study Design	Observer-blind multi-center randomized, controlled study to evaluate pharyngeal carriage of <i>Neisseria meningitidis</i> in young adults	Observer-blind, single-center, randomized, safety, and immunogenicity study in healthy adults	Open-label, multi-center, safety, and immunogenicity study in healthy (at-risk) adults

Source: Table created by reviewing statistician utilizing data provided in CSRs within the BLA submission ----- (b)(4)-----

Table 1 b) Summary of Safety Studies Submitted to BLA-CDC Immunization Campaign

Study	V72_68TP (*)	V72_70TP (*)
Vaccinated with Bexsero®	5520	9831
Vaccinated with Comparator	none	None
Phase	n/a	n/a
Safety Follow-up/ Timing	Up to 1 year follow up	Up to 1 year follow up
Location	USA	USA
Age	16-65 years of age	16-68 years of age
Study Design	Open label	Open label

Source: Table created by reviewing statistician utilizing data provided in CSRs within the BLA submission-----
----- (b)(4) -----

The studies provided in this submission appear to support the applicant's conjecture that the Bexsero® product is safe when utilized in the active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. BEXSERO® is approvable for use in individuals 10 through 25 years of age based on the statistical analyses examined and performed by the statistician reviewing the safety data.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Invasive meningococcal disease (IMD) occurs when the normally asymptotically carried encapsulated gram-negative bacterium *Neisseria meningitidis* enters the bloodstream, multiplies, and causes meningitis or sepsis. Each year approximately 500,000 cases and 50,000 deaths are caused by *N. meningitidis* globally. Meningococcal carriage prevalence varies across age groups. In a meta-analysis of published surveys, the prevalence ranged from 4.5% in early infancy to 23.7% in adolescents (up to 19 years of age). Declines were noted in older age groups, with 7.8% meningococcal prevalence at 50 years of age.

Meningococci can be classified into 12 serogroups based on differences in their polysaccharide capsules. Six of these capsular serogroups (A, B, C, X, W, and Y) are associated with invasive disease and are responsible for the majority of endemic disease, as well as epidemics and outbreaks worldwide.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

A comprehensive listing of products that are approved to treat *N. meningitidis* serogroup B can be found in the medical officer's review.

2.4 Previous Human Experience with the Product (including Foreign Experience)

There is one vaccine licensed in the U.S. for the prevention of *N. meningitidis* serogroup B (MenB), Trumenba®, a Pfizer vaccine approved on October 29, 2014. Since January

2013, the Bexsero® vaccine, the subject of this BLA, was licensed for use in the EU, Australia, Canada, and Chile.

The clinical development program of rMenB+OMV NZ vaccine consisted of studies in healthy adults, adults with occupational exposure to *N. meningitidis*, adolescents, young children, and infants. These studies have shown robust functional immune responses induced against the selected indicator strains, as measured by serum bactericidal activity using human complement in all age cohorts studied. Additionally, the safety data collected in these studies illustrate safety outcomes, including adverse events, and local and systemic reactogenicity, comparable to those observed in other approved Meningitis vaccines for other serogroups, including A, C, W, and Y.

A total of 6 Novartis sponsored clinical studies and 2 CDC immunization campaigns comprise the clinical program conducted to evaluate the safety and efficacy of Bexsero®. This includes Phase I-III studies and open-label immunization campaign conducted by the CDC at Princeton University and the University of California Santa Barbara. A comprehensive list of all studies submitted to this BLA, including the location of the study, allocation of patients to treatment arms, as well as the age range of patients, can be observed in the following table.

Table 1.4 a) Summary of Submitted Studies comprising the Novartis Bexsero® Clinical Development Program-Adults and Pediatric Subjects

Study Number	Phase	Study Location	Objective	Total # Subjects	Total # Bexsero®	Total # Placebo or Comparator	Age Range (Years)
V72_P5	1	Switzerland	Safety	28	28	none	18-40 years old
V72_P4	2	Switzerland	Safety/ Immunogenicity	53	53	none	18-50 years old
V102_03	2	Poland/ USA	Safety/ Immunogenicity	229	120	109- Placebo/ MenACWY	10-25 years old
V72_41	3	Canada/ AUS	Safety/ Immunogenicity	342	342	none	11-17 years old
V72_29	3	UK	Safety/ Immunogenicity	2943	974	984- MenACWY/ Placebo 985- Ixiaro	18-24 years old
V72 P10	2b/3	Chile	Safety/ Immunogenicity	1631	1503 (1622* within 6 months)	128-Placebo	11-17 years old
V72_68TP	Open Label	USA	Open Label/ Safety	5520	5520	none	16-65 years old
V72_70TP	Open Label	USA	Open Label/ Safety	9831	9831	none	16-68 years old
Total				20577	18490	2206	

Source: Table created by reviewing statistician utilizing data provided in:

----- (b)(4) -----

Additional experience with Bexsero® can be found in the medical officer's review.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Additional information related to the Pre- and Post-submission Regulatory Activity related to this submission can be found in the medical officer's review.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This BLA submission includes the summary of 6 pre-marketing studies and 2 expanded access IND studies, all of which gathered safety data. Approximately 18,500 subjects

were exposed to Bexsero® in a variety of types of studies, including open-label, Phase II, and Phase III.

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review of the safety data. The safety data were presented both within the individual study reports as well as within the Integrated Summary of Safety, for select studies that were comparable and had been agreed upon during the Pre-BLA meeting with CBER.

3.2 Compliance with Good Clinical Practices and Data Integrity

Based on the submitted material and current evaluation, it appears that the clinical trials were conducted in accordance with acceptable ethical standards.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

No statistical issues have been identified that would impact the reviews conducted by other review disciplines that examined this submission.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

The BLA submission provided by Novartis is stored in the following location:

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This file path includes the clinical overview, summary of safety, summary of efficacy, as well as datasets for the 8 safety studies that were examined and analyzed by the agency statistician in the review of this product.

5.1 Review Strategy

The applicant provided a summary of and detailed results, as well as the datasets of 8 safety/efficacy studies. The primary studies of interest for the safety analysis of this product include the Phase I/II/III Safety and Efficacy Studies, as well as the open label expanded access IND study. Within this BLA, only two Phase II/III safety/efficacy studies were performed under US IND, and the open label studies were performed under an expanded access IND. The data and the detailed and comprehensive write-up of the studies are found within Module 2 and Module 4 of the original submission of this BLA, 1255446 amendment 0, submitted to CBER on July 24, 2014.

Individual study results were provided for both safety and efficacy; combined results were also examined, particularly for safety/tolerability and adverse events. The Integrated Summary of Safety (ISS) pooled data from the clinical studies proposed and implemented by Novartis. Within this review the integrated overview of safety examined and presented the safety results of subjects from 10-25 years of age to reflect the proposed label indication.

This BLA includes the following 8 clinical trials that comprise the clinical program, which were conducted to evaluate the efficacy and safety of Bexsero®:

- One Phase I safety trial
 - Adults (18-40 years of age)
 - V72_P5: Switzerland
- Two Phase II safety and efficacy trials in
 - Adults (18-50 years of age)
 - V72_P4: Switzerland
 - Adolescents and young adults (10-25 years of age)
 - V102_03: USA/Poland
- Three Phase III or II/III safety and efficacy trials in
 - Children (11-17 years of age)
 - V72_P10: Chile
 - V72_P41: Canada/Australia
 - Adults (18-24 years of age)
 - V72_P29-UK
- Two open label expanded access IND safety studies:
 - College Age Students/Adults:
 - V72_68TP: US-Princeton
 - V72_70TP: US-UC Santa Barbara

The Phase I/II studies contribute data and information on the overall safety of this product and will be discussed briefly in the safety section of this review.

The Phase II/III studies that are of most interest were the studies performed under US-IND or larger international studies. These include:

- V72_29
- V72_41
- V102_03

and will be described and examined in further detail within this review.

5.2 BLA/IND Documents that Serve as the Basis for the Statistical Review

The BLA submitted by the applicant is stored in the following location:

----- (b)(4) -----

This includes the clinical and non-clinical information, background material, protocol(s), case report forms, and datasets of all studies submitted by the applicant.

The datasets are located in the file paths:

----- (b)(4) -----

Additionally, the applicant provided several publications related to the studies submitted within this BLA, including the CDC summary of the two open-label college student immunization campaign/registries.

The following table lists a brief summary of the safety studies provided within this submission (of which the data collected for 2 doses are of most interest as they will be included within the label):

Study #	Study Location	Years/Age Range	Phase/Objective	Treatment	Number of Subjects
V72_P5	Switzerland	18-40 years old	Phase I- Safety	Bexsero®	28
V72_P4	Switzerland	18-50 years old	Phase II- Safety/ Immunogenicity	Bexsero®	53
V102_03	Poland/ USA	10-25 years old	Phase II- Safety/ Immunogenicity	Bexsero® Placebo/ MenACWY	120 109
V72_41	Canada/ AUS	11-17 years old	Phase III- Safety/ Immunogenicity	Bexsero®	342
V72_29	UK	18-24 years old	Phase III- Safety/ Immunogenicity	Bexsero® Placebo/ MenACWY Ixiaro	974 984 985
V72_P10	Chile	11-17 years old	Phase IIb/III- Safety/ Immunogenicity	Bexsero® Placebo	1503 128
V72_68TP	USA	16-65 years old	Open Label/ Safety	Bexsero®	5520
V72_70TP	USA	16-68 years old	Open Label/ Safety	Bexsero®	9831

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Specifically, the applicant submitted the data and summaries of the following safety/tolerability and efficacy studies (in which studies in **bold** are described in detail within this safety review):

- V72_P5: Phase I Safety Study-Switzerland, Adults, 18-40 years of age.
- V72_P4: Phase II Safety and Efficacy Study- Switzerland, Adults, 18-50 years of age.
- **V102_03**: Phase II Safety and Efficacy Study-USA/Poland, Adolescents and Young Adults, 10-25 years of age.
- **V72_P41**: Phase III Safety and Efficacy Study-Canada/Australia, 11-17 years of age.
- **V72_P29**: Phase III Safety and Efficacy Study-UK, 18-24 years of age.
- V72_P10: Phase II/III Safety and Efficacy Study-Chile, Children, 11-17 years of age.
- V72_P68TP: Expanded Access IND Study-Princeton University, 16-65 years of age (predominantly college age students).
- V72_P70TP: Expanded Access IND Study-University of California, Santa Barbara, 16-68 years of age (predominantly college age students).

The studies of primary interest in the examination of the safety of this product, Bexsero®, are the Phase II/III studies performed under US-IND or in large scale international studies: V102_03, V72_P41, and V72_P29.

The majority of these studies examined medical histories, physical examinations, and solicited and unsolicited adverse events. A summary of the typical assessments collected within the studies relevant to the safety data are included in the following table.

Table 6.a) Common Medical History and Safety Assessments Collected in Novartis Studies

Data Collection Mechanism	Timing of data captured	Summary of data captured
Medical History	From birth	All subject-reported <u>significant</u> past diagnoses including allergies, hospitalizations, surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication, i.e., >2 weeks in duration, or other significant medical conditions which may impair the assessment of safety of the investigational vaccine.
Medications	Throughout study	All prescription medications used to treat any SAE or any medically attended AEs (see medically attended AEs). All non-study vaccinations administered to the subject during the study period should be recorded on the concomitant medications eCRF. At the enrollment visit all current prescription medications being taken by the subject must be recorded on the concomitant medications eCRF.
Medications-during study	For 7 days post-vaccination (including day of vaccination)	All prescription medications taken and all antipyretic over the counter medications taken.
Immediate Reactions	For 30 minutes post vaccination	Signs or symptoms of anaphylaxis.
Temperature	For 7 days post-vaccination (including day of vaccination)	Axillary temperature. If temperature >38°C, fever is to be noted
Local Reactions	For 7 days post-vaccination (including day of vaccination)	Pain, erythema, induration, and swelling. If persisting beyond Day 7, it will be reported as an AE.
Systemic Reactions	For 7 days post-vaccination (including day of vaccination)	Nausea, fatigue, myalgia, arthralgia, headache, fever, and rash. If persisting beyond Day 7, it will be reported as an AE.
All Adverse Events	For 7 days post-vaccination (including day of vaccination)	All Adverse Events
Withdrawal of subjects due to All SAEs and all Medically Attended	Throughout study	All SAEs and all Medically Attended AE and/or resulting in withdrawal of subjects from the study.
SAEs and Medically Attended AEs:	At study termination (and beyond, if warranted)	If an AE remains unresolved at study termination, a clinical assessment will be made by the clinician, who in collaboration with the Novartis Vaccines and Diagnostics Medical Monitor will determine whether continued follow up of the AE is warranted.

Source: reviewer adaptation of data collection based on Clinical Study reports and data provided within the adverse event, COMMENTS, demog, medhx, and POSTINJ datasets provided in the applicant submitted BLA documents

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*Note: Medically attended adverse events: any adverse event requiring a medical visit (medical visit: a visit by a doctor or a nurse entitled to conduct medical visit, according to local regulations).

The solicited Adverse Events of special interest were related to the local and systemic adverse events commonly seen in vaccinations. In some studies, the solicited Adverse Events were collected from all participants, while in other studies only select participants were identified for additional data collection with respect to solicited adverse events. The solicited adverse events included the following symptoms that were reported in daily diary cards typically recording experiences during the 7 days immediately following each injection.

Local Reactions:

Local reactions include: pain, erythema, induration, and swelling.

Systemic Reactions:

Systemic reactions include: nausea, fatigue, myalgia, arthralgia, headache, fever, and rash.

Other Indicators of Reactogenicity (as applicable)

Other indications of reactogenicity include but are not limited to: body temperature, use of analgesic or antipyretic medications, quality of life parameters (i.e., stayed home due to reaction).

In addition to the self-assessments of symptoms, the severity of events reported on the “Adverse Events” CRF was also determined by the clinician utilizing the following scale:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The relationship of the study treatment to an AE was determined by the clinician based on the following definitions:

- a) **Not Related**-The AE was not related to a study vaccine if there was evidence that clearly indicated an alternative explanation. If the subject did not receive the vaccine, the timing of the exposure to the vaccine and the onset of the AE were not reasonably related in time, or other facts, evidence or arguments exist that strongly suggest an alternative explanation, then the AE was considered as not related.
- b) **Possibly Related**-The administration of the study vaccine and AE were considered reasonably related in time and the AE could be explained either by exposure to the study vaccine or by other causes.
- c) **Probably Related**-Exposure to the study vaccine and AE were reasonably related in time and no alternative explanation could be identified.

The relationship of the study vaccine to an AE was typically determined by the investigator or clinician.

Tabulations of these observed adverse events indicating systemic and local reactions were to be presented; however, statistical tests were not pre-specified.

Of interest to the review team were the Phase II/III studies performed under US-IND or in large scale international studies: V102_03, V72_P41, and V72_P29 which are described in detail further below.

6.1 Trial #1: V72_29: UK Phase III Study

This study entitled, “*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*” was designed to examine the safety and efficacy of two doses administered 1 month apart of Bexsero®/ rMenB+OMV when compared to a treatment regimen of one dose of MenACWY followed by placebo 30 days later and a control group in which the treatment regimen was two doses of Ixiaro®, a Japanese encephalitis vaccine administered 30 days apart. This study enrolled students 18-24 years of age in the UK. The study collected carriage, immunogenicity, local and systemic reactogenicity data, as well as expected and unexpected adverse events for 12 months from study day 1, thus approximately 11 months post vaccination.

6.1.1 Objectives

The primary objective of this study was to examine the carriage prevalence of virulent sequence types of N meningitidis group B at one month following administration of the rMenB+OMV NZ product. Details related to the immunogenicity and carriage objectives identified by the applicant are included in the Statistical Review of Efficacy.

The secondary objective of this study was to examine the immunogenicity as well as the safety of the product. The secondary objectives of this study relevant to the safety of this product are as follows.

Safety Objectives (secondary):

1. To evaluate the safety and tolerability of two doses of rMenB+OMV NZ vaccine, given one month apart, and a single dose of MenACWY conjugate vaccine in healthy young adults.

Within the remainder of this statistical review, only safety endpoints, objectives, and analyses will be discussed. Additional details on the immunogenicity and efficacy analysis can be found in the Statistical Efficacy Review.

6.1.2 Design Overview

This was a Phase III, multi-center, observer-blind randomized trial that enrolled university students 18 to 24 years of age in the UK. All subjects received two injections 1 month apart and were followed for a total of 12 months. Subjects were randomized to one of the three treatment arms.

- **rMenB+OMV:** The rMenB+OMV group received two doses of rMenB+OMV NZ vaccine, first dose on day 1 and second dose on day 31.
- **MenACWY:** The MenACWY group received one dose of MenACWY-CRM197 conjugate vaccine (Menveo) on day 1 and a placebo on day 31.
- **Control:** The control group received two doses of Japanese encephalitis vaccine (Ixiaro®) [Intercell, Vienna, Austria]), first dose on day 1 and second dose on day 31.

At the conclusion of the study, all subjects in rMenB+OMV and control groups received one dose of MenACWY vaccine as a non-test vaccine. Subjects in the MenACWY group did not receive an additional MenACWY dose at the last study visit.

From study day 1 to study termination, there were 6 clinic visits spanning 12 months. 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 second injection, to assess the immunogenicity of rMenB+OMV and MenACWY vaccines in this young adult population. The following table summarizes the treatment and data collection for the study.

Table 6.1.2.a) Schedule of Vaccination, Blood Draw, and Pharyngeal Swabs

Group		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Time	Day 1	Month 1	Month 2	Month 4	Month 6	Month 12
rMenB + OMV	Treatment	rMenB + OMV	rMenB + OMV				MenACWY
	Collection	Blood ^a		Blood ^a	Blood ^a	Blood ^a	Blood ^a
		Swab	Swab	Swab	Swab	Swab	Swab
MenACWY	Treatment	MenACWY	Placebo				
	Collection	Blood ^a		Blood ^a	Blood ^a	Blood ^a	Blood ^a
		Swab	Swab	Swab	Swab	Swab	Swab
Control (Ixiaro®)	Treatment	JE vaccine (Ixiaro®)	JE Vaccine (Ixiaro®)				MenACWY
	Collection	Blood ^a		Blood ^a	Blood ^a	Blood ^a	Blood ^a
		Swab	Swab	Swab	Swab	Swab	Swab

Source: Reviewer adaptation of Table provided in original BLA 125546, Study V72_29, Clinical Study Report page 112-113

Note: ^aBlood samples collected from a pre-specified subset of subjects

The subject was observed for 30 minutes following each study vaccination for any immediate reactions. Serious adverse events (SAEs), medically attended adverse events (AEs), and any prescription medications taken for these AEs were recorded on a diary card by all subjects throughout the study period. For subjects included in the immunogenicity subset, solicited local and systemic reactions, all AEs, prescription medications, and antipyretics administered within 7 days after each vaccination were recorded on a separate diary card.

6.1.3 Population

Subjects were healthy young adults who fulfilled all the inclusion criteria, had none of the exclusion criteria, and were 18-24 years of age enrolled at select universities in the UK. Subjects were enrolled at ten treatment sites in the UK.

Overall, 3000 subjects were planned to be enrolled, with 1000 subjects per treatment group who were to be randomized in a 1:1:1 ratio in a blinded manner. Additionally, 200 subjects per treatment arm were to have immunogenicity data collected.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomly assigned in a 1:1:1 ratio to receive either 2 doses of rMenB+OMV NZ vaccine, 1 dose MenACWY conjugate vaccine + 1 dose placebo, or 2 doses of Japanese encephalitis vaccine (Ixiaro®). Regardless of the treatment assignment, the 2 doses were to be separated by 30 days. Additional details related to the study treatment can be seen within the medical officer's review.

6.1.6 Sites and Centers

The study was conducted in the UK across 10 different sites. Additional details related to the study locations can be found in the medical officer's and/or chairperson's review.

6.1.7 Surveillance/Monitoring

Study progress was to be monitored by Novartis Vaccines and Diagnostics or its representative (e.g., a contract research organization-(b)(4) as frequently as necessary 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 applicable regulatory requirements. Arrangements for monitoring visits were to be made in advance in accordance with the monitoring plan, except in case of emergency.

6.1.8 Endpoints and Criteria for Study Success: Safety

Criteria for Evaluation: Safety Endpoints

A brief medical history was to be obtained and physical examination performed for each subject who entered into the study. All medically attended and serious adverse events, both expected and unexpected, were to be collected from all subjects throughout the trial.

Local and systemic reactions and all adverse events were to be collected for the 7-day period after the first and second vaccination for subjects participating in the immunologic portion of this trial. This included approximately 200 subjects per treatment arm.

The safety endpoints and criteria for study success were based on observed local and systemic reactions 7 days post vaccination via a daily diary card for the immunologic portion of the study.

For the selected subjects, local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [axillary temperature $>38.0^{\circ}\text{C}$, nausea, fatigue, myalgia, arthralgia, headache) reactions were assessed for 7 days (including the day of vaccination) post each vaccination. All adverse events (AEs) which occurred during the 7 days (including the day of vaccination) post each vaccination were collected on a Diary Card.

Serious adverse events (SAEs), medically attended AEs, and AEs that resulted in a subject's withdrawal from the study were collected throughout the study period.

A detailed summary of the data gathered, the subjects and the timing in which these data were gathered during this study was provided in Table 6.1.2.a) previously.

6.1.9 Statistical Considerations & Statistical Analysis Plan - Safety

The statistical considerations related to the safety analyses were divided into two different groups. One group included all 3000 subjects randomized to treatment (1000 in each treatment arm). Meanwhile, a smaller subset of approximately 200 subjects per treatment arm gathered additional details related to immunogenicity and safety endpoints, including local and systemic adverse events that were predominantly collected within a 7 day daily diary card.

For the immunogenicity subset in which additional safety data were collected, the following analyses were performed:

- Percentages of subjects reporting local reactions (injection site erythema, induration, swelling, and pain) by severity and by vaccine group, within 7 days after first and second vaccination.
- Percentages of subjects reporting systemic reactions (chills, nausea, malaise, myalgia, arthralgia, headache, fever, and rash) by severity and vaccine group, within 7 days after first and second vaccination.
- Percentages of subjects with reported body temperature analyzed in 0.5°C increments as $<38.0^{\circ}\text{C}$ (no fever), $38.0^{\circ}\text{C} - 38.4^{\circ}\text{C}$, $38.5^{\circ}\text{C} - 38.9^{\circ}\text{C}$, $39.0^{\circ}\text{C} - 39.4^{\circ}\text{C}$, $39.5^{\circ}\text{C} - 39.9^{\circ}\text{C}$, $\geq 40.0^{\circ}\text{C}$, use of analgesic or antipyretic, and quality of life parameters (i.e., stayed home due to reaction).

- Percentages of subjects with any adverse event within 7 days after first and second vaccination.

For the overall safety set:

- Percentages of subjects with serious adverse events (SAEs) or medically attended AEs or AEs resulting in withdrawal from the study.

Statistical Methods:

Safety:

- Frequencies and percentages of subjects experiencing each local and systemic reaction were presented for each symptom and severity.
- For other adverse events, the original verbatim terms used by clinicians to identify adverse events in the eCRFs were mapped to preferred terms using the MedDRA dictionary; the adverse events were then grouped by MedDRA preferred terms into frequency tables according to system organ class.
- Additionally, three separate summaries were produced for serious adverse events, adverse events that are possibly or probably related to vaccine, and adverse events that are unrelated to vaccine.

6.1.10 Study Population and Disposition

The overall target for enrollment was 3000 subjects randomized to three arms in equal proportion, with 1000 subjects in each vaccine group. Approximately 200 subjects from each vaccine group were planned to be included in the immunogenicity/additional safety subset.

6.1.10.1 Populations Enrolled/Analyzed

This study was designed to enroll 3000 subjects in three treatment groups. Overall, 2968 subjects were enrolled in this study and randomized in approximately a 1:1:1 ratio into three vaccine groups. A total of 14 enrolled subjects were not randomized to any of the study arms for a variety of reasons related to the subject not meeting the entry criteria (inclusion/exclusion), that would not affect the conduct of the study particularly since the withdrawals were prior to randomization. All subjects who received study medication were considered to be a part of the safety dataset. Within this study, a subset of approximately 20% of subjects or 200 subjects per treatment arm, were to be included in the immunogenicity subgroup. These subjects would have additional study visits, as well

as additional safety data collected via study visit questions and a daily diary card that gathered systemic and local reactogenicity data for 7 days post vaccination.

A total of 2968 subjects were actually enrolled, and 99% of these subjects were included in the MITT population. Also, 87% (post first vaccination) and 77% (post second vaccination) of subjects were included in the PP population, for pharyngeal carriage analyses (an efficacy endpoint not to be discussed further in this review).

The immunogenicity analyses were planned to be performed in a subset of subjects. Within this analysis subgroup, additional safety endpoints were to be collected during study visits as well as via daily diary cards, collecting systemic and local reactions 7 days post vaccination. In the modified intention-to-treat (MITT immunogenicity) population for immunogenicity, 20% of subjects were included. In the per protocol (PP) population for immunogenicity, 17% (post first vaccination) and 15% (post second vaccination) of subjects were included. For ease of discussion, within this review, the statistical safety reviewer refers to this subset as the immunogenicity/safety subset or safety subset.

6.1.10.1.1 Demographics

The demographic variables such as age, sex distribution, and ethnic origin were generally similar across vaccine groups in the enrolled population. The mean age of the subjects was 19.9 years in the overall population. A slightly higher percentage of females were enrolled than males (54% versus 46% respectively), and the majority of subjects were Caucasian (88%).

Other baseline characteristics such as mean weight and height were balanced across vaccine groups. Overall, 14 subjects who were enrolled did not meet the study entry criteria.

Figure 6.1.10.2.a) Demographic and Other Baseline Characteristics-Enrolled Population

	rMenB + OMV	MenACWY	Control (Ixiaro®)	Not Randomized	Total
	N=979	N=988	N=987	N=14	N=2968
Age (Years)	19.9±1.6 (N=977)	19.9±1.6	19.8±1.6	19.2±1.2	19.9±1.6
Sex					
Male	463 (47%)	455 (46%)	440 (45%)	11 (79%)	1369 (46%)
Female	516 (53%)	533 (54%)	547 (55%)	3 (21%)	1599 (54%)
Race					
Asian	60 (6%)	49 (5%)	52 (5%)	0	161 (5%)
Black	19 (2%)	14 (1%)	19 (2%)	0	52 (2%)
Caucasian	860 (88%)	876 (89%)	866 (88%)	8 (57%)	2610 (88%)
Hispanic	3 (<1%)	3 (<1%)	3 (<1%)	0	9 (<1%)
Other	37 (4%)	45 (5%)	47 (5%)	0	129 (4%)
Not done	0	1 (<1%)	0	2 (14%)	3 (<1%)
Unknown	0	0	0	4 (29%)	4 (<1%)

Source: reviewer created table based on -----
----- (b)(4) ----- clinical study report page 147

Overall, there appears to be balance between the various treatment groups based on the demographic variables for both the overall population as well as the immunogenicity/safety subgroup.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects enrolled in this study were to be healthy volunteers, enrolled in various Universities in the UK, meeting inclusion/exclusion criteria that were from 18-24 years of age.

6.1.10.1.3 Subject Disposition

A summary of the 2968 study participants enrolled in this study can be seen in the following table.

**Table 6.1.10.3.a) Summary of Study Participants for Entire Study Period (from Day 1 to Month 12)-
Enrolled Population**

	rMenB + OMV	MenACWY	Control (Ixiaro®)	Not Randomized	Total
Enrolled	979	988	987	14	2968
Completed	796 (81%)	844 (85%)	826 (84%)	0	2466 (83%)
Premature withdrawals	183 (19%)	144 (15%)	161 (16%)	14 (100%)	502 (17%)
Primary reasons for withdrawal					
Adverse Events	11 (1%)	8 (<1%)	3 (<1%)	0	22 (<1%)
Withdrawal of consent	38 (4%)	31 (3%)	28 (3%)	2 (14%)	99 (3%)
Lost to Follow-up	124 (13%)	98 (10%)	123 (12%)	0	345 (12%)
Inappropriate enrollment	2 (<1%)	1 (<1%)	0	11 (79%)	14 (<1%)
Administrative reason	1 (<1%)	0	0	0	1 (<1%)
Protocol deviation	5 (<1%)	5 (<1%)	6 (<1%)	1 (7%)	17 (<1%)
Undetermined/unable to classify	2 (<1%)	1 (<1%)	1 (<1%)	0	4 (<1%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

----- (b)(4) -----

The disposition of participants enrolled in the immunogenicity/safety subgroup for additional immunogenicity and safety endpoints can be observed in the following table.

Table 6.1.10.3.b) Summary of Study Participants–Enrolled Population, Immunogenicity/Safety Subset

	rMenB + OMV	MenACWY	Control (Ixiaro®)	Not Randomized	Total
Enrolled	979	988	987	14	2968
MITT	193 (20%)	194 (20%)	198 (20%)		585 (20%)
PP Population					
1 month post 1 st vaccination	161 (16%)	164 (17%)	167 (17%)		492 (17%)
1 month post 2 nd vaccination	151 (15%)	159 (16%)	150 (15%)		460 (15%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

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Overall, there appears to be balance between the various treatment groups and similar dropout out and withdrawal rates for both the overall population as well as the immunogenicity/safety subgroup.

6.1.11 Efficacy Analyses

The efficacy analysis was predominantly based on immune response including assays. Additional details can be found in the Statistical Review of the Efficacy Endpoints.

6.1.12 Safety Analyses

All subjects who received at least one vaccination and provided some safety data were considered evaluable for the safety analyses. All safety analyses were run using the safety population as defined previously in section 6.1.10.1. The safety of the study vaccines was assessed in terms of number of subjects exposed to study vaccines with reported local and systemic reactions, as well as the number of all subjects with reported SAEs and/or AEs (as specified for each time period) per vaccine group. All SAEs and AEs were judged by the clinician as probably related, possibly related, or not related to vaccine and were tabulated. All SAEs and AEs resulting in withdrawal from the study were summarized.

Table 6.1.12.a) Summary of Study Participants –Safety Data

	rMenB + OMV	MenACWY	Control (Ixiaro®)	Not Randomized	Total
Enrolled	979	988	987	14	2968
Exposed	974 (99%)	984 (99%)	985 (99%)	0	2943 (99%)
Safety Population	974 (99%)	984 (99%)	985 (99%)	0	2943 (99%)
Safety Subset-Solicited AEs: 30 minutes post-vaccination	193 (20%)	196 (20%)	198 (20%)	0	587 (20%)
Safety Subset-Solicited AEs: 30 minutes post-vaccination	185 (19%)	176 (18%)	182 (18%)	0	543 (18%)

Source: Reviewer created table summarizing data provided within applicant provided study report and datasets

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Solicited AEs:

Based on examination of data provided by the applicant in the datasets POSTINJ, COMMENTS, and AE, a majority of subjects from the rMenB+OMV treatment group reported solicited local and systemic AEs after each vaccination (98% after first and 94% after second vaccination). There was a slight decrease in the percentage of subjects with local and systemic AEs after second rMenB+OMV NZ vaccination when compared to the AEs reported after first rMenB+OMV NZ vaccination.

Solicited AEs in the MenACWY and control groups were reported by a lower percentage of subjects than in the rMenB+OMV group after first vaccination and after second vaccination. In the MenACWY group, there was no substantial difference in the percentages of subjects reporting solicited AEs after first vaccination with MenACWY-conjugate vaccine and after a placebo as second injection. A summary of the solicited AEs by vaccine group after any vaccination is provided in the following table.

Table 6.1.12.b) Summary of Solicited AEs during the 7 Day Period after Each Vaccination-Immunogenicity/Safety Subset population: Number and Percentage of Subjects with Solicited Reactions

	rMenB + OMV	MenACWY	Control (Ixiaro®)
First Vaccination	N=190	N=186	N=191
Any	187 (98%)	144 (77%)	150 (79%)
Local	180 (95%)	115 (62%)	117 (61%)
Systemic	161 (85%)	103 (55%)	117 (61%)
Other	44 (23%)	13 (7%)	19 (10%)
Second Vaccination	N=185	N=175	N=182
Any	174 (94%)	130 (74%)	121 (66%)
Local	166 (90%)	123 (70%)	92 (51%)
Systemic	134 (72%)	88 (50%)	91 (50%)
Other	47 (25%)	14 (8%)	9 (5%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

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Unsolicited AEs:

Within the different vaccine groups, approximately 35% to 40% of subjects reported unsolicited AEs within the protocol specified reporting period which are detailed below.

The Bexsero® rMenB+OMV group reported a higher percentage of subjects with unsolicited AEs within days 1 to 7 in the immunogenicity subset, compared to the other treatment groups (31% in rMenB+OMV group versus 13% and 19% in MenACWY and control group after first vaccination; 29% in Bexsero® rMenB+OMV group versus 22% in MenACWY and control groups after second vaccination). However, all unsolicited AEs were noted to be self-limiting and resolved by the end of the study period.

SAEs were reported by 2% to 3% of subjects across vaccine groups including 2% of subjects in the Bexsero® treatment group and 2-3% of subjects in the comparator group.

Premature withdrawals were reported by 1% of subjects in all vaccine groups. In the majority of subjects, the AEs leading to premature withdrawal were considered to be possibly or probably related to the study vaccination for all treatment groups. A detailed summary of the unsolicited AEs noted during the study can be seen in the following table which provides both the count and % response rate for each treatment group.

Table 6.1.12.c) Summary of Unsolicited AEs during the Entire Study Period-Safety Population: Number and Percentage of Subjects with Unsolicited Reactions

	Bexsero® rMenB + OMV	MenACWY	Control (Ixiaro®)
	N=974	N=984	N=985
Any AE	386 (40%)	344 (35%)	380 (39%)
At least possible related AE	70 (7%)	36 (4%)	38 (4%)
Serious AE	31 (3%)	26 (3%)	20 (2%)
At least possible related SAE	3 (<1%)	0 (0%)	0 (0%)
Premature withdrawal due to AE	12 (1%)	9 (1%)	5 (1%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

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Solicited local AEs:

Considering the data provided in the POSTINJ dataset, which collected patient responses within daily diary cards of selected AEs from subjects in the immunogenicity/safety subset population, there was a slightly higher reported rate of solicited AEs in the Bexsero®/ rMenB+OMV treatment group. Specifically, all solicited local AEs (pain, erythema, induration, and swelling) were reported by a higher percentage of subjects from the rMenB+OMV group than in the MenACWY and control groups. The most commonly reported solicited local AE across vaccine groups was injection site pain (93% after 1st vaccination of rMenB+OMV and 7-48% of subjects in the comparator group). Most of the subjects reported pain of mild or moderate intensity. Severe pain was reported only in the rMenB+OMV group by 8% of subjects after 1st vaccination, by 8% in the rMenB+OMV group, and by 2% in the MenACWY group after second vaccination. All other solicited local AEs, i.e., erythema, induration, and swelling were reported by a lower percentage of subjects in the comparator treatment groups compared to subjects in the rMenB+OMV treated group. Local AEs of rash >100 mm were rare and reported mostly in the rMenB+OMV group after first and second vaccination.

Regardless of treatment group, there was a general tendency of decrease in percentage of subjects reporting each local reaction after second vaccination compared to the reports after first vaccination. This finding may be a function of decreased reactogenicity upon subsequent exposures to vaccine. The onset of solicited local AEs was mostly within 2 days after each vaccination, and in most of the cases the reaction did not continue beyond the 7-day observation period. Additional details of the solicited adverse events based on local reactions after the first and second injection can be seen in the following table.

Table 6.1.12.d) Summary of Solicited Local AEs after the First Injection-Immunogenicity/Safety Subset population: Number and Percentage of Subjects with Solicited Local Reactions

	Bexsero® rMenB + OMV	MenACWY	Control (Ixiaro®)
First Vaccination	N=190	N=186	N=191
Pain-any	176 (93%)	93 (7%)	92 (48%)
Severe Pain	16 (8%)	0 (0%)	0 (0%)
Erythema-any	77 (41%)	49 (26%)	52 (27%)
Severe Erythema	1 (1%)	0 (0%)	0 (0%)
Induration-any	50 (26%)	27 (15%)	14 (7%)
Severe Induration	1 (1%)	0 (0%)	0 (0%)
Swelling-any	49 (26%)	19 (10%)	11 (6%)
Severe Swelling	2 (1%)	0 (0%)	0 (0%)
Second Vaccination	N=185	N=175	N=182
Pain-any	162 (88%)	111 (63%)	73 (40%)
Severe Pain	15 (8%)	3 (2%)	0 (0%)
Erythema-any	73 (39%)	38 (22%)	37 (20%)
Severe Erythema	3 (2%)	0 (0%)	0 (0%)
Induration-any	42 (23%)	19 (11%)	12 (7%)
Severe Induration	0 (0%)	0 (0%)	0 (0%)
Swelling-any	48 (26%)	16 (9%)	12 (7%)
Severe Swelling	0 (0%)	1 (1%)	0 (0%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

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Solicited systemic AEs:

Considering the data provided in the POSTINJ dataset, which collected patient responses within daily diary cards of selected AEs from subjects in the immunogenicity/safety subset population, there was a slightly higher reported rate of solicited systemic AEs in the Bexsero®/rMenB+OMV treatment group. Specifically, based on all solicited systemic AEs, the rMenB+OMV group reported a higher percentage of subjects with myalgia (75% of subjects after first and 69% after second vaccinations), arthralgia (12% of subjects after first and 13% after second vaccinations), and nausea (13% of subjects after first and 10% after second vaccinations) compared to the MenACWY and control groups which had <50% of subjects reporting myalgia and <10% of subjects reporting nausea for the subjects in the comparator vaccine groups.

None of the subjects reported a temperature of $\geq 40^{\circ}\text{C}$. The onset of fever was reported from day 1 to day 7, and most of the subjects recovered within the 7-day observation window. The duration of fever reported was mostly 1 to 2 days in all treatment groups.

A higher percentage of subjects from the MenB group used drugs to treat symptoms, including antipyretics after each vaccination (19% in the rMenB+OMV versus 5% and 9% in the other groups after first vaccination, and 21% in the rMenB+OMV versus 6% and 4% in the other groups). However, in all treatment groups the majority of subjects did not stay home due to solicited AEs.

Additional details of the solicited adverse events based on systemic reactions after the first and second injection can be seen in the following table.

Table 6.1.12.e) Summary of Solicited Systemic AEs after the First Injection-Immunogenicity/Safety Subset Population: Number and Percentage of Subjects with Solicited Systemic Reactions

	Bexsero® rMenB + OMV	MenACWY	Control (Ixiaro®)
First Vaccination	N=190	N=186	N=191
Arthralgia-any	22 (12%)	14 (8%)	19 (10%)
Severe Arthralgia	2 (1%)	1 (1%)	0 (0%)
Nausea-any	25 (13%)	18 (10%)	15 (8%)
Severe Nausea	1 (1%)	0 (0%)	1 (%)
Malaise-any	34 (18%)	28 (15%)	38 (20%)
Severe Malaise	1 (1%)	1 (1%)	3 (2%)
Myalgia-any	143 (75%)	78 (42%)	96 (50%)
Severe Myalgia	11 (6%)	1(1%)	3 (2%)
Headache-any	55 (29%)	46 (25%)	57 (30%)
Severe Headache	2 (1%)	0 (0%)	2 (1%)
Rash-any	3 (2%)	8 (4%)	9 (5%)
Severe-Rash	2 (1%)	6 (3%)	5 (3%)
Fever (>38°)	2 (1%)	3 (2%)	5 (3%)
(38°-39°)	2 (1%)	3 (2%)	5 (3%)
(39°-40°)	0 (0%)	0 (0%)	0 (0%)
Severe Fever (>40°)	0 (0%)	0 (0%)	0 (0%)
Use analgesic/ antipyretic -Prophylactic	7 (4%)	2 (1%)	1 (1%)
Use analgesic /antipyretic-Therapeutic	36 (19%)	10 (5%)	17 (9%)
Stayed home due to reactions	6 (3%)	4 (2%)	3 (2%)
Second Vaccination	N=185	N=175	N=182
Arthralgia-any	24 (13%)	16 (9%)	14 (8%)
Severe Arthralgia	2 (1%)	2 (1%)	0 (0%)
Nausea-any	18 (10%)	8 (5%)	12 (7%)
Severe Nausea	1 (1%)	0 (0%)	2 (1%)
Malaise-any	41 (22%)	19 (11%)	23 (13%)
Severe Malaise	4 (2%)	1 (1%)	1 (1%)
Myalgia-any	127 (69%)	83 (47%)	64 (35%)
Severe Myalgia	12 (7%)	2 (1%)	0 (0%)
Headache-any	38 (21%)	20 (11%)	42 (23%)
Severe Headache	3 (2%)	1 (1%)	3 (2%)
Rash-any	6 (3%)	2 (1%)	3 (2%)
Severe-Rash	2 (1%)	2 (1%)	2 (1%)
Fever (>38°)	5 (3%)	2 (1%)	2 (1%)
(38°-39°)	3 (2%)	2 (1%)	2 (1%)
(39°-40°)	2 (1%)	0 (0%)	0 (0%)
Severe Fever (>40°)	0 (0%)	0 (0%)	0 (0%)
Use analgesic/ antipyretic -Prophylactic	16 (9%)	5 (3%)	2 (1%)
Use analgesic /antipyretic-Therapeutic	39 (21%)	11 (6%)	8 (4%)
Stayed home due to reactions	10 (5%)	2 (1%)	1 (1%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

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Unsolicited AEs – by System Organ Class (SOC)

Unsolicited AEs in immunogenicity subset:

The unsolicited AEs analyzed in the immunogenicity/safety subset of subjects included all AEs reported by day 7, and all SAEs and medically attended AEs reported throughout the study. Similar to other AEs, a higher percentage of subjects from the rMenB+OMV group reported unsolicited AEs compared to the MenACWY and control groups (87 subjects or 45% in the rMenB+OMV group versus 56 subjects or 29% in the MenACWY group and 69 subjects or 35% in the control groups). Additional details of the unsolicited AEs in the immunogenicity/safety subset population can be found in the medical officer's review.

Unsolicited AEs in overall safety set:

The unsolicited AEs in the overall safety set included all SAEs, medically attended AEs, and withdrawals from the study due to AEs, reported throughout the study. Across vaccine groups, 35% to 40% of subjects reported unsolicited AEs, with 40% in the rMenB+OMV group and 35-39% in the comparator groups. The majority of these AEs were reported beyond the 7-day reporting period. Based on the applicant's clinician's evaluation, the majority of the AEs assessed to be at least possibly related to the study vaccine were reported within the 7-day window (6% in the rMenB+OMV group and 3% in the comparator groups).

The most commonly reported SOC across vaccine groups during the entire study period, was "infections and infestations," which occurred at similar rates among all treatment groups (18% in the rMenB+OMV and 17% in the comparator treatment groups).

Based on data provided in the AE dataset, other commonly reported AEs were "general disorders and administration site conditions" (6% in the rMenB+OMV group and 3% or less in the comparator treatment groups), most including solicited local and systemic reactions beyond the 7-day window.

Additional details related to the unsolicited AEs occurring anytime post vaccination during the study can be seen in the following table.

Figure 6.1.12.a) Summary of All Unsolicited AEs after Any Vaccination throughout the study duration by System Organ Class (SOC) –Safety Population: Number and Percent (%) of Subjects with AEs

System Organ Class (SOC)	All AE rMenB+ OMV	All AE MenACWY	All AE Control	Related AE rMenB+ OMV	Related AE MenACWY	Related AE Control
	N=974	N=984	N=985	N=974	N=984	N=985
Any AE	386 (40)	344 (35)	380 (39)	70 (7)	36 (4)	38 (4)
Blood & Lymphatic System	12 (1)	4 (<1)	8 (1)	2 (<1)	1 (<1)	1 (<1)
Cardiac Disorder	1 (<1)	2 (<1)	2 (<1)	0	0	0
Congen./Genetic Disorder	0	0	1 (<1)	0	0	0
Ear & Labyrinth Disorders	2 (<1)	4 (<1)	3 (<1)	0	1 (<1)	0
Endocrine Disorders	1 (<1)	3 (<1)	0	1 (<1)	0	0
Eye Disorders	6 (1)	5 (1)	7 (1)	0	1 (<1)	2 (<1)
Gastrointestinal Disorders	48 (5)	39 (4)	44 (4)	4 (<1)	1 (<1)	4 (<1)
Gen Disorder& Admin Site Cond.	56 (6)	29 (3)	27 (3)	41 (4)	4 (<1)	7 (1)
Immune System Disorders	4 (<1)	4 (<1)	4 (<1)	0	0	0
Infections and Infestations	175 (18)	168 (17)	170 (17)	7 (1)	11 (1)	13 (1)
Injury and Poisoning	57 (6)	57 (6)	60 (6)	1 (<1)	1 (<1)	0
Investigations	4 (<1)	3 (<1)	4 (<1)	1 (<1)	0	0
Metabolism & Nutrition Disorders	3 (<1)	1 (<1)	5 (1)	0	1 (<1)	1 (<1)
Musc., Connect Tis & Bone Disorders	37 (4)	22 (2)	25 (3)	19 (2)	4 (<1)	2 (<1)
Neo. Ben/Malig (incl. cysts/polyps)	3 (<1)	7 (1)	3 (<1)	0	0	0
Nervous system disorders	31 (3)	21 (2)	30 (3)	6 (1)	4 (<1)	8 (1)
Pregnancy/Perinatal Cond	1 (<1)	0	0	0	0	0
Psychiatric Disorders	29 (3)	22 (2)	21 (2)	0	1 (<1)	2 (<1)
Renal & Urinary Disorders	2 (<1)	7 (1)	5 (1)	0	0	0
Reproduct. Sys & Breast Disorders	12 (1)	14 (1)	22 (2)	0	0	0
Resp, Thoracic, & Mediastinal Disorder	41 (4)	47 (5)	38 (4)	3 (<1)	3 (<1)	3 (<1)
Skin & Subcutaneous Tis. Disorders	52 (5)	50 (5)	46 (5)	13 (1)	10 (1)	5 (1)
Social Circumstances	1 (<1)	0	1 (<1)	0	0	0
Surgical & Medical Procedures	7 (1)	11 (1)	6 (1)	0	0	0
Vascular Disorders	1 (<1)	2 (<1)	3 (<1)	0	0	1 (<1)

Source: Reviewer created table based on BLA 125546 Clinical Study Report of Study V72_P29 and data provided in

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Similar results can be seen when examining all adverse events noted during the initial 7 days post vaccination. Of note is the most commonly reported AEs within days 1 to 7 were “general disorders and administration site conditions” which were reported by a higher percentage of subjects from the rMenB+OMV group (5%) than in the MenACWY (1%) and placebo control groups (1%). A second AE noted within 7 days of vaccination was “infections and infestations,” which was noted in 3% of the rMenB+OMV group while the comparator treatment groups had 1% in the control group and 3% in the MenACWY. Additional details related to the unsolicited AEs with an onset of 1-7 days post vaccination can be seen in the following table.

Figure 6.1.12.b) Summary of All Unsolicited AEs with Onset between 1-7 Days after Any Vaccination by System Organ Class (SOC)–Safety Population: Number and Percent (%) of Subjects with Unsolicited AEs

	All AE	All AE	All AE	Related AE	Related AE	Related AE
System Organ Class	rMenB+OMV	MenACWY	Control	rMenB+OMV	MenACWY	Control
	N=974	N=984	N=985	N=974	N=984	N=985
Any AE	121 (12)	70 (7)	90 (9)	61 (6)	25 (3)	25 (3)
Ear & Labyrinth Disorders	1 (<1)	2 (<1)	2 (<1)	0	1 (<1)	0
Ear & Labyrinth Disorders	0	1 (<1)	1 (<1)	0	0	0
Eye Disorders	1 (<1)	1 (<1)	2 (<1)	0	1 (<1)	2 (<1)
Gastrointestinal Disorders	12 (1)	7 (1)	14 (1)	3 (<1)	1 (<1)	4 (<1)
Gen Disorders & Admin Site Cond.	45 (5)	9 (1)	9 (1)	41 (4)	4 (<1)	6 (1)
Infections and Infestations	25 (3)	23 (2)	31 (3)	5 (1)	6 (1)	6 (1)
Injury and Poisoning	9 (1)	7 (1)	6 (1)	1 (<1)	1 (<1)	0
Investigations	1 (<1)	0	0	1 (<1)	0	0
Metabolism & Nutrition Disorders	1 (<1)	0	0	0	0	0
Musc., Connect Tis & Bone Disorders	21 (2)	6 (1)	5 (1)	18 (2)	3 (<1)	2 (<1)
Nervous system disorders	9 (1)	6 (1)	10 (1)	5 (1)	4 (<1)	6 (1)
Psychiatric Disorders	6 (1)	2 (<1)	1 (<1)	0	0	0
Renal & Uninary Disorders	0	0	1 (<1)	0	0	0
Repro. Sys. & Breast Disorders	2 (<1)	1 (<1)	3 (<1)	0	0	0
Resp., Thoracic & Mediastinal Disorders	20 (2)	14 (1)	14 (1)	3 (<1)	3 (<1)	3 (<1)
Skin & Subcutaneous Tis Disorders	17 (2)	11 (1)	8 (1)	11 (1)	8 (1)	3 (<1)
Vascular Disorders	0	0	1 (<1)	0	0	1 (<1)

Source: Reviewer created table based on data provided in BLA 125546 Clinical Study Report of Study V72_P29

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6.1.12.1 Methods

Only descriptive statistics for the safety endpoints were to be presented. The presentation of results was to include tabulations of both expected and unexpected adverse events, as well as systematically collected local and systemic adverse events noted on the 7-day patient daily card detailing reactions and the 7 day post-injection experiences. No further statistical methods were to be implemented utilizing the safety data collected in this study.

6.1.12.2 Deaths

No deaths were reported in this study.

6.1.12.3 Nonfatal Serious Adverse Events

As can be seen in the previous tables across vaccine groups, 2% to 3% of subjects reported SAEs. Most commonly reported SAEs were categorized as “infections and infestations” (1%). All other reported SAEs were recorded in $\leq 1\%$ of subjects across vaccine groups. Most of the SAEs were rated moderate or severe in intensity by the applicant’s clinician and were transient in nature. SAEs in three subjects were assessed to be at least possibly related to the study product. These AEs were noted to be: 1 subject in the rMenB+OMV group diagnosed with dyspnea 2 days after vaccination, which resolved by study termination; one subject in the rMenB+OMV treatment group with thyroiditis diagnosed 18 days after vaccination, which persisted; and 1 subject in the rMenB+OMV treatment group diagnosed with tremor 18 days post vaccination, who was referred to a neurologist. Additional information on these subjects can be seen in the medical officer’s review.

6.1.12.4 Adverse Events of Special Interest (AESI)

Approximately 1% of all subjects (26 of approximately 3000) withdrew from the study due to AEs. Most of these AEs were categorized under “general disorders and administration site conditions.” The majority of these AEs were assessed by the applicant’s clinician to be at least possibly related to the study vaccination. However, it is of note that the rates for withdrawals due to AEs were comparable for the three treatment arms, with rates of discontinuation due to AEs as 11/979, 8/988, and 3/987 for the rMenB+OMV, MenACWY, and control arm, respectively.

6.1.12.5 Clinical Test Results

Individual laboratory measurements were not routinely performed to assess safety in this study. Thus, no clinical test results are available for analysis or discussion.

6.1.12.6 Dropouts and/or Discontinuations

A total of 502 subjects (17%) withdrew from the study. The primary reason for withdrawal was “lost to follow-up,” which varied from 10-13% of subjects in the different treatment groups. The second most common reason for dropout/discontinuation was “withdrawal of consent,” which varied from 3-4% of the subjects in the different treatment groups. Overall, these rates were consistent between treatment arms and are similar to rates in other studies that are up to a year in duration.

Reviewer Comment: *This study appeared to be well-organized and effectively implemented. This study was performed in the UK in students 18-24 years of age; thus, the age range studied is consistent with the proposed label indication. No sites in this study were in the US. While the observed dropout rate approached 17%, the dropout rate for each treatment group was fairly comparable with a slightly higher rate for the Bexsero® /rMenB+OMV treatment group. Furthermore, the explicit withdrawal rate was less than 3%, and the rates were comparable between treatment arms. The observed Severe Adverse Events were slightly higher in the Bexsero® /rMenB+OMV treatment group; however, for all treatment groups, the rates were consistently less than 5% for specific diagnosed conditions and less than 10% for system organ classes. Additionally, for AEs that were thought to be treatment related by the applicant’s clinician and concurred by the Agency’s medical officer, the observed Severe Adverse Events were less than 5% for all AEs for all treatment groups. Based on the data provided in this study, the rMenB+OMV vaccine had a higher frequency of severe local and systemic reactogenicity and Adverse Events, but all events were self-limiting and resolved by the study’s conclusion.*

6.2 Trial #2: V72_41: Canada/Australia Phase III Study

This study, entitled “A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with Outer Membrane Vesicle (OMV) Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years,” was designed to examine the safety and efficacy of two doses administered 1 month apart of two different lots of Bexsero® in Canada and Australia. The study collected immunogenicity, local and systemic reactogenicity data, as well as expected and unexpected adverse events for up to 2 months post-vaccination.

6.2.1 Objectives (Primary, Secondary, Safety, etc.)

Primary Objective

The primary objective of this study was to examine the immunogenicity of both lots of product. Details related to the immunogenicity objectives identified by the applicant are included in the Statistical Review of Efficacy.

Secondary objectives

The secondary objective of this study was to further examine additional immune responses to both lots of product and is also included in the Statistical Review of Efficacy.

Safety Objective:

The safety objective of this study was to evaluate the safety and tolerability of two doses of two rMenB+OMV NZ vaccine lots formulated with OMV manufactured at 2 different manufacturing sites, given one month apart, in healthy adolescents.

6.2.2 Design Overview

This is a Phase 3, multicenter, observer-blind randomized trial in adolescents (11-17 years of age, inclusive). All subjects received two rMenB+OMV NZ vaccinations one month apart and were followed for a total of 2 months (that is, until one month following the second vaccination). Subjects were randomized to 1 of 2 treatment arms to receive either two doses of rMenB+OMV NZ vaccine Lot 1 or 2 doses of rMenB+OMV NZ Lot 2. Lot 1 was formulated with OMV manufactured in the Novartis Rosia facility and Lot 2 from the Novartis (b)(4) facility.

Table 6.2.2. Overview of the Study Design

	Visit 1	Visit 2	Visit 2b*	Visit 3
	Day 1	Month 1	Month 1.5	Month 2
Group1				
MenB: Bexsero® Lot1 (n=160)	Blood Draw MenB: Bexsero® Lot1	MenB: Bexsero® Lot1	Blood	Blood
Group2				
MenB: Bexsero® Lot2 (n=160)	Blood Draw MenB: Bexsero® Lot2	MenB: Bexsero® Lot2	Blood	Blood

Source: Table summarizes data within applicant provided study report and datasets

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Note: *At Visit 2b (Month 1.5), sera were collected in a subset of approximately 160 subjects (approximately 80 subjects in Group 1 and approximately 80 subjects in Group 2). Pre-selected sites enrolled the subset of subjects who required an additional blood draw at two weeks after the second vaccination.

6.2.3 Population

Subjects were healthy adolescents who fulfilled all the inclusion criteria, had none of the exclusion criteria, and were 11-17 years of age. Subjects were located in thirteen treatment sites in two countries: Canada and Australia.

In this study, 320 subjects were planned to be enrolled, with 160 subjects per lot who were to be randomized in a 1:1 ratio. With a total drop-out rate of 15% assumed, a sample size of 135 evaluable subjects per arm were planned to be vaccinated with rMenB+OMV NZ in groups Lot 1_Rosia and Lot 2_(b)(4), respectively.

6.2.4 Study Treatments or Agents Mandated by the Protocol

There were two treatment arms in this study that compared two different lots of MenB vaccine. Specifically, the two investigational treatments were as follows:

Novartis Meningococcal B Recombinant+OMV NZ vaccine (rMenB+OMV NZ), Lot 1 formulated with OMV manufactured in the Rosia site.

Novartis Meningococcal B Recombinant+OMV NZ vaccine (rMenB+OMV NZ), Lot 2 formulated with OMV was manufactured in the (b)(4) site.

Vaccines at both sites were supplied as a single 0.5 mL dose administered intramuscularly (IM) into the deltoid area. Each dose contained purified antigens from *N. meningitidis* 961c (50 µg), *N. meningitidis* 936-741 (50 µg), *N. meningitidis* 287-953 (50 µg), OMV from *N. meningitidis* Strain NZ 98/254 (25 µg), and Aluminum hydroxide (1.5 mg).

Since this study was a lot comparison study, no placebo comparator arm was planned.

6.2.6 Sites and Centers

The study was conducted in Canada and Australia in 13 different sites. Specifically, there were 6 centers located in Australia and 7 centers located within Canada. Additional details related to the study locations can be found in the medical officer's and/or chairperson's review.

6.2.7 Surveillance/Monitoring

Study monitoring and auditing were performed in accordance with the applicant's standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, ICH, and GCP guidelines).

At visits during and after the study, the site was monitored by a study monitor for compliance, including accurate and complete recording of data on eCRFs, source documents, and drug accountability records. The study was conducted according to the principles of GCP.

Study progress was monitored by Novartis Vaccines and Diagnostics as frequently as necessary to ensure the rights and well-being of study subjects were protected, to verify adequate, accurate, and complete data collection, and protocol compliance, and to determine that the study was being conducted in conformance with applicable regulatory requirements. Arrangements for monitoring visits were made in advance in accordance with the monitoring plan, except in case of emergency.

6.2.8 Endpoints and Criteria for Study Success: Safety Related

Criteria for Evaluation: Safety Endpoints

The Safety endpoints and criteria for study success were based on observed local and systemic reactions 7 days post vaccination via a daily diary card. Additionally, expected and unexpected Serious Adverse Events were to be collected throughout the study.

Local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever of axillary temperature $>38.0^{\circ}\text{C}$, nausea, fatigue, myalgia, arthralgia, headache) reactions were assessed for 7 days (including the day of vaccination) post each vaccination. All adverse events (AEs) which occurred during the 7 days (including the day of vaccination) post each vaccination were collected on a Diary Card.

Serious adverse events (SAEs), medically attended AEs, and AEs that resulted in a subject's withdrawal from the study were collected throughout the study period.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical Methods: The statistical evaluation of the results was performed by biostatistics and clinical data management (BCDM) as predefined in the statistical analysis plan (SAP). The statistical tables and graphs were generated using SAS® version 9.1 or higher. Detailed statistical methods, associated with each of the primary and secondary immunogenicity objectives, can be found in the statistical review of the efficacy data; however, the statistical considerations for the safety parameters are summarized below.

Safety Objective

To evaluate the safety and tolerability of two doses of two rMenB+OMV NZ vaccine lots formulated with OMV manufactured at 2 different manufacturing sites, given one month apart, in healthy adolescents.

Safety was assessed in a descriptive fashion. No statistical comparisons between the vaccine groups were made.

Analysis of Local and Systemic Reactions

Frequencies and percentages of subjects experiencing each reaction were presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and after each vaccination were presented.

Post-vaccination reactions reported from day 1 to day 7 after each vaccination were summarized by maximal severity and by vaccine group. The severity of local reactions, including injection-site erythema, induration, and swelling was categorized as none (0 mm), 1 to <25 mm, 25 to <50 mm, 50 to <100 mm, and ≥ 100 mm (severe local reactions).

The severity of pain and systemic reactions (i.e., nausea, fatigue, myalgia, arthralgia, headache, and rash) occurring up to 7 days (including the day of vaccination) after each

vaccination was categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity).

Rash was categorized as none, urticarial, and other. Frequencies and percentages of subjects experiencing each local and systemic reaction during days 1 to 3 after vaccination were similarly summarized, as well as daily frequencies and the time of onset of the first reactions.

Each local and systemic reaction was also categorized as none vs. any. Body temperature (regardless of the route of measurement) was analyzed in 0.5°C increments as follows: <38.0°C (no fever), 38.0-38.4°C, 38.5°C - 38.9°C, 39.0°C – 39.4°C, 39.5°C – 39.9°C, ≥40.0°C.

Additionally, the number and percentage of subjects who used analgesic or antipyretic medication were summarized, as well as the number and percentage of subjects who stayed home due to a reaction.

No statistical tests were performed to compare the responses of the two groups based on local and systemic reaction safety endpoints.

Analysis of Other Adverse Events

All the adverse events occurring during the study judged either as related to vaccination or not by the clinician were recorded, as specified in the protocol. The original verbatim terms used by clinicians to identify adverse events in the eCRFs were mapped to preferred terms using the MedDRA dictionary. The adverse events were then grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the clinician as at least possibly related to study vaccine, were summarized according to system organ class and preferred term within system organ class. These summaries were presented by vaccination group. When an adverse event occurred, more than once for a subject, the maximal severity was counted.

Additionally, three separate summaries were produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Definition of populations analyzed relevant to the safety:

(a) **All Enrolled Population**-all subjects who:

- signed an informed consent, underwent screening procedure(s), and were randomized.

(b) **Exposed population**-all enrolled subjects who:

- actually received a study vaccination.

(c) **Safety population**-all subjects in the Exposed population who:

- provided post vaccination safety data.

6.2.10.1.1 Demographics

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for age, height, and weight at enrollment were calculated overall and by vaccine group.

Distribution of subjects, by sex and ethnic origin, was summarized overall and by vaccine group and is illustrated in the following table.

Table 6.2.10.1.1 a) Demographics and Other Baseline Characteristics of Subjects-All Enrolled

	Lot 1_Rosia (n=170)	Lot 2_(b)(4) (n=174)	Total (n=344)
Age (Years) ±SD:	13.6±1.9	13.8±1.8	13.7±1.9
Sex			
Male	98(58%)	92(53%)	190(55%)
Female	72(42%)	82(47%)	154(45%)
Ethnic Origin			
Asian	17(10%)	18(10%)	35(10%)
Black, Non-Hispanic	4(2%)	1(<1%)	5(1%)
White, Non-Hispanic	134(79%)	141(81%)	275(80%)
Native America/Alaskan	9(5%)	6(3%)	15(4%)
Pacific Hawaiian	0	1(<1%)	1(<1%)
Other	6(4%)	7(4%)	13(4%)
Weight (kg)±SD	57.86±17.10	57.37±16.23	57.61±16.64
Height (cm)±SD	162.6±10.9	162.3±11.0	162.5±10.9

Table summarizes calculations within applicant provided study report and confirmed by reviewing statistician

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Overall baseline characteristics such as gender, race, age, mean weight, and mean height were balanced across vaccine groups for the enrolled subjects.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects enrolled in this study were to be healthy volunteers, meeting inclusion/exclusion criteria, who were 11-17 years of age.

6.2.10.1.3 Subject Disposition

In this study, 344 individuals were enrolled. Of those 344 individuals, 170 subjects were randomized to Lot 1_Rosia while 174 subjects were randomized to Lot 2_(b)(4). A total of 338 subjects (98%) completed the study as described in the protocol.

A more comprehensive listing of subject disposition can be seen in the following table, Summary of Subject Disposition.

Table 6.2.10.1.3 a) Summary of Subject Disposition (Number and % of Subjects)

	Lot 1_Rosia	Lot 2_(b)(4)	Total
Enrolled	170	174	344
Received Treatment	169 (>99%)	173 (>99%)	342 (>99%)
Completed protocol	168 (99%)	170 (98%)	338 (98%)
Premature Withdrawal	2 (1%)	4 (2%)	6 (2%)
AE	0	1 (<1%)	1 (<1%)

Table summarizes calculations within applicant provided study report and confirmed by reviewing statistician

-----**(b)(4)**-----

Overall, there appears to be balance between the two treatment groups and similar dropout and withdrawal rates for both groups, for the two lots examined in this study.

It is important to note that the single withdrawal due to “AE” was a subject that withdrew because of “Infectious Mononucleosis.” The applicant suggests that the case of mononucleosis was unlikely to have been related to the vaccination. Further details related to this subject’s withdrawal and disease manifestation are noted in the medical officer’s review.

6.2.11 Efficacy Analyses

The efficacy analysis was predominantly based on immune response. Additional details can be found in the Statistical Review of Efficacy.

6.2.12 Safety Analyses

All subjects who received at least one vaccination and provided some safety data were considered evaluable for the safety analyses. These data included solicited AEs for both local and systemic reactions, and unsolicited AEs collected throughout the study. Predominantly, these data were presented in tabulations stratified by treatment group (Lot).

Analysis of Extent of Exposure

There were 344 subjects randomized to treatment and administered at least one dose of study material. Of the 344 randomized subjects, 2 subjects did not receive any vaccination. Of these 342 subjects receiving any vaccination, 169 subjects in the Lot 1_Rosia and 173 subjects in the Lot 2_(b)(4) treatment group received the randomized study treatment. Furthermore, 168 subjects in the Lot1_Rosia and 170 subjects in the Lot2_(b)(4) treatment groups continued the study through the entire duration, including

administering dose 1 of vaccine on day 1, dose 2 of vaccine approximately 1 month later, and a safety follow-up for 2 months following second dose of vaccine.

Analysis of Local and Systemic Reactions

Frequencies and percentages of subjects experiencing each reaction were presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and after each vaccination were presented.

Post-vaccination reactions reported from day 1 to day 7 after each vaccination were summarized by maximal severity and by vaccine group. The severity of local reactions, including injection-site erythema, induration, and swelling was categorized as none (0 mm), 1 to <25 mm, 25 to <50 mm, 50 to <100 mm, and 100 mm (severe local reactions).

Within the daily diary card and based on clinician assessments, the severity of pain and systemic reactions (i.e., nausea, fatigue, myalgia, arthralgia, headache, and rash) occurring up to 7 days (including the day of vaccination) after each vaccination was categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity).

In this study, rash was categorized as none, urticarial, and other. Frequencies and percentages of subjects experiencing each local and systemic reaction during days 1 to 3 after vaccination were similarly summarized, as well as daily frequencies and the time of onset of the first reactions.

Each local and systemic reaction was also categorized as none vs. any. Body temperature (regardless of the route of measurement: axillary, oral, etc.) was analyzed in 0.5°C increments as follows: <38.0°C (no fever), 38.0-38.4°C, 38.5°C - 38.9°C, 39.0°C – 39.4°C, 39.5°C – 39.9°C, and >40.0°C.

Additionally, the number and percentage of subjects who used analgesic or antipyretic medication were summarized, as well as the number and percentage of subjects who stayed home due to a reaction based on self-reported assessments within the daily diary card.

No statistical tests were planned or performed to compare the responses of the two groups based on local and systemic reaction safety endpoints.

Analysis of Other Adverse Events

Within the protocol, it was stated that all the adverse events occurring during the study judged either as related to vaccination or not by the clinician were recorded. As per the applicant, the original verbatim terms used by clinicians to identify adverse events in the eCRFs were mapped to preferred terms using the MedDRA dictionary. These adverse

events could then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). For completeness, all reported adverse events, as well as adverse events judged by the clinician as at least possibly related to study vaccine, were summarized according to system organ class and preferred term within system organ class. These summaries were to be presented by vaccination group. When an adverse event occurred repeatedly after vaccination (i.e., more than once for a subject), the maximal severity was to be counted and presented within the tabulations.

In addition to tabulations based on frequencies of adverse events, three separate summaries were produced:

- a) serious adverse events (as defined by the clinician),
- b) adverse events that are possibly or probably related to vaccine, and
- c) adverse events that are unrelated to vaccine.

In addition, a listing of subjects withdrawn from the study because of an adverse event was presented, as well as a listing of adverse events leading to hospitalization. These analyses utilized the data provided by the applicant, including the COMMENTS, AE, and POSTINJ datasets.

6.2.12.1 Methods

Descriptive statistics for the safety endpoints were presented, including both expected and unexpected adverse events, as well as systematically collected local and systemic adverse events noted on the 7-day patient daily diary card detailing the 7-day post-injection experiences. No further statistical methods were to be implemented utilizing the safety data collected in this study.

Safety results:

All subjects who received at least one vaccination and provided some safety data were considered evaluable for the safety analyses. All safety analyses were run using the safety population as defined previously in section 6.1.10.1. Safety was assessed in terms of number of subjects exposed to the study vaccines with reported local and systemic reactions, as well as the number of all subjects with reported SAEs and/or AEs (as specified for each time period) per vaccine group. All SAEs and AEs were judged by the clinician either as probably related, possibly related, or not related to vaccine and were tabulated. All SAEs and AEs resulting in withdrawal from the study were summarized.

Table 6.2.12.1.a) Summary of Study Participants –Safety Data

	Lot 1_Rosia	Lot 2_(b)(4)	Total
Enrolled	N=170	N=174	N=344
Exposed-Dose 1	169 (>99%)	173 (>99%)	342 (>99%)
Exposed-Dose 2	168 (99%)	170 (99%)	368 (99%)

Reviewer created table summarizing data within applicant provided study report and datasets

------(b)(4)-----

Solicited AEs:

Based on data provided by the applicant in the datasets POSTINJ, COMMENTS, and AE, a majority of subjects (nearly all) from both lots of the Bexsero® treatment groups reported any solicited local and systemic AEs after each vaccination: 96-98% after first and 92-96% after second vaccination for each of the vaccine lots. Additionally, the data collected and provided by the applicant demonstrate that there was a slight decrease in the percentage of subjects with local and systemic AEs after second Bexsero® vaccination when compared to the AEs reported after first Bexsero® vaccination for both lots. Details of the observed reactions can be observed in the following table.

Table 6.2.12.1.b) Summary of Solicited AEs during the 7 Day Period after Each Vaccination-Immunogenicity/Safety Subset Population (Number and % of Subjects with Solicited Reactions)

	Dose 1	Dose 1	Dose 2	Dose 2	Any dose	Any dose
Treatment	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173	Lot 1_Rosia N=168	Lot 2_(b)(4) N=170	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173
Reaction						
Any	163 (96%)	169 (98%)	154 (92%)	163 (96%)	165 (98%)	171 (99%)
Local	160 (95%)	167 (97%)	153 (91%)	162 (95%)	163 (96%)	170 (98%)
Systemic	126 (75%)	136 (79%)	95 (57%)	112 (66%)	136 (80%)	150 (87%)
Other	74 (44%)	79 (46%)	54 (32%)	63 (37%)	87 (51%)	96 (55%)

Reviewer created table summarizing data within applicant provided study report and datasets

------(b)(4)-----

Unsolicited AEs:

Within the two different vaccine groups, Lot1_Rosia and Lot2_(b)(4), approximately 35% to 40% of subjects reported unsolicited AEs within the protocol specified reporting period. All unsolicited AEs were noted to be self-limiting and resolved by the end of the study period.

No SAEs were reported by any subjects within either lot group. Premature withdrawals were reported by 1-2% of subjects within each vaccine lot. In the majority of subjects, the AEs leading to premature withdrawal were considered by the clinician to be possibly or probably related to the study vaccination, for both lot groups.

A detailed summary of the unsolicited AEs noted during the study can be seen in the following table.

Table 6.2.12.c) Summary of Unsolicited AEs during the Entire Study Period (Number and % of Subjects with Unsolicited Reactions)

	Lot 1_Rosia	Lot 2_(b)(4)	Total
	N=169	N=173	N=342
Any AE	68 (40%)	65 (38%)	133 (39%)
At least possible related AE	34 (20%)	38 (22%)	72 (21%)
Serious AE	0 (0%)	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)
Premature withdrawal due to AE	0 (0%)	1 (1%)	1 (<1%)
Dose reduction, interruption or delay due to an AE	2 (1%)	3 (2%)	5 (1%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets

------(b)(4)-----

Solicited local AEs:

Based on data provided in the POSTINJ dataset, which contains patient responses within daily diary cards of selected AEs from subjects in the safety population, there were similar reported rates of solicited AEs in both Bexsero®/rMenB+OMV lot groups, Lot1_Rosia and Lot2_(b)(4). Similar rates were also observed when considering “severe” local reactions. From the table below, it can be seen that the most common side effect of this vaccination was pain, with well over 90% of subjects experiencing some pain after both doses. The next most common adverse event was erythema, with between 40-65% of subjects experiencing this AE. Swelling and induration were experienced by approximately 30% of subjects; however, like the other solicited local reactions, very few subjects experienced severe symptoms. Regardless of lot group there was a general tendency of decrease in percentage of subjects reporting each local reaction after second vaccination when compared to the reports after first vaccination. This may be a function of decreased reactogenicity upon subsequent exposures to vaccine. A more detailed examination of the local reaction rates can be seen in the following table.

Table 6.2.12.1.d) Number and % of Subjects with Any and “Severe” Local Reactions in Vaccination-Safety Population

		Dose 1	Dose 1	Dose 2	Dose 2	Any dose	Any dose
	Treatment	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173	Lot 1_Rosia N=168	Lot 2_(b)(4) N=170	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173
Pain	Any	159 (94%)	167 (97%)	149 (89%)	158 (93%)	162 (96%)	170 (98%)
	Severe	18 (11%)	19 (11%)	10 (6%)	19 (11%)	24 (14%)	30 (17%)
Induration	Any	41 (24%)	51 (29%)	47 (28%)	46(27%)	65 (38%)	74 (43%)
	Severe (≥ 100mm)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Erythema	Any	80 (48%)	75 (43%)	87 (52%)	88 (52%)	110 (65%)	111 (64%)
	Severe (> 100mm)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Swelling	Any	50 (30%)	43 (25%)	59 (35%)	57 (34%)	80 (47%)	74 (43%)
	Severe (> 100mm)	0 (0%)	0 (0%)	1/167 (1%)	0 (0%)	1 (1%)	0 (0%)

Reviewer created table summarizing data within applicant provided study report and datasets particularly the POSTINJ dataset

------(b)(4)-----

Solicited systemic AEs:

There was a similar reported rate of solicited systemic AEs in both Bexsero® lot groups. Based on all solicited systemic AEs, both lot groups receiving the rMenB+OMV vaccine reported similar percentages of subjects with various systemic AEs. The most commonly occurring systemic AEs were myalgia (53-59% of subjects after the first dose and 37-41% after second vaccinations), fatigue (~35% of subjects after the first dose and 29-36% after the second dose,) arthralgia (12-17% of subjects after the first dose and 9-16% after second vaccinations), and nausea (~20% of subjects after first dose and second dose). The majority of systemic AEs decreased after the first dose; however, in some cases the systemic reactogenicity did increase after the second dose. Additional details of the systemic AEs can be observed in the following table.

Table 6.2.12.1.e) Number and % of Subjects with Any and “Severe” Systemic Reactions in Vaccination-Safety Population

		Dose 1	Dose 1	Dose 2	Dose 2	Any dose	Any dose
	Treatment	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173	Lot 1_Rosia N=168	Lot 2_(b)(4) N=170	Lot 1_Rosia N=169	Lot 2_(b)(4) N=173
Arthralgia	Any	20 (12%)	29 (17%)	15 (9%)	28 (16%)	28 (17%)	44 (25%)
	Severe	0 (0%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	3 (2%)
Fatigue	Any	60 (36%)	61 (35%)	48 (29%)	61 (36%)	75 (44%)	85 (49%)
	Severe	4 (2%)	3 (2%)	1 (1%)	7 (4%)	5 (3%)	10 (6%)
Headache	Any	54 (32%)	63 (36%)	47 (28%)	66 (39%)	75 (44%)	89 (51%)
	Severe	2 (1%)	4 (2%)	4 (2%)	3 (2%)	6 (4%)	6 (3%)
Myalgia	Any	90 (53%)	102 (59%)	62 (37%)	70 (41%)	99 (59%)	118 (68%)
	Severe	9 (5%)	6 (3%)	2 (1%)	9 (5%)	11 (7%)	13 (8%)
Nausea	Any	31 (18%)	33 (19%)	30 (18%)	36 (21%)	49 (29%)	56 (32%)
	Severe	2 (1%)	3 (2%)	1 (1%)	4 (2%)	3 (2%)	7 (4%)
Rash	Any	7 (4%)	7 (4%)	6 (4%)	11 (6%)	11 (7%)	16 (9%)
	Severe	1 (1%)	0 (0%)	1 (1%)	2 (1%)	1 (1%)	2 (1%)
Fever	>38°	5 (3%)	4 (2%)	4 (2%)	1 (1%)	8 (5%)	5 (3%)
Other							
Temp	≤38°	164 (97%)	169 (98%)	164 (98%)	169 (99%)	164 (98%)	169 (98%)
	>40°	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Use Analgesic	Yes	71 (42%)	75 (43%)	47 (28%)	59 (35%)	82 (49%)	92 (53%)
Stay Home	Yes	13 (8%)	16 (9%)	18 (11%)	12 (7%)	23 (14%)	23 (13%)

Reviewer created table summarizing data within applicant provided study report and datasets particularly the POSTINJ dataset

------(b)(4)-----

Unsolicited AEs in overall safety set:

The unsolicited AEs in the overall safety set included all SAEs, medically attended AEs, and withdrawals from the study due to AEs, reported throughout the study. Across the two vaccine lots, 35% to 40% of subjects in each vaccine group reported unsolicited AEs. Based on clinician’s assessment, approximately 20% of subjects experienced Adverse Events that were at least possibly related to study vaccine. The majority of AEs assessed to be at least possibly related to study vaccination were injection site pain (6-7%), injection site induration (3-4%), and myalgia (3%). Additional details related to the observed adverse events can be seen in the following table.

Table 6.2.12.1.f) Number and % of Subjects with Unsolicited Adverse Events-Safety Population

	All AE	All AE	All AE	Related AE	Related AE	Related AE
	Lot 1_Rosia	Lot 2_(b)(4)	Total	Lot 1_Rosia	Lot 2_(b)(4)	Total
	N=169	N=173	N=342	N=169	N=173	N=342
Any Adverse Event	68 (40%)	65 (38%)	133 (39%)	34 (20%)	38 (22%)	72 (21%)
Injection Site Pain	10 (6%)	12 (7%)	22 (6%)	10 (6%)	12 (7%)	22 (6%)
Upper Respiratory Tract Infection	8 (5%)	4 (2%)	12 (4%)	4 (2%)	2 (1%)	6 (2%)
Injection Site Induration	3 (2%)	7 (4%)	10 (3%)	3 (2%)	7 (4%)	10 (3%)
Nasopharyngitis	3 (2%)	7 (4%)	10 (3%)	0	0	0
Abdominal Pain Upper	6 (4%)	2 (1%)	8 (2%)	3 (2%)	0	3 (1%)
Dizziness	6 (4%)	2 (1%)	8 (2%)	2 (1%)	1 (1%)	3 (1%)
Myalgia	5 (3%)	6 (3%)	11 (3%)	5 (3%)	6 (3%)	11 (3%)
Swelling	0	6 (3%)	6 (2%)	0	5 (3%)	5 (1%)
Arthralgia	0	5 (3%)	5 (1%)	0	4 (2%)	4 (1%)

Reviewer created table summarizing data within applicant provided study report and datasets particularly the AE and COMMENTS --
----- (b)(4) -----

Additional details of the solicited and unsolicited AEs in the safety population can be found in the medical officer's review.

6.2.12.3 Deaths

No deaths were observed during this study.

6.2.12.4 Nonfatal Serious Adverse Events

There was a single non-fatal serious adverse event that caused the subject to withdraw from this study. This subject withdrew because of "Infectious Mononucleosis." The applicant suggested that it is unlikely that the mononucleosis case was related to the vaccination. Further details related to this subject's withdrawal and disease manifestation are noted in the medical officer's review.

6.2.12.5 Adverse Events of Special Interest (AESI)

No additional Adverse Events of Special Interest were noted.

6.2.12.6 Clinical Test Results

No additional Clinical Tests were performed.

6.2.12.7 Dropouts and/or Discontinuations

A total of 6 subjects prematurely withdrew from the study. Two individuals dropped out from the Lot 1_Rosia treatment group, and 4 individuals dropped out from the Lot2_(b)(4) treatment group, less than 2% of individuals overall and per treatment arm.

Of these individuals, only one subject in the Lot 2_(b)(4) group withdrew due to an AE. The other individuals withdrew consent. More details related to the dropouts and discontinuations can be found in the medical officer's review.

Overall Summary and Conclusion on Safety Data for Study V72_P41:

Overall, 344 subjects aged 11 to 17 years were enrolled in the study. Of these, 170 were to receive Lot1_Rosia and 174 subjects were to receive Lot2_(b)(4). The safety population was composed of 342 subjects: 169 subjects in Lot1_Rosia and 173 subjects in Lot2_(b)(4). Two of the enrolled subjects (59/001/Lot1_Rosia and 52/023/Lot2_(b)(4)) did not receive any vaccination at all, and were therefore excluded from safety analyses.

The demographic and other baseline characteristics for the enrolled population in the Lot1_Rosia and Lot2_(b)(4) groups were well matched, except for gender differences. There was a 5% difference in percentage of males (58% and 53%) and females (42% and 47%) between Lot1_Rosia and Lot2_(b)(4), respectively. The majority of subjects in the Lot1_Rosia and Lot2_(b)(4) groups were White. These gender differences did not affect the lot consistency conclusions for this study.

Both lots were generally well tolerated, with a slightly higher frequency of systemic reactions in adolescents who received rMenB+OMV NZ vaccine from Lot2_(b)(4). However, the lot groups had similar overall safety profiles with regard to the frequency of adverse events.

Reviewer Comment: *The reviewing statistician was able to recreate the applicant's results, and determine that the data from this study demonstrate safety trends similar to those observed in other studies. Despite the lack of a placebo control, this study provides supportive evidence that this product is reasonably safe in the 10-17 year age range. However, if there are fundamental differences in safety responses between children in the US versus Canada and Australia, this study would not account for these differences. Additionally, without a placebo control arm, calculating the background rate of adverse events is not possible within this study; however, based on other studies, it appears that the rates of AEs observed in this study are comparable to those in other studies which included placebo treatment arms. Based on the data provided within this study, this product elicited systemic and local reactions after both the first and second vaccination. However, all reactions noted were self-limiting and resolved by the end of the study.*

6.3 Trial #3: V102_3: Poland/US Phase II Study

This study, entitled "*Phase 2, Observer Blinded, Controlled, Randomized Multi-Center Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of -----(b)(4)----- Combination Vaccination Formulations,*" was designed to examine the safety and efficacy of two doses administered 1 month apart of two different formulations of Bexsero® in the USA and Poland. The study collected

immunogenicity, and local and systemic reactogenicity data, as well as expected and unexpected adverse events for up to 240 days or ~8 months post initial vaccination.

6.3.1 Objectives

Primary Objective

The primary objective of this study was to examine the immunogenicity of both lots of product as well as to identify to optimal formulation. The immunogenicity is reviewed within the Statistical Review of Efficacy of this product.

Safety Objectives:

The pre-specified safety objective was to evaluate the safety of 2 doses of each of the (b)(4) formulations of ---(b)(4)----- vaccine, based on both solicited and unsolicited adverse events. However, for the purposes of this submission, the additional treatment group of rMenB+OMV alone was also of interest. Moreover, the Placebo/MenACWY treatment group was considered a comparator, although it was not strictly considered a placebo comparator because of the administration of MenACWY during the second vaccination phase.

6.3.2 Design Overview

This was a phase 2, observer-blinded, controlled, randomized, multicenter study in healthy adolescents and young adults to evaluate the safety and immunogenicity of----- (b)(4)----- vaccine formulations. Subjects 10 through 25 years of age were to be enrolled in this study.

6.3.3 Population

A total of approximately 480 healthy subjects in the US and Poland, who met the inclusion criteria and did not meet any exclusion criteria, who were 10 to 25 years of age were to be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups and regimens over the course of 2 months, with follow-up to occur for approximately 8 months post vaccination. The actual number of subjects enrolled was 484; of these, a total of 480 subjects received at least one vaccination and were analyzed.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The four study groups to which subjects were to be randomized in a 1:1:1:1 ratio as follows:

1. Study group ----(b)(4)----- received the ----(b)(4)----- vaccine formulation (containing a ‘full dose’ of outer membrane vesicles [OMV]) on a 0, 2-month schedule. *Vaccine composition:* -----(b)(4)-----

2. Study group ---(b)(4)----- received the ---(b)(4)----- vaccine formulation (containing a ‘quarter dose’ of OMV) on a 0, 2-month schedule.
Vaccine composition----- (b)(4)-----
3. Study group rMenB+OMV received the rMenB+OMV vaccine (containing a ‘full dose’ of OMV) on a 0, 2-month schedule.
Vaccine composition: (rMenB + 25 Pg OMV)
4. Study group Placebo/MenACWY received a single dose of placebo and a single dose of MenACWY vaccine on a 0, 2-month schedule, respectively.
Vaccine composition: Placebo-first dose then MenACWY/Menveo®-second dose

Subjects were to have 2 blood draws (20 mL [\pm 5 mL] each) during the study period. The first one was before the first vaccination on study day 1. A second blood draw was scheduled 30 days following the second vaccination which was approximately study day 91 (-4/ + 14 days).

Subjects were to be given a diary card after each vaccination to collect all solicited AEs (local and systemic), unsolicited AEs, medications associated with any of these AEs, and body temperature daily for 7 days (i.e., day 1 through day 7 after each vaccination). From day 8 through day 91, all unsolicited AEs and associated concomitant medications were to be collected on the diary card. Additionally, subjects were to be given a memory aid worksheet for collection, from day 92 through day 241. These worksheets were designed to collect details of medically attended AEs, AEs leading to study withdrawal, and serious AEs (SAEs). The site was to make a scripted phone call on day 241 to collect final safety data and to carry out study termination procedures. A summary of the proposed schedule is listed below, including treatment group, timeframe, and tasks to be completed.

Table 6.3.3.a) Schedule of Treatment, Timing, and Data Collected

Study Group	Group	No. of subjects	Visit 1 (Day 1) (-1/0 days)	Visit 2 (Day 61) (-6/+14 days)	Visit 3 (Day 91) (-4/+14 days)	Visit 4 (Day 241) (-20/+25 days)
----- (b)(4) -----	1 (I)	120	Blood draw Vaccination	— Vaccination	Blood draw —	Scripted interview phone call/memory aid
----- (b)(4) -----	2 (II)	120	Blood draw Vaccination	— Vaccination	Blood draw —	Scripted interview phone call/memory aid
rMenB+OMV	3 (III)	120	Blood draw Vaccination	— Vaccination	Blood draw —	Scripted interview phone call/memory aid
Placebo/ACWY	4 (IV)	120	Blood draw Placebo vaccination	— Vaccination	Blood draw —	Scripted interview phone call/memory aid

Source: Modification of Applicant provided table from the Clinical Study Report of Study V102_03 page 5

Note: Group 1 and 3 provided information on the MenB dose submitted for consideration in this BLA, while group 2 provided information on a reduced dose formula since only ¼ of OMV was included within this vaccine.

A pilot group of the first 10% of subjects enrolled was to have their safety data from day 1 through day 7 following each vaccination evaluated by an external Data Monitoring

Committee (DMC); enrollment and vaccination for other subjects were paused while this evaluation was carried out. If there were no safety concerns raised by the DMC, the remaining subjects were allowed to receive their next scheduled vaccination.

In addition, instructions in the diary card directed any subject who reported rash within 7 days of vaccination to call the study site and provide additional details about the rash episode. Study site personnel were to be provided with a worksheet that specified the clinical information to be elicited during a structured phone call.

6.3.6 Sites and Centers

This study was conducted in 13 sites, of which 8 sites were in the US and 5 sites were in Poland.

6.3.7 Surveillance/Monitoring

Study monitoring and auditing were performed in accordance with the applicant's standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, ICH, and GCP guidelines).

Study progress was to be monitored by Novartis Vaccines and Diagnostics or its representative (e.g., a contract research organization) as frequently as necessary to ensure that the rights and well-being of study subjects were protected, to verify adequate, accurate, and complete data collection, to verify protocol compliance, and to determine that the study was being conducted in conformance with applicable regulatory requirements. Arrangements for monitoring visits were to be made in advance in accordance with the monitoring plan, except in case of emergency.

The data collected throughout this study to ensure study integrity as well as the safety of study subjects was pre-specified, as provided in the following table which incorporates timing and events.

Table 6.3.4.a) Schedule of Study Monitoring-timing and Data Collected (All Groups)

Study Month	0			2		3		8
Study Day (Window)*	Day 1 (-1/0)	Day 3 2 days after Vaccinat. 1 (0/+2)	Day 8 7 days after Vaccinat. 1 (0/+2)	Day 61 60 days after Vaccinat. 1 (-6/+14)	Day 63 2 days after Vaccinat. 2 (0/+2)	Day 68 7 days after Vaccinat. 2 (0/+2)	Day 91 30 days after Vaccinat. 2 (- 4/+14)	Day 241 180 days after Vaccinat. 2 (-20/+25)
Visit Number	1			2			3	4
Informed Consent	X							
Inclusion/Exclusion	X							
Medical history	X							
Physical exam/assessment	X			X			X	
Meningococcal serology blood draw	20mL						20mL	
Pregnancy test	X			X				
Injection	Yes			Yes				
Diary Card/Memory Aid Worksheet	Distribute Diary Card 1	Reminder	Scripted Interview Phone Call	Review Diary Card 1; Distribute Diary Card 2	Reminder	Scripted Interview Phone Call	Review Diary Card 2 / Distrib. Memory Aid Worksheet	Scripted Interview Phone Call
Assess local/systemic reactions	X		X	X		X		
Assess AEs and SAEs	X		X	X		X	X	X
Prior/Concomitant medications	X		X	X		X	X	X
Study termination								X

Source: Applicant provided table within Clinical Study Report of Study V102_03 page 71

At visits during and after the study, the site was monitored by a study monitor for compliance, including accurate and complete recording of data on eCRFs, source documents, and drug accountability records. The study was conducted according to the principles of GCP.

Data recorded in the eCRF were to be verified by checking the eCRF entries against source documents (i.e., all original records, laboratory reports, scripted phone call worksheet, medical records, subject diaries) in order to ensure data completeness and accuracy, as required by study protocol.

6.3.8 Endpoints and Criteria for Study Success-Safety

Criteria for Evaluation-Safety Endpoints

The Safety endpoints and criteria for study success were based on observed local and systemic reactions 7 days post vaccination via a daily diary card. Additionally, expected and unexpected Serious Adverse Events were to be collected throughout the study.

Local solicited reactions (i.e., pain, erythema, and induration), systemic solicited reactions (i.e., chills, nausea, fatigue, myalgia, arthralgia, loss of appetite, headache, rash, and fever [defined as body temperature $\geq 38^{\circ}\text{C}$]), unsolicited AEs, and SAEs were to be collected daily for 7 days after each vaccination. These local reactions were to be collected within the daily diary card in which subjects were to rate local and systemic reactions within explicit questions within the daily diary card, as well as open ended responses related to unsolicited AEs and SAEs included within the daily diary card.

Serious adverse events (SAEs), medically attended AEs, and AEs that resulted in a subject's withdrawal from the study were collected throughout the study period. Specifically, the data to be collected after the initial 7-day daily diary card reporting time period were as follows:

- From day 8 through day 91, all unsolicited AEs, SAEs, and concomitant medications;
- From day 92 (31 days following vaccination 2) through day 241 (180 days following vaccination 2), only medically attended AEs, SAEs, and AEs leading to withdrawal from the study

6.3.9 Statistical Considerations & Statistical Analysis Plan

The statistical considerations for this study were based on primarily immunogenicity endpoints and as a phase II study were typically exploratory in nature. Safety analysis was to be predominantly based on the presentation of safety endpoints in tabular formats comparing treatment groups.

6.3.10 Study Population and Disposition

Of 484 enrolled subjects, 480 subjects (99%) received at least 1 study vaccination. The demographic variables and baseline characteristics were well balanced across study groups. The mean age of the subjects was 15.0 (± 4.9) years and the majority (61%) of subjects were Caucasian.

6.3.10.1 Populations Enrolled/Analyzed

Populations for Analysis

There are a variety of populations examined in this study, including both safety/tolerability and efficacy datasets. These datasets include:

All Enrolled Population: All subjects who signed an ICF, underwent screening procedure(s), and were randomized.

Safety Populations

The following are the safety sets analyzed in this study, including the timing and type of data collected and examined:

All Exposed Set: All subjects in the All Enrolled Population who actually received a study vaccination.

Solicited Safety Sets: All subjects in the All Exposed Set who provided post-vaccination solicited AE data from day 1 (6 hours) through day 7. There are separate Solicited Safety Sets for each vaccination: Solicited Safety Set (vaccinat.1) and Solicited Safety Set (vaccinat.2).

Unsolicited Safety Set: All subjects in the All Exposed Set who provided post-vaccination unsolicited AE data.

Overall Safety Set: All subjects in the All Exposed Set who provided post vaccination solicited or unsolicited AE data.

Restricted Safety Set: Analysis of the Restricted Safety Set was only to be performed if the size of the Unsolicited Safety Set and Restricted Safety Set differed by more than 10%. This set consists of all subjects in the Unsolicited Safety Set who:

- correctly received the vaccine at visit 1 (day 1) and visit 2 (day 61) and
- did not receive vaccines or take investigational products forbidden in the protocol (identified as major deviations) and
- did not require the randomization code to be broken and
- completed the long-term safety follow-up (i.e., completed visit 4/day 241).

In case of randomization errors, subjects were to be analyzed "as treated" in all safety analyses and were excluded from the Restricted Safety Set.

6.3.10.1.1 Demographics

Demographic characteristics were comparable across all four treatment groups in this study. The median age was 13 years overall; the minimum age in each group was 10 years, and the maximum was 24 or 25 years. Approximately half the subjects were male (44% to 51% across groups). Median weights were 56 to 57 kg across study groups. Ethnicity was also comparable across groups: 61% of all subjects were Caucasian, 32% were Hispanic, 5% were Black, and the remainder were Asian or of other ethnicities. Approximately one-fourth of the subjects were from Poland, with the remainder of subjects (approximately 75%) from the US. Further details regarding the demographic make-up of subjects enrolled in this study are shown in the following table.

Table 6.3.10.a) Demographic and Baseline Characteristics of All Enrolled Subjects

	(b)(4)-----	(b)(4)-----	rMenB+ OMV	Placebo/ ACWY	Total
	N=120	N=121	N=122	N=121	N=484
Age, years					
Mean \pm SD	14.7 \pm 4.7	15.1 \pm 4.9	15.3 \pm 4.9	15.0 \pm 5.1	15.0 \pm 4.9
Median	12.0	13.0	14.0	12.0	13.0
Sex, N (%)					
Male	59 (49%)	53 (44%)	62 (51%)	57 (47%)	231 (48%)
Female	61 (51%)	68 (56%)	60 (49%)	64 (53%)	253 (52%)
Ethnic Origin, N (%)					
Asian	1 (<1%)	0	2 (2%)	0	3 (<1%)
Black	6 (5%)	7 (6%)	4 (3%)	5 (4%)	22 (5%)
Caucasian	72 (60%)	76 (63%)	74 (61%)	72 (60%)	294 (61%)
Hispanic	38 (32%)	37 (31%)	41 (34%)	41 (34%)	157 (32%)
Other	3 (3%)	1 (<1%)	1 (<1%)	3 (2%)	8 (2%)
Weight, kg					
Mean \pm SD	58.5 \pm 19.8	59.1 \pm 18.2	57.7 \pm 17.6	61.1 \pm 20.6	59.1 \pm 19.0
Median	55.8	57.4	56.3	56.6	56.5
Height, cm					
Mean \pm SD	158.1 \pm 14.0	159.7 \pm 13.8	159.0 \pm 13.8	157.2 \pm 13.2	158.5 \pm 13.7
Median	159.5	160.0	160.0	160.0	160.0
Country, N (%)					
Poland	32 (27%)	33 (27%)	33 (27%)	34 (28%)	132 (27%)
USA	88 (73%)	88 (73%)	88 (73%)	88 (72%)	352 (73%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets particularly the Demog.xpt datasets: -----(b)(4)-----

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects enrolled in this study were to be healthy volunteers meeting inclusion/exclusion criteria, who were 10-25 years of age from the US and Poland.

6.3.10.1.3 Subject Disposition

A total of 484 subjects who provided informed consent were enrolled into the study and randomized. Visit 3 (day 91) was completed by 444 subjects (92%), and 419 subjects (87%) completed the entire study through visit 4 (day 241, 6 months following the second vaccination).

A total of 40 subjects (8%) withdrew prematurely through visit 3 (day 91), while 65 subjects (13%) withdrew overall, i.e., before day 241. The most common reasons for premature withdrawal throughout the study were loss to follow-up (10% of subjects overall) and withdrawal of consent (3% overall). One subject, in the rMenB+OMV group, withdrew due to an AE that was assessed to be related to the study product as the primary reason. This subject experienced lymphadenopathy (enlarged lymph nodes) on day 6 after first vaccination. The lymphadenopathy was resolved by study termination. Additional details regarding this subject can be found in the medical officer's review. A comprehensive listing of subject disposition can be seen in the following table, Summary of Subject Disposition.

Table 6.3.10.1.3.a) Summary of Subject Disposition-All Enrolled Set (As Randomized)

	----- (b)(4)-----	----- (b)(4) -----	rMenB+ OMV	Placebo/ ACWY	Total
Enrolled	N=120	N=121	N=122	N=121	N=484
Completed Visit 3 (day 91)	108 (90%)	110 (91%)	116 (95%)	110 (91%)	444 (92%)
Completed Study (through day 241)	103 (86%)	100 (83%)	109 (89%)	107 (88%)	419 (87%)
Reason for Premature Withdrawal					
Adverse Event	0	0	2 (1%)	0	2 (<1%)
Withdrawal of Consent	2 (2%)	6 (5%)	3 (2%)	2 (2%)	13 (3%)
Lost to follow-up	15 (13%)	14 (12%)	8 (7%)	10 (8%)	47 (10%)
Inappropriate Enrollment	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Protocol Deviation	0	1 (<1%)	0	1 (<1%)	2 (<1%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets particularly the COMMENTS.xpt datasets: : ----- (b)(4) -----

Two subjects, both in the rMenB+OMV group, reported an AE that led to premature withdrawal from the study. One subject reported lymphadenopathy, on day 6 after the first vaccination. The other subject reported convulsion, on day 60 after the first vaccination. These two adverse events are further discussed in the medical officer's review.

6.3.11 Efficacy Analyses

The efficacy analysis was predominantly based on immune response. Additional details can be found in the Statistical Review of Efficacy.

6.3.12 Safety Analyses

Analyses of Safety and Tolerability

All subjects who received at least 1 vaccination and provided any safety data were to be considered evaluable for the safety analyses. All safety data were evaluated using descriptive statistics only.

Analysis of extent of exposure

The number of subjects actually receiving each vaccination was summarized by study group.

Analysis of local and systemic solicited AEs and other indicators of reactogenicity

Frequencies and percentages of subjects experiencing each local and systemic solicited AE occurring during the 7 days after each vaccination were tabulated by study group. Percentages of subjects experiencing each local and systemic AE during 30 minutes, 6 hours through day 3, day 4 through day 7, and 6 hours through day 7 after vaccination were summarized, as was the time of onset of the first reaction. In addition, the numbers of subjects who stayed at home or who used analgesic or antipyretic medication were summarized by study group. All these parameters were summarized by vaccination (first or second) and for any vaccination. Summary tables showing the occurrence of any local or systemic AE overall and after each vaccination were also presented.

Similar to other studies, the severity grading for local and systemic solicited AEs was as described below.

Local solicited adverse events

- 1) Pain: mild, moderate, or severe.
- 2) Erythema and induration were summarized using 2 categorization schemes:
 - Categorization 1: none (0 mm), any (1-24 mm, 25-50 mm, 51-100 mm, >100 mm);
 - Categorization 2: none (< 25 mm), any (25-50 mm, 51-100 mm, >100 mm).

Systemic solicited adverse events

The systemic AEs that were evaluated in this study were chills, nausea, fatigue, myalgia, arthralgia, loss of appetite, headache, rash, and fever that occurred within 7 days after each vaccination, based on an assessment of mild, moderate, or severe. Fever (body temperature $\geq 38.0^{\circ}\text{C}$, irrespective of route of measurement) was categorized as present or absent. The severity of rash was categorized as none, urticarial, or other. The severity of the other systemic AEs was categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), or severe (unable to perform normal daily activity).

Other indicators of reactogenicity that were evaluated were medically attended fever, medication used to prevent or treat fever or other symptoms, and staying home due to reaction.

Certain local and systemic solicited AEs were directly measured by the subject, and were not subjected to a reconciliation process even if they were biologically implausible. As per the applicant, implausible measurements were not to be included in summary analyses but were to be listed in the individual data listings for completeness.

Analysis of unsolicited AEs

All the AEs occurring during the study were judged as either related to vaccination or not by the clinician. The original verbatim terms used by clinicians to identify AEs in the CRFs were mapped to preferred terms using the MedDRA dictionary. The AEs were then grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). All reported AEs, as well as AEs judged by the clinician as at least possibly related to study vaccine, were summarized according to SOC and preferred term within the SOC.

When an AE occurred more than once in a subject, the maximum severity was counted. AEs were summarized according to the following categories: seriousness, relation to study vaccine (all, possibly, or probably related, unrelated, where “all” is assessed to be definitely related to the study vaccine), period of onset, worst severity, overall frequency, occurring in at least 5% of subjects, data source, and after any vaccination and by vaccination.

The following summaries were also produced: AEs leading to premature withdrawal, AEs leading to interruption or delay in study, or hospitalization. In addition, all treatment-emergent AEs (TEAEs), all possibly and probably related TEAEs, and unrelated TEAEs reported with onset during the following windows were to be summarized:

- Day 1 through day 30 after each and after any study vaccination;
- Day 31 through day 60;
- Day 1 through day 91;
- Day 1 through day 241 (entire study period).

The denominators were appropriately adjusted for subjects who withdrew from the study prior to the period of interest.

6.3.12.1 Methods

Descriptive statistics for the safety endpoints were to be presented, including both expected and unexpected adverse events. Also included were systematically collected local and systemic adverse events noted on the 7-day patient daily card detailing the 7-day post-injection reaction experiences, as well as observations and comments made

during the post-vaccination follow-up, 241 days after the initial vaccination. No further statistical methods were implemented utilizing the safety data collected in this study.

A total of 480 of the 484 enrolled subjects received at least 1 dose of study vaccination; these subjects comprise the Exposed Set.

Each of these 480 subjects provided data on unsolicited AEs. The 11 subjects in the Placebo/ACWY group who received their vaccinations in the incorrect order were excluded from summaries of the Placebo/ACWY group.

Overall, 120 subjects in each of the -----(b)(4)-----, and rMenB+OMV groups, and 109 subjects in the Placebo/ACWY group, comprised the Overall Safety Set and the Unsolicited Safety Set. Likewise, the Solicited Safety Set (vaccination1) in each of the study groups was comprised of 107 subjects, 109 subjects, 114 subjects, and 96 subjects, respectively, and the Solicited Safety Set (vaccination2) was comprised of 102, 105, 109, and 93 subjects, respectively.

The Restricted Safety Set, as pre-specified in the Analysis Plan, consisted of all subjects in the Unsolicited Safety Set who correctly received both the first and second vaccinations, did not receive non-study vaccines or investigational products forbidden by the protocol, did not necessitate breaking of the randomization code, and completed the safety follow-up at visit 4 (day 241, 180 days after the second vaccination). Overall, 74% of enrolled subjects were included in the Restricted Safety Set, with comparable proportions across study groups (71% to 78%). A tabular listing of the safety datasets can be seen in the following table.

Table 6.3.10.1.3.a) Overview of Safety Datasets: All Enrolled, As Treated

	----- (b)(4)-----	(b)(4) -----	rMenB+ OMV	Placebo/ ACWY	Total
Randomized	N=120	N=121	N=122	N=121	N=484
Overall Safety Dataset	N=120	N=121	N=122	N=110	N=473
All Enrolled Set	120 (100%)	121 (100%)	122 (100%)	110 (100%)	473 (100%)
All Exposed Set	120 (100%)	120 (99%)	120 (98%)	109 (99%)	469 (99%)
Unsolicited Safety Set	120 (100%)	120 (99%)	120 (98%)	109 (99%)	469 (99%)
Solicited Safety Set (vaccination1)	107 (89%)	109 (90%)	114 (93%)	96 (87%)	426 (90%)
Solicited Safety Set (vaccination2)	102 (85%)	105 (87%)	109 (89%)	93 (85%)	409 (86%)
Restricted Safety Set	91 (76%)	86 (71%)	95 (78%)	80 (73%)	352 (74%)

Source: Reviewer Adaptation based on independent analysis of data provided by the applicant confirming the table provided within the Clinical Study report page 117

Adverse Events

Brief Summary of Adverse Events

The percentage of subjects with any solicited AE reported from day 1 (6 hours) through day 7 after the first vaccination was 92% in the -----(b)(4)----- group, 86% in the -----(b)(4)----- group, 93% in the rMenB+OMV group, and 63% in the Placebo/ACWY group. The following table summarizes numbers and percentages of subjects, by group, with any solicited AEs reported after each study vaccination and after any study vaccination.

Table 6.3.10.1.3.b) Number (%) of Subjects with at Least One Solicited AE Reported from 6 Hours through Day 7 by Vaccination: Solicited Safety Dataset

	Dose 1				Dose 2			
	----- (b)(4)-	----- (b)(4)-	rMenB+ OMV	Placebo/ ACWY	----- (b)(4)-	----- (b)(4)-	rMenB+ OMV	Placebo/ ACWY
Overall Safety Data	N=120	N=121	N=122	N=110	N=102	N=105	N=109	N=93
Any	98 (92%)	94 (86%)	106 (93%)	60 (63%)	87 (85%)	83 (79%)	93 (85%)	59 (63%)
Local	96 (90%)	92 (84%)	105 (92%)	36 (38%)	84 (82%)	77 (73%)	91 (83%)	49 (53%)
Systemic	71 (66%)	76 (70%)	71 (62%)	45 (47%)	60 (59%)	57 (54%)	71 (65%)	43 (46%)
Other	25 (23%)	31 (28%)	23 (20%)	8 (8%)	21 (21%)	14 (13%)	23 (21%)	10 (11%)

Source: Reviewer Adaptation based on independent analysis of data provided by the applicant confirming the table provided within the Clinical Study report page 119

Note: 'Other' refers to other indicators of reactogenicity, specifically, subject stayed home due to reaction or subject took medication to prevent or treat fever or other symptoms. As pre-specified in the protocol, data from the 11 subjects in the Placebo/ACWY group who received their vaccinations in the wrong order were not included in safety analyses for the Placebo/ACWY group.

There were no differences in proportions of subjects reporting any solicited AE overall or any category of solicited AE (local or systemic), or other indicators of reactogenicity, among subjects who received the -----(b)(4)----- or rMenB+OMV vaccine as the first vaccination. At least 1 local solicited AE was reported by 84% to 92% of subjects and at least 1 systemic solicited AE was reported by 62% to 70% of subjects in these 3 groups, after the first vaccination, compared with 38% and 47% of subjects, respectively, in the Placebo/ACWY group after a first vaccination with placebo.

The rates of any solicited AEs were lower after the second than after the first vaccination: 92% after the first and 85% after the second in the --- (b)(4)----- group, 86% and 79%, respectively, in the ----(b)(4)----- group, and 93% and 85%, respectively, in the rMenB+OMV group. This trend was also observed for percentages of subjects with any local and with any systemic solicited AE (except for systemic solicited AEs in the rMenB+OMV group).

As can be seen from the previous table, slightly lower percentages of subjects in the -----(b)(4)----- group than in either the -----(b)(4)----- or rMenB+OMV groups reported any, any local, and any systemic solicited AEs after the second vaccination. Additionally, reported rates of solicited AEs after administration of the MenACWY vaccine (the second vaccination in the Placebo/ACWY group) were slightly lower than after the rMenB- containing vaccines (63% to 79-85% for any observed and reported AE).

Observations of AEs can be further examined in the following table which summarizes unsolicited AEs reported during various study periods, and other categories of AEs, including medically attended AEs, SAEs, and AEs that led to withdrawal from the study.

Table 6.3.10.1.3.c) Number (%) of Subjects with at Least One Unsolicited AE after Vaccination: Unsolicited Safety Set

	----(b)(4)----- -----	----(b)(4)----- -----	rMenB+OMV	Placebo/ ACWY
	N=120	N=120	N=120	N=109
Any AE within 30 days of first vaccination (days 1–30)	21 (18%)	28 (23%)	33 (28%)	20 (18%)
At least possibly related	8 (7%)	8 (7%)	12 (10%)	4 (4%)
Any AE within 30 days of second vaccination (days 61–91)	9 (8%)	5 (5%)	9 (8%)	7 (7%)
At least possibly related	2 (2%)	1 (1%)	1 (1%)	1 (1%)
Any AE from days 1–91	51 (43%)	55 (46%)	66 (55%)	50 (46%)
At least possibly related	13 (11%)	10 (8%)	16 (13%)	6 (6%)
Any AE from days 1–241	56 (47%)	60 (50%)	71 (59%)	60 (55%)
At least possibly related	13 (11%)	10 (8%)	16 (13%)	6 (6%)
Medically attended AEs from days 92–241	26 (22%)	24 (20%)	30 (25%)	31 (28%)
At least possibly related	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs (days 1–241)	2 (2%)	2 (2%)	1 (1%)	3 (3%)
At least possibly related	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs leading to premature withdrawal (days 1–241)	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Deaths (days 1–241)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets particularly the

COMMENTS.xpt datasets:----- (b)(4)-----

It can be seen in the previous table that at least 1 unsolicited AE was reported within 30 days after the first vaccination by 18%, 23%, 28%, and 18% of subjects in the -----(b)(4)-----, rMenB+OMV, and Placebo/ACWY groups, respectively. Substantially smaller percentages of subjects in each group reported at least 1 unsolicited AE after the second vaccination (8%, 5%, 8%, and 7%, respectively).

From the same table it can be seen that during the primary vaccination phase (days 1 through 91, i.e., through 30 days after the second vaccination), unsolicited AEs were reported by a greater percentage of subjects in the rMenB+OMV group (55%) than in the other groups (43% to 46%). A similar trend was observed for percentages of unsolicited AEs reported during the entire study period (from days 1 through 241): 59% of subjects in the rMenB+OMV group vs. 47% through 55% in the other groups. Additionally, from days 92 through 241, medically attended AEs were reported by 22%, 20%, 25%, and 28% of subjects in the -----(b)(4)-----, rMenB+OMV, and Placebo/ACWY groups, respectively.

SAEs were reported by 1% to 3% of subjects in each group. Two subjects, both in the rMenB+OMV group, reported an AE that led to premature withdrawal from the study, although the AE was the primary reason for withdrawal in only 1 of those cases. No subject died during this study.

Summary of Adverse Events

Solicited Adverse Events

The reactogenicity profile of subjects experiencing local and systemic solicited AEs within 30 minutes post vaccination, from day 1 (6 hours) through day 7, are presented in tables below. The reactogenicity results for this interval are consistent with the data confirmed but not presented for the 6 hour to day 3, and from day 4 through 7-day post vaccination periods (based on both the daily diary cards as well as telephone follow-up 3 days post vaccination). Details and tabular listings of the reactions are presented below.

Local Solicited AEs

The following table summarizes local solicited AEs (erythema, induration, and pain) reported by subjects from 6 hours through 7 days after vaccination.

Table 6.3.10.1.3.d) Number (%) of Subjects with Local Solicited AEs, after Each Vaccination, from 6 Hours through Day 7: Solicited Safety Sets for each Treatment Group

	Dose 1	Dose 1	Dose 1	Dose 1	Dose 2	Dose 2	Dose 2	Dose 2
	----- (b)(4)-----	----- (b)(4)-----	rMenB+ OMV	Placebo/ ACWY	----- (b)(4)---	----- (b)(4)-----	rMenB+ OMV	Placebo/ ACWY
	N=107	N=108	N=114	N=96	N=100	N=104	N=109	N=91
Erythema	48 (45%)	41 (38%)	57 (50%)	12 (12%)	40 (40%)	30 (29%)	49 (45%)	23 (25%)
>100 mm	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Induration	39 (36%)	46 (43%)	36 (32%)	10 (10%)	27 (27%)	26 (25%)	30 (28%)	21 (23%)
>100 mm	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Pain	92 (86%)	91 (84%)	103 (90%)	26 (27%)	81 (79%)	77 (73%)	91 (83%)	39 (42%)
Severe	15 (14%)	19 (18%)	22 (19%)	2 (2%)	22 (22%)	16 (15%)	31 (28%)	7 (8%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets particularly the COMMENTS.xpt datasets:-----

From the above table it can be seen that the most common local solicited AE was injection site pain, reported after the first vaccination by 84% to 90% of subjects in the rMenB-containing study groups (i.e., groups -----(b)(4)-----, and rMenB+OMV) and 27% of subjects in the Placebo/ACWY group. After the second vaccination, injection site pain was reported by 73% to 83% and 42% of subjects, respectively.

Additionally, severe pain was reported by 14% to 19% of subjects in the groups that received an rMenB-containing vaccine after the first vaccination, and by 15% to 28% of subjects after the second vaccination. In the Placebo/ACWY group, severe pain was reported by 2% of subjects after vaccination with placebo and by 8% of subjects after vaccination with MenACWY.

Erythema was reported by 29% to 50% of subjects in the rMenB-containing study groups after either vaccination, versus 12% and 25% in the Placebo/ACWY group after the first and second vaccination, respectively. Induration was reported by 25% to 43% of subjects in the rMenB-containing study groups after either vaccination, versus 10% and 23% in the Placebo/ACWY group after the first and second vaccination, respectively. Severe erythema was reported by one subject from the --- (b)(4)----- group, and one subject from the --- (b)(4)----- group reported severe induration (i.e., >100 mm) after first vaccination. Severe erythema was reported by 2 subjects in the Placebo/ACWY group after the second vaccination.

Based on the above results provided by the applicant and confirmed by the reviewing statistician, each of the local solicited AEs was reported by smaller percentages of subjects after the second vaccination than after the first vaccination in all study groups except for the Placebo/ACWY group.

Overall, no remarkable differences in frequencies of individual local solicited AEs were observed across the -----(b)(4)-----, and rMenB+OMV groups.

Systemic Solicited AEs

The following table, created by the reviewing statistician (confirming the applicant's results within the BLA), summarizes systemic solicited AEs reported from 6 hours through 7 days after vaccination. Most subjects experienced onset of systemic solicited AEs within 2 days following vaccination. The majority of these reactions were of short duration.

Table 6.3.10.1.3.e) Number (%) of Subjects with Systemic Solicited AEs, after Each Vaccination, from 6 Hours through Day 7: Solicited Safety Sets for each Treatment Group

	Dose 1	Dose 1	Dose 1	Dose 1	Dose 2	Dose 2	Dose 2	Dose 2
	---(b)(4)---	---(b)(4)---	rMenB+OMV	Placebo/ACWY	---(b)(4)---	---(b)(4)---	rMenB+OMV	Placebo/ACWY
	N=107	N=108	N=114	N=96	N=100	N=104	N=109	N=91
Chills	7 (7%)	15 (14%)	18 (16%)	4 (4%)	12 (12%)	12 (11%)	22 (20%)	9 (10%)
Severe Chills	0 (0%)	2 (2%)	1 (1%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)	0 (0%)
Nausea	8 (7%)	18 (17%)	22 (19%)	4 (4%)	10 (10%)	9 (9%)	20 (18%)	4 (4%)
Severe Nausea	0 (0%)	4 (4%)	4 (4%)	0 (0%)	2 (2%)	1 (1%)	4 (4%)	0 (0%)
Fatigue	25 (23%)	39 (36%)	41 (36%)	21 (22%)	18 (18%)	31 (30%)	38 (35%)	18 (20%)
Severe Fatigue	3 (3%)	8 (7%)	4 (4%)	0 (0%)	2 (2%)	2 (2%)	7 (6%)	2 (2%)
Myalgia	52 (49%)	56 (52%)	55 (49%)	25 (26%)	44 (43%)	41 (39%)	52 (48%)	23 (25%)
Severe Myalgia	10 (9%)	10 (9%)	13 (12%)	1 (1%)	9 (9%)	3 (3%)	14 (13%)	4 (4%)
Arthralgia	9 (8%)	21 (19%)	15 (13%)	4 (4%)	14 (14%)	7 (7%)	17 (16%)	4 (4%)
Severe Arthralgia	0 (0%)	3 (3%)	2 (2%)	0 (0%)	4 (4%)	2 (2%)	2 (2%)	0 (0%)
Headache	24 (23%)	31 (29%)	37 (32%)	19 (20%)	21 (21%)	26 (25%)	37 (34%)	21 (23%)
Severe Headache	3 (3%)	3 (3%)	5 (4%)	1 (1%)	3 (3%)	2 (2%)	7 (6%)	3 (3%)
Loss of appetite	10 (9%)	18 (17%)	19 (17%)	9 (9%)	8 (8%)	7 (7%)	14 (13%)	7 (8%)
Severe Loss of Appetite	0 (0%)	3 (3%)	0 (0%)	0 (0%)	3 (3%)	1 (1%)	3 (3%)	0 (0%)
Rash	6 (6%)	6 (6%)	2 (2%)	0 (0%)	0 (0%)	3 (3%)	3 (3%)	6 (7%)
Fever (≥38°C)	4 (4%)	3 (3%)	1 (1%)	1 (1%)	3 (3%)	3 (3%)	5 (5%)	0 (0%)
Medically attended fever	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Prophylactic antipyretics use	11 (10%)	8 (7%)	12 (11%)	0 (0%)	10 (10%)	6 (6%)	8 (7%)	7 (8%)
Therapeutic antipyretics use	11 (10%)	21 (19%)	15 (13%)	6 (6%)	11 (11%)	9 (9%)	16 (15%)	4 (4%)

Source: Reviewer created table summarizing data within applicant provided study report and datasets particularly the COMMENTS.xpt datasets:-----

----- (b)(4) -----

From the above table, it can be seen that the most commonly reported systemic solicited AEs after the first vaccination were myalgia (49% to 52% of subjects in rMenB-containing vaccine groups vs. 26% of subjects in the Placebo/ACWY group), followed by fatigue (23% to 36% of subjects in rMenB-containing vaccine groups vs. 22% of subjects in the Placebo/ACWY group) and headache (23% to 32% % of subjects in rMenB-containing vaccine groups vs. 20% of subjects in the Placebo/ACWY group), respectively.

Also noteworthy is that each of the most common systemic AEs (myalgia, fatigue, and headache) were reported by smaller percentages of subjects after the second vaccination than after the first in all study groups, except for headache in the rMenB+OMV and Placebo/ACWY groups.

Among severe systemic solicited AEs reported in rMenB-containing study groups, the most common, after any vaccination, were myalgia (3% to 13% of subjects after either vaccination), fatigue (2% to 7%), and headache (2% to 6%). In comparison, these severe AEs occurred in 2% to 4% of subjects in the Placebo/ACWY group.

Rash was reported as a systemic solicited AE by subjects using diary cards; it was also reported as an unsolicited AE. Rash was reported within 7 days after vaccination by 2-6% in subjects receiving an rMenB containing vaccine, while rash was reported by 0% of subjects receiving Placebo and 6% for those receiving MenACWY

Fever was reported by 1% to 5% of subjects in each of the rMenB-containing groups after either vaccination, compared with 0% to 1% of subjects in the Placebo/ACWY group. Specifically, it should be noted that the Placebo dosage was administered first, while the ACWY vaccine was administered second. The placebo group had 1% subjects experiencing fever, while the ACWY vaccine had 0 (0%) of subjects experiencing fever.

Analgesics and/or antipyretics for treatment of post vaccination symptoms were taken by 9% to 19% of subjects in the rMenB-containing study groups and by 4% to 6% of subjects in the Placebo/ACWY group. Additional details related to systemic AEs, rash, fever, and medications administered within 7 days post-vaccination can be seen in the medical officer's review.

Unsolicited Adverse Events

The following applicant table summarizes all unsolicited AEs by system organ class (SOC) and preferred term, respectively. This table, in which select relevant outcomes were confirmed by the reviewing statistician, also summarizes those AEs considered at least possibly related to study vaccination as noted by the applicant.

Figure 6.3.10.1.3.a) Number (%) of Subjects with Unsolicited AEs after Any Vaccination, from Days 1 through 241 by SOC: Unsolicited Safety Set

SOC	All AEs				At least possibly related AEs			
	(b) (4) N=120	(b) (4) N=120	rMenB +OMV N=120	Pbo/ACWY ^a N=109	(b) (4) N=120	(b) (4) N=120	rMenB +OMV N=120	Pbo/ACWY ^a N=109
Any AE	56 (47%)	60 (50%)	71 (59%)	60 (55%)	13 (11%)	10 (8%)	16 (13%)	6 (6%)
Blood & Lymphatic System Disorders	2 (2%)	2 (2%)	2 (2%)	0	0	0	1 (1%)	0
Ear & Labyrinth Disorders	3 (3%)	0	1 (1%)	2 (2%)	0	0	0	0
Eye Disorders	2 (2%)	3 (3%)	3 (3%)	2 (2%)	0	0	0	0
Gastrointestinal Disorders	13 (11%)	12 (10%)	13 (11%)	14 (13%)	2 (2%)	1 (1%)	3 (3%)	2 (2%)
General Disorders & Admin. Site Conditions	22 (18%)	12 (10%)	11 (9%)	14 (13%)	13 (11%)	8 (7%)	10 (8%)	4 (4%)
Immune System Disorders	0	1 (1%)	1 (1%)	2 (2%)	0	0	0	0
Infections & Infestations	30 (25%)	39 (33%)	37 (31%)	38 (35%)	0	0	0	0
Injury & Poisoning	6 (5%)	9 (8%)	12 (10%)	13 (12%)	0	0	0	0
Investigations	1 (1%)	0	0	2 (2%)	0	0	0	0
Metabolism & Nutrition Disorders	1 (1%)	2 (2%)	3 (3%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)	0
Musculoskeletal, Connective Tissue & Bone Disorders	11 (9%)	6 (5%)	6 (5%)	4 (4%)	1 (1%)	2 (2%)	3 (3%)	1 (1%)
Neoplasms Benign/Malignant (Incl. Cysts/Polyps)	2 (2%)	1 (1%)	3 (3%)	0	0	0	0	0
Nervous System Disorders	3 (3%)	5 (4%)	10 (8%)	8 (7%)	1 (1%)	1 (1%)	3 (3%)	1 (1%)
Psychiatric Disorders	3 (3%)	2 (2%)	2 (2%)	3 (3%)	0	0	0	0

Source: Clinical Study Report, Study v102-03 page 130-131

From the above table, it can be seen that the pattern of reported unsolicited AEs was comparable across all 4 study groups and across all system organ classes (SOC's).

At least 1 unsolicited AE was reported within 30 days after the first vaccination by 18%, 23%, 28%, and 18% of subjects in the -----(b)(4)-----, rMenB+OMV, and Placebo/ACWY groups, respectively. Substantially smaller percentages of subjects in each group reported AEs after the second vaccination (8%, 5%, 8%, and 7%, respectively) compared to the first vaccination.

The most commonly reported unsolicited AEs in any study group (over the entire study period, i.e., through day 241) were classified under the SOC "Infections and Infestations." The reported rates were 25%, 33%, 31%, and 35% of subjects in the -----(b)(4)-----, and Placebo/ACWY groups, respectively.

The percentages of subjects with possibly related unsolicited AEs were 11% and 8% in the -----(b)(4)-----, groups, respectively, 13% in the rMenB+OMV group, and 6% in the Placebo/ACWY group.

At least possibly related AEs were most frequently reported in the SOC "General Disorders and Administrative Site Conditions." The most commonly reported preferred term within this SOC was injection site induration (2% to 6% across rMenB-containing vaccine study groups, versus 0% in the Placebo/ACWY group).

Although not presented within this review, when frequencies of all unsolicited AEs and at least possibly related AEs were compared, the patterns were comparable, if not identical between the various treatment groups examined within this study, when analyses were restricted to day 1 through day 91.

Medically attended AEs were reported by 20% to 25% of subjects in the rMenB containing vaccine groups versus 28% of subjects in the Placebo/MenACWY comparator groups from days 91 through 241. As per the applicant, none of these AEs was assessed as related to study vaccine. Furthermore, none of these medically attended AEs were noted by the applicant's clinician to be related to study vaccine.

The profile of unsolicited AEs reported by the 11 subjects in the Placebo/ACWY group who received placebo and MenACWY vaccinations in the incorrect order was comparable to that of the overall Placebo/ACWY group, except for subject 11/024, who reported an SAE of multiple sclerosis.

Two subjects, both in the rMenB+OMV group, reported an AE that led to withdrawal from the study. One subject reported lymphadenopathy, considered possibly related to vaccination, on day 6 after the first immunization. The other subject reported convulsion, considered by the clinician to be not related, on day 60 after the first vaccination. Additional details regarding these subjects can be seen in the medical officer's and epidemiologist's reviews.

Reviewer Comment: *Overall, based on unsolicited data, less than 30% of subjects reported any unsolicited AE within 30 days of the first vaccination, and less than 10% of subjects reported unsolicited AEs within 30 days of the second vaccination. These rates appear to be reasonable and fairly consistent with those reported in other MenB vaccine studies. Similarly, additional unsolicited AEs noted during the study, while affecting a variety of organ classes, appeared to be limited in nature and self-resolving. Additional details regarding AEs can be found in the medical officer's and epidemiologist's reviews.*

6.3.12.3 Deaths

No deaths were observed during this study.

6.3.12.4 Nonfatal Serious Adverse Events

Serious AEs (SAEs) were reported by 1% to 3% of subjects across study groups. No SAE by preferred term was reported by more than 1 subject in any study group. None of these SAEs was considered possibly or probably related by the applicant's clinician.

6.3.12.5 Adverse Events of Special Interest (AESI)

No additional Adverse Events of Special Interest were noted.

6.3.12.6 Clinical Test Results

No additional Clinical test results were performed.

6.3.12.7 Dropouts and/or Discontinuations

Two subjects in the rMenB+OMV group reported unsolicited AEs that led to premature withdrawal from the study; no subject in the other study groups reported an AE in this category. One subject each reported lymphadenopathy and convulsion. Additional details related to both of these patients can be found in the medical officer's and epidemiologist's reviews.

Overall Summary and Conclusion on Safety Data for Study V102__03:

Reviewer Comment 1: *In this study, 11 subjects were excluded from the safety analysis because they received an incorrect vaccination rather than what they were randomized to receive. These 11 subjects were from study site "11" in Poland. These subjects, instead of receiving placebo then MenACWY, received the active comparator MenACWY first and then the placebo vaccination. Based on the actual vaccination these subjects received, the solicited and unsolicited AE rates were similar to the rates observed in the appropriate treatment group. Further details related to these study participants are not included in this review, since at no time were these subjects administered the Novartis MenB product and the MenACWY product has been approved and has a well-defined safety profile.*

Reviewer Comment 2: *While slight differences in AEs were observed between the various treatment groups (particularly when comparing the rMenB containing vaccine to the Placebo/MenACWY treatment group), no difference between formulations was seen in terms of reactogenicity or unsolicited adverse events. The observed reactogenicity and AE responses (both solicited and unsolicited) were comparable to other meningitis vaccines, including Menveo® and Menactra®.*

Several additional studies were included within this BLA. These included smaller Phase II studies, a Phase III study that had irregularities noted in the BIMO inspection (and upon review of the data) and two uncontrolled studies which provided Novartis MenB Bexsero® vaccine to students, faculty, and staff at Princeton University and UC Santa Barbara. An overview of the safety results of these studies will be provided within the Integrated Overview of Safety in Section 8.

7. INTEGRATED OVERVIEW OF EFFICACY

The efficacy analysis for all studies provided within this submission was predominantly based on immune response. Additional details and analysis of immunogenicity endpoints and analysis can be found in the Statistical Review of Efficacy.

8. INTEGRATED OVERVIEW OF SAFETY

The safety methods incorporated a variety of active and passive adverse event reporting mechanisms, depending on the study. Subjects were provided daily diary cards in which adverse event symptoms could be noted. Additionally, regular clinic visits were scheduled for the various studies in which subjects were to be asked questions to assess if any symptoms that could be considered adverse events had occurred.

Six studies sponsored by Novartis and 2 studies sponsored by the United States Centers for Disease Control and Prevention (CDC) are included in this integrated overview of safety (ISS). These results were provided by the applicant to support the safety and tolerability of the vaccine, recombinant meningococcal group B vaccine formulated with the outer membrane vesicle (OMV) derived from the New Zealand serogroup B strain NZ98/254 (rMenB+OMV NZ vaccine) or Bexsero®.

Four controlled Novartis-sponsored studies provide data on safety in subjects from 10 through 25 years of age, including 2 studies (V72P10 and V72_41) in adolescents 11 through 17 years of age, 1 study (V72_29) in university students of 18 through 24 years of age, and 1 study (V102_03, part of the clinical development program for -----(b)(4)----- in subjects 10 through 25 years of age where rMenB+OMV NZ served as a control vaccine. Data from two (2) Novartis-sponsored supportive studies (V72P4 and V72P5) in adults 18 through 50 years of age are also discussed briefly in this summary. Study V72P4 subjects were healthy adult laboratory workers 18 through 50 years of age at risk of infection, while study V72P5 subjects were healthy adults 18 through 40 years of age.

Two additional open label studies were performed in late 2013 and early 2014 in college students at Princeton University and the University of California, Santa Barbara. These two studies provide additional safety data that were derived from CDC reports of serious adverse events (SAEs) from 15,351 students and staff. The majority of these subjects within these studies were college students, with a median age of 20 years. Data from these vaccination campaigns are reported as CDC-sponsored third party (TP) immunization campaign, V72_68TP for Princeton and V72_70TP for UCSB. A succinct description of the safety monitoring procedures and the demographic details, as well as the serious adverse event (SAE) reported within these studies will be provided.

Additional details related to safety assessment methods can be seen in the medical officer's and epidemiologist's reviews.

8.1 Safety Assessment Methods

The safety datasets provided in this submission include the studies described in Section 2, Table 2.4 a: Summary of Studies. Within Table 2.4.a, information about each of the safety studies is provided, including the protocol, time of study, study title, study design, and objectives, study population, treatment doses and schedule, number of patients exposed, and treatment duration. As can be seen in this table, the total number of individuals exposed to at least 1 dose of rMenB+OMV NZ in these 8 studies (V72P4,

V72P5, V72P10, V72_29, V72_41, V102_03, V72_68TP, and V72_70TP) was 18,490. Within the 6 Novartis Phase I-III clinical trials, 3,139 subjects were exposed to at least one dose of rMenB+OMV NZ, Bexsero®.

Solicited Adverse Events

Solicited AEs were recorded daily for 7 days by the subjects or the subjects' parents/legal guardians on study-specific diary cards and returned to the clinician during post-vaccination visits. In addition, subjects were contacted by phone and scheduled for follow-up visits, as defined in the respective study protocols. Solicited AEs were categorized as local reactions, systemic reactions, and other indicators of reactogenicity.

The local AEs of erythema, induration, and swelling were graded according to the size of the lesion. Injection site pain and systemic reactions (except fever) were graded as none, mild, moderate, and severe in a pre-specified manner.

In all studies, subjects were observed for immediate reactions for at least 30 minutes after each vaccination. Selected local and systemic AEs were solicited and recorded on a diary card on the day of vaccination and on each of the following 6 days after each vaccination.

Unsolicited Adverse Events

Subjects or subjects' parents and/or legal guardians were also asked to record any AEs in the diary cards that represented a change in health status from baseline/study inception. This information, including any other AEs that occurred that were identified, was then recorded in the Case Report Forms (CRFs) by the study clinician.

In all studies, all unsolicited AEs were collected on the day of study vaccination and on each of the 6 days after vaccination. In study V102_03, all AEs were also collected from day 7 to day 91, while only selected unsolicited AEs were collected after the 7-day period in the other studies. These selected AEs included all SAEs, AEs leading to premature withdrawal, and AEs necessitating a physician's visit (termed medically attended AEs). In all studies, SAEs and AEs leading to withdrawal were collected for the entire duration of the study.

Medically attended AEs were collected for the entire study duration in studies V72P10, V72_29, V72_41, and V102_03. In the supportive study V72P4, AEs requiring medical visit/medical advice were also collected from day 8 through day 30 after each vaccination, and medically attended AEs from day 31 onwards after each vaccination. In supportive study V72P5, medically attended AEs and AEs requiring medical advice were collected for 30 days after each vaccination, while medically significant AEs, defined as "AEs requiring a physician's visit, Emergency Room visit, but excluding pre-planned visits, medical office visits for routine medical care and common acute conditions," were collected from 1 month after the third vaccination (month 3) until the end of the study (month 8).

All unsolicited AEs were graded as mild, moderate, or severe by the clinician, according to the definitions in the table below:

Table 8.1.a) Terminology and Assessment of Unsolicited Adverse Events

Severity		All Studies (*not in V72P4, V72P5)
Mild		(*Transient with) No limitation of normal daily activities
Moderate		Some limitation of normal daily activities
Severe		Unable to perform normal daily activities
Causality		All Studies (*only in V72P5)
Not Related		Exposure to the investigational vaccine had not occurred, or the occurrence of the AE was not reasonably related in time, or the AE was considered unlikely to be related to use of the investigational vaccine, i.e. there were no facts (evidence) to suggest a causal relationship.
Possibly Related		The administration of the investigational vaccine and an AE were considered reasonably related in time and the AE could be explained (*equally well) by causes other than exposed to the investigational vaccine.
Probably Related		Exposure to the investigational vaccine and an AE were reasonably related in time and the investigational vaccine was more likely than other (*factors or) causes to be responsible for the AE, or was most likely cause of the AE

Source: BLA 125546 amendment 2, Study Report, Integrated Summary of Safety, page 22-23

As per the applicant, the original verbatim terms used by the study clinicians to identify AEs in the CRFs were mapped to preferred terms using the medical dictionary for regulatory activities (MedDRA) version that was in use when the trial was locked. The AEs were then grouped by MedDRA preferred terms into frequency tables according to System Organ Classes (SOCs). All reported unsolicited AEs were summarized according to SOC and preferred terms within each SOC.

In the studies included within this submission, medically attended AE tables include only subjects who had a record of the following actions, which defined an AE as being a medically attended AE:

- Procedure or physical therapy
- Administration of blood or blood products
- Hospitalization
- Administration of intravenous fluids
- Physician visit.

When an AE was reported more than once for a subject, the episode with maximum severity was counted in the summary tables, while all episodes and severities were provided in the AE listings for the individual subject, both within the ISS as well as the individual study reports. Within this review, the global assessment utilizing the summary tables will be presented and discussed, while the specific and detailed assessments of individual subjects that are considered clinically meaningful will be presented and discussed in the medical officer's review.

Reviewer comment: *The applicant's proposed mechanism for assessment and contribution of each individual's results for both solicited and unsolicited AEs and SAEs within the ISS is sufficient and should provide a reasonable assessment of the AEs and SAEs that may be expected from this MenB vaccine product, Bexsero®.*

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The overall exposure and demographics of the safety database based on the treatment groups were provided by the applicant and confirmed by the reviewing statistician via SAS and JMP, versions 9.3 and 9, respectively. The results of the tabulations of the pooled exposure to treatment, active comparator, or placebo can be seen within tables provided in this section of this review.

The safety data to support the intended indication is derived from the following studies:

- **Study V72P10.** Study V72P10 compared rMenB+OMV NZ vaccine to placebo in various schedule combinations in subjects 11 through 17 years of age. This study examined several different dosing schedules for the Novartis MenB vaccine, including a 0, 1-month; 0, 2-month; and 0, 6-month schedule, as well as several 3-dose schedules and associated placebo dose schedules. This study provided safety data for the proposed 2-dose indication in adolescents, and also provided additional safety data from the first 2 doses of the three dosing schedules including the 0, 1, 2-month schedule, the 0, 1, 6-month schedule, and the 0, 2, 6-month schedule.
- **Study V72_41.** Study V72_41 compared the safety and tolerability of 2 lots of rMenB+OMV NZ formulated with OMV manufactured at 2 different sites, in healthy adolescents 11 through 17 years of age, according to a 0, 1-month vaccination schedule.
- **Study V72_29.** Study V72_29 was a carriage study designed to examine the safety and immunogenicity of the Novartis MenB vaccine that enrolled university students 18 through 24 years of age in the UK. One group of subjects received 2 injections of rMenB+OMV NZ 1 month apart. Two other groups received control vaccines (2 injections of the Japanese encephalitis vaccine (Ixiaro), or 1 injection of placebo followed 1 month later by one injection of MenACWY conjugate vaccine (Menveo).
- **Study V102_03.** Study V102_03 was primarily designed to evaluate the safety and immunogenicity of -----(b)(4)-----
----- vaccine formulations in healthy adolescents and young adults (10 through 25 years of age). This study had an additional group of participants given 2 doses of rMenB+OMV NZ 2 months apart.

Data from these 4 studies will be pooled and examined in limited detail to give a broader picture of the safety of rMenB+OMV NZ in subjects 10 through 25 years of age.

Several additional studies provided supportive safety data of Novartis's MenB vaccine, Bexsero®. These studies were either early Phase I/II or did not include a control comparator arm; thus, limited conclusions related to the safety of this product in comparison to placebo or active comparators can be assessed. However, additional general safety information can be gleaned.

- **Studies V72P5 and V72P4:** The safety of the rMenB+OMV NZ vaccine in adults 18 through 50 years of age has also been evaluated in the 2 supportive studies. Safety data for a 2-dose schedule, administered at least 1 month apart, has been generated from the first 2 doses of the 3-dose 0, 1, 2- and 0, 2, 6-month schedules evaluated in studies V72P5 and V72P4, respectively. Only 15 of the 81 subjects in these studies were 25 years of age or younger (9 subjects in V72P4 and 6 subjects in V72P5). Note that only these 15 subjects are included in the pooled analysis discussed in this ISS since the ISS and this summary of safety results include only the individuals 10-25 years of age proposed in the label claim.
- **Studies V72_68TP (Princeton) and V72_70TP (UC Santa Barbara):** The safety of rMenB+OMV NZ vaccine in adolescents and adults 16 through 68 years of age has also been evaluated in the two third-party immunization campaign studies conducted by the US CDC at Princeton University (V72_68TP) and UCSB (V72_70TP). Most individuals taking part in these studies were university students 18 through 25 years of age.

The following table summarizes the extent of exposure to any treatment (including placebo and all dosages of Novartis's MenB vaccine submitted but not necessarily selected as the optimal dosage for consideration within this BLA) in all studies provided within this BLA.

Table 8.2.1.a. Exposure to Treatment or Placebo of All Subjects

Study (Phase)	Objective	Age	Schedule	rMenB + OMV NZ	Control/comparator
V72P10 (Phase 2b/3)	Observer-blind, multi-center, randomized, controlled, safety, and immunogenicity study in healthy adolescents with various schedules	11-17 years	6; 0,1; 0,2; 0,6; 0,1,2; 0,1,6; 0,2,6-month schedules with 6-months safety follow-up after last vaccination (overall, 12 months safety follow-up from day 1)	1503 Visits 1-4 1622(*)	128 (Placebo) Visits 1-4
V72_29 (Phase 3)	Observer-blind multi-center randomized, controlled study to evaluate pharyngeal carriage of <i>Neisseria meningitidis</i> in young adults	18-24 years	0,1-month schedule with 11 months safety follow-up after second vaccination (overall, 12 months safety follow-up from day 1)	974	984 (MenACWY/Placebo) 987 (Ixiaro®)
V72_41 (Phase 3)	Observer-blind multi-center randomized, controlled study to evaluate safety and immunogenicity of rMenB+OMV NZ formulated with OMV manufactured at two different sites	11-17 years	0,1 month schedule with 1 month safety follow-up after second vaccination (overall, 2 months safety follow-up from day 1)	342	None
V102_03 (Phase 2)	Observer-blind, multi-center randomized, controlled study to evaluate safety and immunogenicity of ----- ------(b)(4)----- ----- combination vaccination formulations.	10-25 years	0,2 month schedule with 6 months safety follow-up after second vaccination (overall, 8 months safety follow-up from day 1)	120	109 (Placebo/ MenACWY)
V72P4 (Phase 2)	Open-label, multi-center, safety, and immunogenicity study in healthy (at-risk) adults	18-50 years	0,2,6-month schedule with 2-months safety follow-up after last dose of vaccine (overall, 8 months safety follow-up from day 1)	53 (of which 9 subjects ≤25 years)	None
V72P5 (Phase 1)	Observer-blind, single-center, randomized, safety, and immunogenicity study in healthy adults	18-40 years	0,1,2-month schedule with 6-months safety follow-up after last dose of vaccine (overall, 8 months safety follow-up from day 1)	28 (of which 6 subjects ≤25 years)	None
V72_68TP (n/a)	Open label	> 17 years	2 doses at an interval between 1 to 6 months	5520	None
V72_70TP (n/a)	Open label	Adolescent & adults	2 doses at an interval between 1 to 6 months	9831	None

Source: Table created by reviewing statistician utilizing data and study information provided in: ------(b)(4)-----

Note: (*) Visits 1-7 (additional subjects who received placebo initially then received Novartis MenB vaccine by study completion)

The total number of individuals exposed to at least 1 dose of rMenB+OMV NZ in these 6 studies and the 2 immunization campaigns sponsored by the US CDC for all age groups was 18,490, with slightly fewer individuals studied in the planned label indication of 18-25 years of age.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The following table provides insight into the demographics of individuals in the studies provided within this submission. The table includes the sample size (n) and percentage of individuals for the Safety Analysis set based on race, gender, and age stratified by treatment group and study.

Figure 8.2.2.a) Demographic and Baseline Characteristics of All Subjects in Safety Set-Novartis Studies

Study	V72_P10	V102_03		V72P4	V72P5
Group	rMenB +OMV NZ	rMenB+ OMV NZ	Placebo/ MenACWY	rMenB+ OMV NZ	rMenB+ OMV NZ
Demographic Characteristic	N=1631	N=122	N=121	N=54	N=28
Mean age (years ± SD)	13.8±1.9	15.3±4.9	15.0±5.1	31.8±6.1	32.0±5.6
Male	718 (44%)	62 (51%)	57 (47%)	27 (50%)	18 (64%)
Ethnic origin:					
Caucasian	0	74 (61%)	72 (60%)	52 (96%)	25 (89%)
Asian	1 (<1%)	2 (2%)	0	0	0
Black	0	4 (3%)	5 (4%)	1 (2%)	0
Hispanic	1619 (99%)	41 (34%)	41 (34%)	1 (2%)	0
Native American/ Alaskan Pacific/Hawaiian Islander	0	0	0	0	0
Other	11 (<1%)	1 (<1%)	3 (2%)	0	3 (11%)
Mean weight (kg ± SD):	56.26± 12.65	57.70± 17.63	61.06± 20.56	71.52± 14.94	69.96± 11.39
Mean height, (cm + SD)	158.0±9.6	159.0±13.8	157.2± 13.2	172.4 ± 9.9	172±8.4

Source: Table created by reviewing statistician utilizing data and study information provided in:------(b)(4)-----

Figure 8.2.2.a) cont. Demographic and Baseline Characteristics of All Subjects in Safety Set-Novartis Studies

Study	V72_29	V72_41				
Group	rMenB +OMV NZ	Men ACWY	Ixiaro ^a	Lot1_ Rosia	Lot2_ (b)(4)	Pooled Lots
Demographic Characteristic	N=974	N=984	N=985	N=169	N=173	N= 342
Mean age (years ± SD)	19.9±1.6 (N=973)	19.9± 1.6	19.8±1.6	13.6±1.9	13.8±1.8	13.7±1.7
Male	461 (47%)	453 (46%)	440 (45%)	98 (58%)	91 (53%)	189 (55%)
Ethnic origin:						
Caucasian	855 (88%)	873 (89%)	864 (88%)	134 (79%)	140 (81%)	274 (80%)
Asian	60 (6%)	49 (5%)	52 (5%)	17 (10%)	18 (10%)	35 (10%)
Black	19 (2%)	14 (1%)	19 (2%)	4 (2%) ^c	1 (<1%) ^c	5 (1%)
Hispanic	3 (<1%)	3 (<1%)	3 (<1%)	0	0	0
Native American/ Alaskan	0	0	0	9 (5%)	6 (3%)	15 (4%)
Pacific/ Hawaiian Islander	0	0	0	0	1 (<1%)	1 (<1%)
Other	37 (4%)	45 (5%)	47 (5%)	5 (3%)	7 (4%)	12 (4%)
Mean weight (kg ± SD):	69.65± 13.21 (N=969)	68.79± 13.44 (N=982)	69.16± 13.50 (N=984)	57.90± 17.14	57.28± 16.24	57.59± 16.67
Mean height, (cm + SD)	172.6± 9.4	172.5± 9.5	172.0± 9.4	162.6± 11.0	162.2± 10.9	162.4± 10.9

Source: Table created by reviewing statistician utilizing data and study information provided in: -----(b)(4)-----

Figure 8.2.2.b) Demographic and Baseline Characteristics of All Subjects in Safety Set-CDC Immunization Campaign

Demographic	V72_68 TP	V72_70TP
Characteristic	N=5520	N=9831
Median age (range) (years)	20 (16-65)	20 (16-68)
Gender		
Male	2854 (52%)	4268 (43%)
Female	2656 (48%)	5562 (57%)
Ethnicity Race		
American Indian/Alaskan Native	4 (<1%)	79 (<1%)
Asian	1292 (23%)	-
Black	416 (8%)	360 (4%)
Hispanic	471 (9%)	-
Latino/other Spanish American	-	530 (5%)
Native Hawaiian/Pacific Islander	-	-
Pacific	-	31 (<1%)
Islander/Micro/Polynesian		
White	2739 (50%)	4064 (41%)
Unknown	1069 (19%)	484 (5%)
Mexican American	-	1694 (17%)
Chinese/Chinese American	-	1019 (10%)
East India/Pakistani	-	272 (3%)
Japanese/Japanese American	-	207 (2%)
Korean/Korean American	-	270 (3%)
Other	-	7 (<1%)
Other Asian	-	1298 (13%)
Philipino/Filipino	-	351 (4%)
Vietnamese/ Vietnamese	-	341 (3%)
American		

Source: Table created by reviewing statistician utilizing data and study information provided in----- (b)(4)-----

Overall, the individuals in the various studies examined by both Novartis as well as in the CDC immunization campaign have a variety of genders, age ranges and race/ethnicity groups represented in each of the treatment groups. One noticeable difference that can be seen in the above tables, is that there were slightly more females in the majority of these studies than males (52% to 60% for the active and placebo treated groups in the various studies).

8.3 Caveats Introduced by Pooling of Data across Studies/Clinical Trials

These studies were performed in a variety of different locations in the US, Canada, Australia, and select countries in Europe and the UK under different INDs with a variety of treatment dosing schedules. Thus, pooling studies and utilizing a model which incorporates the studies is likely not appropriate and could lead to challenges in interpreting results and drawing conclusions regarding the safety. However, to provide additional insight, particularly related to select subgroups, including gender and race, several safety endpoints will be pooled and presented below. Since the majority of these studies had similar time points and data collection mechanisms for safety data, including solicited and unsolicited adverse events, as described in the protocols, these data were combined in a single pooled dataset.

8.4 Safety Results

In studies V72P10, V72_41, V102_03, and V72_29, a large majority of subjects showed at least 1 sign of reactogenicity within 7 days after each of the 2 rMenB+OMV NZ injections. Within the 7-day observation window after each vaccination, solicited AEs were reported by a higher percentage of subjects in the rMenB+OMV NZ groups than in the placebo or control vaccine groups. There was an indication of increase in tolerance of the vaccine administered, as there was a slight reduction in the frequency of these reports after the second rMenB+OMV NZ injection.

In the pooled analysis by schedule, the overall reactogenicity profile was similar across the 2-dose schedules of rMenB+OMV NZ vaccine. Of particular note, the solicited AE profile of the 2-dose schedule, administered with an interval of 1, 2 or 6 months were comparable. Summaries of the safety and tolerability data can be seen in the tables below.

Table 8.4.a) Overview of Solicited Adverse Events of rMenB+OMV NZ Vaccine by Vaccination in Subjects 10-25 Years of Age

Study	V72P10	V72P10	V72_41	V102_03	V102_03	V72_29	V72_29	V72_29
Reaction	rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	Ixiaro	MenACWY
Dose 1	N=1622	N=1492	N=342	N=120	N=109	N=193	N=198	N=196
Any	1503 (93%)	1104 (74%)	332 (97%)	107 (89%)	59 (54%)	187 (97%)	150 (76%)	147 (75%)
Local	1480 (91%)	1025 (69%)	327 (96%)	106 (88%)	41 (38%)	180 (93%)	117 (59%)	118 (60%)
Systemic	1214 (75%)	732 (49%)	260 (76%)	71 (59%)	42 (39%)	161 (83%)	117 (59%)	104 (53%)
Other	646 (40%)	260 (17%)	153 (45%)	23 (19%)	8 (7%)	44 (23%)	19 (10%)	13 (7%)
Dose 2	N=1153	N=914	N=338	N=112	MenACWY N=97	N=190	N=191	Placebo N=187
Any	1032 (90%)	662 (72%)	317 (94%)	93 (83%)	55 (57%)	175 (92%)	120 (63%)	131 (70%)
Local	1008 (87%)	618 (68%)	315 (93%)	91 (81%)	49 (51%)	167 (88%)	92 (48%)	124 (66%)
Systemic	787 (68%)	425 (46%)	205 (61%)	68 (61%)	36 (37%)	133 (70%)	90 (47%)	87 (47%)
Other	353 (31%)	116 (13%)	117 (35%)	23 (21%)	10 (10%)	47 (25%)	9 (5%)	14 (7%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

Based on the safety profiles of the first 2 doses in supportive adult studies V72P4 and V72P5 (which included 53 and 28 subjects, respectively, in total and 9 subjects and 6 subjects, respectively, in the 10-25 year-old group) compared to those of the same schedule in the 10 through 25 years pooled populations, the rates observed for any solicited AEs as well as for local and systemic AEs were generally similar, regardless of schedule listed above. Similarly within the pooled population, a trend towards decreased reports of solicited AEs with subsequent vaccinations was observed in the adult populations of the supportive studies, when considering either individuals 18 to 40 years of age or 18 to 25 years of age (the proposed label indication), regardless of the dosing schedule (0-1 month schedule, 0-2 month, or 0-6 month schedule).

Table 8.4.b) Overview of Solicited Adverse Events of rMenB+OMV NZ Vaccine, by Vaccination in Subjects 10 through 25 Years of Age from Studies V72P10, V72_29, V72_41 and V102_03, and in Subjects 10 through 50 Years of Age from Supportive Studies V72P4 and V72P5, by Schedule

	0, 1 Month Schedule	0, 1 Month Schedule	0, 2 Month Schedule	0, 2 Month Schedule	0, 6 Month Schedule
	18 thru 40 years old	10 thru 25 years old	18 thru 50 years old	10 thru 25 years old	11 thru 17 years old
Dose 1	N=28	N=1283	N=53	N=500	N=128
Any	27 (96%)	1224 (95%)	52 (98%)	460 (92%)	122 (95%)
Local	27 (96%)	1199 (93%)	52 (98%)	455 (91%)	122 (95%)
Systemic	24 (86%)	995 (78%)	29 (55%)	358 (72%)	97 (76%)
Other	9 (32%)	499 (39%)	13 (25%)	176 (35%)	61 (48%)
Dose 2	N=28	N=1226	N=52	N=454	N=114
Any	25 (89%)	1124 (92%)	51 (98%)	399 (88%)	94 (82%)
Local	24 (86%)	1103 (90%)	51 (98%)	387 (85%)	91 (80%)
Systemic	19 (68%)	831 (68%)	28 (54%)	290 (64%)	71 (62%)
Other	6 (21%)	380 (31%)	9 (17%)	123 (27%)	37 (32%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----

----- (b)(4) -----

Reviewer comment: Based on the tabulations presented above and other analyses performed by the reviewing statistician, it appears that the overall safety and tolerability profile of a 2-dose schedule of rMenB+OMV NZ, administered 1 or 2 months apart, is similar for individuals 11 through <18 years of age compared to adults 18 through 25 years of age, with an identical dosing schedule. Furthermore, the safety and tolerability profiles are similar to a 2 dose schedule of rMenB+OMV NZ administered 6 months apart in subjects 11 through 17 years of age. Based on these results, it appears that the safety data based on solicited adverse reactions provided within this BLA support a 2-dose vaccination schedule, starting at 10 years of age and continuing through 25 years of age.

Solicited Local and Systemic Reactions

In studies V72P10, V72_41, V102_03, and V72_29, the most commonly reported local reaction was pain (83%-95%), reported by a majority of subjects after each rMenB+OMV vaccination, and at a generally slightly higher rate than in the comparator vaccine group. Other reported reactions were erythema, swelling, and induration. Within the 7-day observation window after each vaccination, solicited local AEs were reported by a higher percentage of subjects in the rMenB+OMV NZ groups than in the placebo or control vaccine groups. Most of the local reactions, including pain, were mild to moderate in intensity. Severe local reactions were mostly reported as severe pain. Most of these reactions were transient and resolved within the 7- day observation period. In all cases where injection site pain persisted beyond day 7, it resolved and the subject recovered. In the rMenB+OMV NZ groups, the percentages of subjects reporting pain did

not increase with subsequent doses. A tabulation of the observed solicited local reactions can be seen in the following tables.

Table 8.4.c) Percentages of Subjects with Solicited Local and Systemic Adverse Events for 7 Days Post Vaccination, by Dose – Study V72P10

		Dose 1	Dose 1	Dose 2	Dose 2
		rMenB + OMV NZ	Placebo	rMenB + OMV NZ	Placebo
		N=1311-1492	N=1192-1365	N=957-1075	N=686-794
Local Adverse Events					
Pain	Any	1424 (96%)	842 (62%)	962 (90%)	515 (65%)
	Severe	279 (19%)	49 (4%)	182 (17%)	34 (4%)
Erythema	Any	799 (56%)	418 (31%)	551 (53%)	211 (27%)
	>100 mm	2 (<1%)	0 (0%)	3 (<1%)	1 (<1%)
Induration	Any	616 (44%)	309 (23%)	449 (43%)	165 (21%)
	>100 mm	2 (<1%)	0 (0%)	3 (<1%)	0 (0%)
Swelling	Any	613 (44%)	275 (20%)	431 (41%)	149 (19%)
	>100 mm	5 (<1%)	1 (<1%)	6 (<1%)	0 (0%)
Systemic Adverse Events					
Malaise	Any	856 (58%)	416 (31%)	556 (52%)	262 (33%)
	Severe	105 (7%)	30 (2%)	85 (8%)	16 (2%)
Nausea	Any	286 (19%)	172 (13%)	180 (17%)	90 (11%)
	Severe	20 (1%)	13 (1%)	18 (2%)	5 (1%)
Myalgia	Any	720 (49%)	351 (26%)	460 (43%)	206 (26%)
	Severe	104 (7%)	24 (2%)	73 (7%)	16 (2%)
Arthralgia	Any	364 (25%)	184 (14%)	242 (23%)	102 (13%)
	Severe	29 (2%)	11 (1%)	36 (3%)	3 (<1%)
Headache	Any	689 (47%)	397 (29%)	448 (42%)	218 (28%)
	Severe	76 (5%)	41 (3%)	64 (66%)	17 (2%)
Fever	≥38°C	53 (4%)	25 (2%)	44 (5%)	15 (2%)
	38.0-38.9°C	43 (3%)	20 (2%)	37 (4%)	13 (2%)
	39.0-39.9°C	9 (1%)	5 (<1%)	7 (1%)	2 (<1%)
	≥40°C	1 (<1%)	0 (0%)	0 (0%)	0 (0%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

Table 8.4.d) Percentages of Subjects with Solicited Local and Systemic Adverse Events for 7 Days Post Vaccination, by Dose – Study V72P29

		Dose 1	Dose 1	Dose 1	Dose 2	Dose 2	Dose 2
Local Adverse Events		rMenB+ OMV NZ N=183- 190	Ixiaro N=187- 190	MenACWY N=182-186	rMenB+ OMV NZ N=177- 183	Ixiaro N=177- 180	Placebo N=171- 175
Pain	Any	176 (93%)	87 (46%)	92 (50%)	162 (89%)	70 (39%)	109 (63%)
	Severe	16 (8%)	0 (0%)	0 (0%)	15 (8%)	0 (0%)	3 (2%)
Erythema	Any	74 (39%)	47 (25%)	46 (25%)	73 (40%)	34 (19%)	33 (19%)
	>100 mm	1 (1%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)
Induration	Any	50 (26%)	14 (7%)	26 (14%)	42 (23%)	11 (6%)	19 (11%)
	>100 mm	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Swelling	Any	48 (25%)	10 (5%)	18 (10%)	48 (27%)	10 (6%)	16 (9%)
	>100 mm	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Systemic Adverse Events							
Malaise	Any	33 (17%)	38 (20%)	28 (15%)	40 (22%)	23 (13%)	19 (11%)
	Severe	1 (1%)	3 (2%)	1 (1%)	4 (2%)	1 (1%)	1 (1%)
Nausea	Any	24 (13%)	14 (7%)	18 (10%)	18 (10%)	12 (7%)	8 (5%)
	Severe	1 (1%)	1 (1%)	0 (0%)	1 (1%)	2 (1%)	0 (0%)
Myalgia	Any	143 (75%)	95 (50%)	478 (2%)	127 (70%)	64 (36%)	83 (47%)
	Severe	11 (6%)	3 (2%)	2 (1%)	12 (7%)	0 (0%)	2 (1%)
Arthralgia	Any	22 (12%)	19 (10%)	14 (8%)	24 (13%)	14 (8%)	16 (9%)
	Severe	2 (1%)	0 (0%)	1 (1%)	2 (1%)	0 (0%)	2 (1%)
Headache	Any	54 (28%)	57 (30%)	45 (25%)	38 (21%)	41 (23%)	20 (11%)
	Severe	2 (1%)	2 (1%)	0 (0%)	3 (2%)	3 (2%)	1 (1%)
Fever	≥38°C	2 (1%)	5 (3%)	3 (2%)	4 (2%)	2 (1%)	2 (1%)
	38.0-38.9°C	1 (1%)	5 (3%)	3 (2%)	3 (2%)	2 (1%)	2 (1%)
	39.0-39.9°C	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
	>40°C	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

Table 8.4.e) Percentages of Subjects with Solicited Local and Systemic Adverse Events for 7 Days Post Vaccination, by Dose – Study V72_41

		Dose 1	Dose 2
		rMenB+OMV NZ N=315-337	rMenB+OMV NZ N=322-337
Local Adverse Events			
Pain	Any	325 (96%)	303 (90%)
	Severe	37 (11%)	29 (9%)
Erythema	Any	145 (43%)	148 (44%)
	>100 mm	1 (<1%)	1 (<1%)
Induration	Any	89 (26%)	86 (26%)
	>100 mm	0 (0%)	0 (0%)
Swelling	Any	87 (26%)	98 (29%)
	>100 mm	0 (0%)	1 (<1%)
Systemic Adverse Events			
Malaise	Any	NA	NA
	Severe	NA	NA
Nausea	Any	60 (18%)	66 (20%)
	Severe	5 (1%)	5 (1%)
Myalgia	Any	188 (56%)	126 (37%)
	Severe	15 (4%)	11 (3%)
Arthralgia	Any	49 (15%)	42 (13%)
	Severe	12 (0%)	3 (1%)
Headache	Any	117 (35%)	113 (34%)
	Severe	6 (2%)	7 (2%)
Fever	≥38°C	9 (3%)	5 (2%)
	38.0-38.9°C	8 (3%)	4 (1%)
	39.0-39.9°C	1 (<1%)	1 (<1%)
	≥40°C	0 (0%)	0 (0%)

Source: Table created by reviewing statistician utilizing data and study information provided in-----
----- (b)(4) -----

Table 8.4.f) Percentages of Subjects with Solicited Local and Systemic Adverse Events for 7 Days Post Vaccination, by Dose – Study V102_03

		Dose 1	Dose 1	Dose 2	Dose 2
		rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	MenACWY
		N=110-114	N=94-96	N=107-109	N=90-92
Local Adverse Events					
Pain	Any	103 (90%)	26 (27%)	91 (83%)	39 (43%)
	Severe	22 (20%)	2 (2%)	30 (28%)	7 (8%)
Erythema	Any	57 (50%)	15 (13%)	49 (45%)	23 (26%)
	>100 mm	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Induration	Any	36 (32%)	10 (10%)	30 (28%)	21 (23%)
	>100 mm	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Swelling	Any	NA	NA	NA	NA
	>100 mm	NA	NA	NA	NA
Systemic Adverse Events					
Malaise	Any	NA	NA	NA	NA
	Severe	NA	NA	NA	NA
Nausea	Any	22 (19%)	4 (4%)	20 (18%)	4 (4%)
	Severe	4 (4%)	0 (0%)	4 (4%)	0 (0%)
Myalgia	Any	55 (49%)	25 (26%)	52 (48%)	23 (25%)
	Severe	13 (12%)	1 (1%)	14 (13%)	4 (4%)
Arthralgia	Any	15 (13%)	4 (4%)	17 (16%)	4 (4%)
	Severe	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Headache	Any	37 (33%)	19 (20%)	37 (34%)	21 (23%)
	Severe	5 (4%)	1 (1%)	7 (6%)	3 (3%)
Fever	≥38°C	1 (1%)	1 (1%)	5 (5%)	0 (0%)
	38.0-38.9°C	1 (1%)	1 (1%)	4 (4%)	0 (0%)
	39.0-39.9°C	0 (0%)	0 (0%)	1 (1%)	0 (0%)
	≥40°C	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Table created by reviewing statistician utilizing data and study information provided in-----
----- (b)(4)-----

As can be observed in the above tables, in studies V29P10, V72_41, V102_03, and V72_29, the most commonly reported systemic reaction was myalgia, followed by fatigue or headache after each vaccination with rMenB+OMV NZ. The rate of systemic reactions was lower after placebo or control vaccine injections, except for study V72_29, where the incidence of headache was similar between the Ixiaro and rMenB+OMV NZ groups after each vaccination. The majority of the subjects reported solicited systemic reactions which were mild to moderate in severity. Severe reactions were reported at a lower frequency, and these reactions were transient in duration. Although not presented here, the reviewing statistician confirmed from the pooled analysis by schedule that local and systemic reaction profiles for the first and second doses of rMenB+OMV NZ vaccine were similar between the 0, 1-month; 0, 2-month; and 0, 6-month schedules. Similar results and rates of adverse events were observed in the small (n=28 and n=54) Phase II studies.

Statistical Reviewer Comment: *Based on findings from FDA inspections conducted by BIMO during the review cycle, concerns arose regarding potential verbal recall of solicited adverse event data in the context of missed source documents. Upon the request of CBER, the applicant submitted a revised set of reactogenicity rates for the 4 pivotal studies (Studies V72_41, V72_29, V72P10, and V102_03) included in this application. The revised reactogenicity rates excluded missing data (which although not missing, were based on subject recall) determined by detailed review of listings of protocol deviations and clinician comments, suggesting verbal recall of solicited adverse event data rather than explicit responses by subjects within daily diary cards. The approach taken by the applicant to obtain these revised rates and subsequent statistical tabulations provided within the revised ISS tabulations and datasets is acceptable to CBER. The revised rates for the 4 pivotal studies are included in this section of this statistical review; however, earlier summaries utilized the original data submitted without the exclusion of data that may have been recalled.*

Unsolicited Adverse Events

In study V72P10 a total of 1,622 adolescent subjects, in study V72_29 a total of 974 adolescents and young adults, in study V72_41 a total of 342 adolescents, and in study V102_03 a total of 120 adolescents and young adults received at least one dose of rMenB+OMV NZ Bexsero® vaccine and were included in the analysis of unsolicited AEs.

During the 30 days following each dose (at month 0, 1, 2, or 6 as applicable), both “any” and possibly or probably related AEs did not increase for the second and third vaccinations in both the rMenB+OMV NZ Bexsero® and placebo groups. However, in all studies, the percentages of rMenB+OMV NZ Bexsero® recipients reporting any AEs were higher than those observed in the placebo group across the 3 doses (11% to 29% vs. 8% to 18%). Regardless of the group, these reports were mostly due to solicited AEs persisting beyond the 7-day observation period or common infections. Within all studies, SAEs were infrequent and, when present, were reported by no more than 1% of subjects across vaccinations in both the rMenB+OMV NZ Bexsero® and control/placebo groups.

Table 8.4.g) Overview of Unsolicited Adverse Events of a Two-dose Schedule of rMenB+OMV NZ within 30 Days of Vaccination, by Vaccination, in Subjects 10 through 25 Years of Age and in Subjects 18 through 50 Years of Age

		0, 1 Schedule	0, 1 Schedule	0, 2 Schedule	0, 2 Schedule	0, 1 Schedule	Pooled Two dose Schedule
		18 thru 40 years old	10 thru 25 years old	18 thru 50 years old	10 thru 25 years old	11 thru 17 years old	10 thru 25 years old
Dose 1		N=28	N=2064	N=53	N=500	N=128	N=2692
	Any AEs	2 (7%)	426 (21%)	9 (17%)	138 (28%)	32 (25%)	596 (22%)
	At least possibly related AEs	0	179 (9%)	3 (6%)	54 (11%)	11 (9%)	244 (9%)
	Serious AEs	0	12 (1%)	0	1 (<1%)	1 (1%)	14 (1%)
Dose 2		N=28	N=1968	N=52	N=453	N=114	N=2536
	Any AEs	2 (7%)	287 (15%)	9 (17%)	70 (15%)	14 (12%)	371 (15%)
	At least possibly related AEs	0	114 (6%)	5 (10%)	27 (6%)	9 (8%)	150 (6%)
	Serious AEs	0	4 (<1%)	0	2 (<1%)	0	6 (<1%)

Source: Table created by reviewing statistician utilizing data and study information in the applicant's provided Integrated Summary of Safety Datasets found within: -----(b)(4)-----

The most commonly occurring unsolicited adverse events can be further examined within the following tables included in the applicant's Integrated Summary of Safety.

Table 8.4.h) Summary of Most Frequently Reported (by at Least 2 % of Subjects in any Group across Studies) Unsolicited Adverse Events by Preferred Term within 30 Days of Vaccination, by Dose - Study V72P10 (Number and % of Subjects with Unsolicited AEs)

	All AE	All AE	All AE	All AE	Related AE	Related AE	Related AE	Related AE
	Dose1	Dose1	Dose 2	Dose 2	Dose 1	Dose 1	Dose 2	Dose 2
	rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	Placebo	rMenB+ OMV NZ	Placebo
	N=1622	N=1492	N=1153	N=914	N=1622	N=1492	N=1153	N=914
Injection Site Pain	54 (3%)	5 (<1%)	17 (1%)	1 (<1%)	54 (3%)	5 (<1%)	16 (1%)	1 (<1%)
Nasopharyngitis	41 (3%)	35 (2%)	18 (2%)	14 (2%)	0	0	0	0

Source: BLA 125546 amendment 2, Study Report, Integrated Summary of Safety, page 84

In the above table, it can be seen within study V72P10, the most commonly occurring unsolicited adverse events were continued injection site pain as well as nasopharyngitis.

Figure 8.4.i) Summary of Most Frequently Reported (by at Least 2 % of Subjects in any Group across Studies) Unsolicited Adverse Events by Preferred Term within 30 Days of Vaccination, by Dose - Studies V72_41, V102_03, and V72_29

MedDRA Preferred Term	Number (%) of Subjects with Unsolicited AEs											
	All						At Least Possibly Related					
	V72_41 rMenB+ OMV NZ	V102_03 rMenB+ OMV NZ	Placebo ^a	V72_29 rMenB+ OMV NZ	Ixiaro	MenACWY	V72_41 rMenB+ OMV NZ	V102_03 rMenB+ OMV NZ	Placebo ^a	V72_29 rMenB+ OMV NZ	Ixiaro	MenACWY
Dose 1	N=342	N=120	N=109	N=974	N=985	N=984	N=342	N=120	N=109	N=974	N=985	N=984
Injection Site Pain	19 (6)	2 (2)	1 (1)	6 (1)	0	0	19 (6)	2 (2)	1 (1)	6 (1)	0	0
Myalgia	9 (3)	0	1 (1)	14 (1)	1 (<1)	3 (<1)	9 (3)	0	1 (1)	14 (1)	1 (<1)	3 (<1)
Nasopharyngitis	7 (2)	2 (2)	1 (1)	6 (1)	6 (1)	4 (<1)	0	0	0	3 (<1)	1 (<1)	1 (<1)
Headache	1 (<1)	5 (4)	3 (3)	1 (<1)	5 (1)	4 (<1)	1 (<1)	2 (2)	1 (1)	1 (<1)	3 (<1)	3 (<1)
Diarrhoea	2 (1)	1 (1)	4 (4)	5 (1)	2 (<1)	0	2 (1)	0	0	1 (<1)	0	0
Upper Respiratory Tract Infection	6 (2)	0	0	1 (<1)	1 (<1)	2 (<1)	2 (1)	0	0	0	0	0
Oropharyngeal Pain	5 (1)	4 (3)	1 (1)	7 (1)	5 (1)	7 (1)	2 (1)	0	0	0	1 (<1)	2 (<1)
Injection Site Erythema	1 (<1)	2 (2)	0	0	0	0	1 (<1)	2 (2)	0	0	0	0
Vomiting	3 (1)	3 (3)	2 (2)	2 (<1)	1 (<1)	0	3 (1)	1 (1)	1 (1)	0	0	0
Dose 2	N=338	N=112	MenACWY N=97	N=932	N=947	Placebo^b N=956	N=338	N=112	MenACWY N=97	N=932	N=947	Placebo^b N=956
Injection Site Pain	6 (2)	3 (3)	1 (1)	4 (<1)	0	0	6 (2)	3 (3)	1 (1)	4 (<1)	0	0
Nasopharyngitis	3 (1)	1 (1)	2 (2)	1 (<1)	3 (<1)	1 (<1)	0	0	0	0	0	0
Headache	3 (1)	3 (3)	1 (1)	1 (<1)	4 (<1)	0	1 (<1)	1 (1)	0	0	0	0
Upper Respiratory Tract Infection	6 (2)	4 (4)	0	0	1 (<1)	1 (<1)	4 (1)	0	0	0	1 (<1)	0
Injection Site Erythema	0	0	2 (2)	3 (<1)	0	0	0	0	2 (2)	3 (<1)	0	0
Fatigue	3 (1)	3 (3)	0	0	0	0	2 (1)	1 (1)	0	0	0	0
Sinusitis	0	3 (3)	0	0	1 (<1)	4 (<1)	0	0	0	0	0	0
Vomiting	3 (1)	2 (2)	0	1 (<1)	2 (<1)	1 (<1)	3 (1)	0	0	0	1 (<1)	0

Source: BLA 125546 amendment 2, Study Report, Integrated Summary of Safety, page 86-87

As shown in the above table, within studies V72_41, V102_03, and V72_29, similar to study V72P10, the most commonly occurring unsolicited adverse event was continued injection site pain, with up to 6% of subjects experiencing this adverse event. Other unsolicited adverse events were noted, but there do not appear to be consistent trends. Additionally, several other unsolicited adverse events appeared to occur in the placebo treated group, thus suggesting the background rate of unsolicited adverse events is not 0% and has variability.

Statistical Reviewer Comment: Based on clinical study reports and the integrated summary of safety, as well as data submitted to this BLA, among subjects 10 up to 18 years of age and 18 through 25 years of age, the most commonly reported unsolicited AEs within 30 days of rMenB+OMV NZ, Bexsero®, vaccination were common infections, or solicited reactions persisting beyond the 7-day observation period, which were considered possibly or probably related to the vaccination. Most of these reactions were of mild or moderate severity and of limited duration. Overall, the most common at least possibly related AE was injection site pain, reported by 3% and 1% of subjects 10 through 25 years of age, regardless of the time interval of the 2- dose schedule after the first and second vaccination, respectively. Additional details related to the unsolicited Adverse Events can be seen in the medical officer's review.

8.4.1 Deaths

There were two deaths in study V72P10, and both were assessed as not related to vaccination. No deaths were reported in the Novartis studies V72_41, V102_03, and V72_29. No deaths were reported in the CDC immunization campaign, V72_68TP, and 1 subject died in study V72_68TP (as of June 27, 2014). The two deaths in V72P10 included one complicated craneo-cerebral trauma secondary to a car accident on day 118 after the second vaccination of Bexsero®, and the other death was acute hepatic failure secondary to paracetamol intoxication which occurred on day 33 after the third Bexsero vaccination. The cause of death in the individual in the CDC immunization campaign V72_68TP, which occurred 27 days after the first vaccination with Bexsero®, was reported by the clinician as sudden cardiac arrest. Additional details and discussions related to the deaths observed during the studies submitted to this BLA can be found in the medical officer's review.

8.4.2 Nonfatal Serious Adverse Events

Several Nonfatal Serious Adverse Events occurred within the study time frame for both the Phase II-III Clinical studies as well as the CDC immunization campaign. A summary of the Adverse Events is listed in the following table. The table below includes the study number, subject number, vaccine group, SAE preferred term, SAE onset, severity, outcome, and relation to study vaccine. Within the table below it can be seen that the eight serious adverse events reported that are possibly or probably related to the study product include: juvenile arthritis, tremor, dyspnea, and acute thyroiditis in the Novartis clinical studies and rhabdomyolysis, cardiac arrest, and anaphylactic reaction in the CDC immunization campaign. Additional details and discussions related to these Adverse Events can be found in the epidemiologist's and medical officer's reviews.

Figure 8.4.2.a) Listing of Possibly and Probably Related Serious Adverse Events in Subjects 10 through 25 Years of Age

Study	Subject Number	Vaccine Group	SAE MedDRA Preferred Term (Verbatim Term)	Onset (days)	Severity	Outcome	Relation to Study Vaccine
V72P10	51/0006	rMenB 0,1,2	Juvenile arthritis (Idiopathic juvenile arthritis)	92 from placebo 198 from 3 rd rMenB+OMV NZ ^a	Moderate	AE persists	Probably related
	61/0004	rMenB 0,1,2	Juvenile arthritis (Juvenile idiopathic arthritis, psoriatic type)	170 from 3 rd rMenB+OMV NZ ^a	Severe	AE persists	Possibly related
V72_29	02/0048	rMenB+OMV NZ	Tremor (Resting fine tremor of both hands)	18 from 1 st rMenB+OMV NZ ^a	Moderate	AE persists	Possibly related
	07/0067	rMenB+OMV NZ	Dyspnea (Dyspnea)	2 days from 1 st rMenB+OMV NZ ^a	Mild	Recovered	Possibly related
	09/0147	rMenB+OMV NZ	Thyroiditis acute (Acute thyroiditis)	18 days from 1 st rMenB+OMV NZ ^a	Severe	AE persists	Probably related
V72_68TP	PU22585	rMenB+OMV NZ	Rhabdomyolysis (Rhabdomyolysis)	2 days after 2 nd rMenB +OMV NZ ^b	-	-	Possibly related
V72_70TP	10048565	rMenB+OMV NZ	Cardiac arrest (Sudden cardiac arrest)	27 days after the 1 st rMenB+OMV NZ ^b	-	-	Unknown ^c
	10038941	rMenB+OMV NZ	Anaphylactic reaction (Anaphylaxis)	day of 1 st rMenB+OMV NZ	-	-	Related ^c

Source: BLA 125546 amendment 2, Study Report, Integrated Summary of Safety, page 104

8.4.3 Study Dropouts/Discontinuations

Subjects did withdraw from the studies submitted in this BLA; however, as per the applicant's narrative and data provided within the submission, less than 5% of subjects withdrew from the studies. Summaries of the withdrawals from the studies are described below.

V72P10

Overall, 3 subjects withdrew from study V72P10 due to an AE: subject 61/0004 withdrew 170 days after receiving the third rMenB+OMV NZ vaccination because of juvenile arthritis. This was an SAE which was assessed as possibly related to vaccination. The other 2 subjects (15/5009, 41/5044) had an outcome of death (road traffic accident on day 118 after the third rMenB+OMV NZ vaccination for subject 15/5009, and suicide on day 33 after the third rMenB+OMV NZ vaccination for subject 41/5044); however, in both cases it was determined by the clinician that these deaths were unrelated to the study vaccination.

V72_41

One subject in study V72_41 (51/013, Lot2_(b)(4)) reported a vaccine unrelated AE, infectious mononucleosis, on day 14 after rMenB+OMV NZ vaccination. This AE led to premature withdrawal from the study.

V102_03

In study V102_03, 2 subjects reported unsolicited AEs that led to premature withdrawal from the study; both were from the rMenB+OMV NZ group. One subject (24/066) developed an SAE, a convulsion, on day 60 after the first vaccination and was hospitalized. The SAE was assessed by the applicant's clinician and confirmed by CBER's medical officer as not related to the study vaccination. The subject had a past medical history of seizure disorder prior to enrollment in the study. The second subject (11/040) developed generalized lymphadenopathy on day 6 after the first rMenB+OMV NZ vaccination (and a slight body temperature increase to 37-38°C). This AE was moderate in severity and was assessed by the applicant's clinician and confirmed by the medical officer as possibly related to vaccination, based on the temporal relationship with vaccination.

V72_29

A total of 26 subjects from study V72_29 reported AEs that led to withdrawal from the study, accounting for 1% of subjects in each vaccine group. Most of these AEs were categorized under SOC "general disorders and administration site conditions." For 4 subjects in the rMenB+OMV NZ group, AEs leading to withdrawal were assessed as serious and included: 1 subject reporting an ovarian germ cell cancer with onset 96 days after the second rMenB+OMV NZ vaccination (subject 03/0282); dyspnea with onset 2 days after the first rMenB+OMV NZ vaccination (subject 07/0067); suicidal ideation with multiple drug overdoses, with onset 10 days after first rMenB+OMV NZ

vaccination (subject 08/0030); and acute thyroiditis with onset 18 days after first rMenB+OMV NZ vaccination (subject 09/0147). Several additional subjects withdrew due to rash or pain at the injection related to the injection. All subjects were followed, and these symptoms resolved by the end of the study.

V72P4 and V72P5

Three subjects prematurely withdrew from studies V72P4 and V72P5 due to AEs, all assessed by the applicant's clinician and confirmed by the medical officer as not related to the study vaccination, and none was reported as serious.

Statistical Reviewer Comment: *Based on the data within this BLA in subjects 10 through 50 years of age, premature withdrawals due to AEs were infrequent, and there did not appear to be a consistent pattern regarding the reason for withdrawal or type of AE reported prior to withdrawal. One study, V72P10, had withdrawals that appeared to not be explicitly listed within the study report and comments within the datasets, but were noted by the BIMO inspector. Additional details related to these discrepancies can be found in the BIMO inspection report, as well as the medical officer's review.*

8.4.4 Common Adverse Events

Common adverse events included injection site pain, induration, and swelling, based on both solicited and unsolicited adverse event reporting. Additionally, subjects also reported headache, myalgia, and arthralgia within the first 7 days post injection. However, with respect to severe adverse events, pain and myalgia tended to be the only AEs that were observed in more than 10% of subjects, depending on the study. These observed reactions tended to be lower by the second vaccination and were noted to be self-limiting in nature.

8.4.5 Clinical Test Results

Clinical laboratory tests (chemistry, hematology, and routine urinalyses) were carried out on samples provided by participants in study V72P5, before vaccination and 7 days after rMenB+OMV NZ. Of the parameters assessed, three abnormal laboratory values were assessed by the applicant's clinician as clinically significant. These were one case of elevated γ GT value (131 U/L) in the rMenB+OMV NZ group, one case of high CRP (25.9, repeat value normal, 2.6), and one HIV positive test (SAE). No abnormal laboratory value was assessed by the applicant's clinician as related to the study vaccine.

8.4.6 Systemic Adverse Events

The most commonly occurring systemic adverse events noted were headache, nausea, and myalgia.

8.4.7 Local Reactogenicity

The most commonly occurring local adverse events were pain, erythema, and induration. Pain in particular was rated as severe in >10% of subjects administered Bexsero®, for nearly all studies.

8.4.8 Adverse Events of Special Interest

There were no additional Adverse Events of Special interest provided or examined within this submission.

8.5 Additional Safety Evaluations

Although this product had both solicited and unsolicited adverse events noted during the studies submitted within this BLA, these AEs were to be expected since this product is an active vaccine designed to prevent meningococcal disease. However, rates observed in this study were similar to types and rates of AEs that are observed in other approved meningococcal disease vaccines: Trumenba®, Menveo®, and Menactra®.

8.5.1 Dose Dependency for Adverse Events

There are no data regarding the dose dependency for Adverse Events of this product provided within this submission.

8.5.2 Time Dependency for Adverse Events

There are no data regarding the time dependency for Adverse Events of this product provided within this submission.

8.5.3 Product-Demographic Interactions

The product-demographic interactions of Bexsero® demonstrate a generally similar response in adverse event reports between treatment groups, regardless of baseline demographic, except for gender.

Solicited AEs

There was a slightly higher percentage of female subjects reporting any solicited AE, any solicited local AE, and any solicited systemic AEs compared with male subjects, after each vaccination in both the rMenB product and control/placebo groups. Approximately 95% of females appeared to report any AE after dose 1 of the rMenB product, while 90% of males reported any AE after dose 1 of the rMenB product; the genders reported rates of 78% and 67%, respectively, for the comparator treatment after dose 1. Similar rates and patterns are observed when considering the local AEs, with slightly lower rates for the systemic AEs (Table 8.5.3.1.a).

Table 8.5.3.1.a) Summary of Solicited Adverse Events by Gender (Observed count and %)

Reaction	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Local AE-Dose 1	Local AE-Dose 1	Systemic AE-Dose 1	Systemic AE-Dose 1	Other AE-Dose 1	Other AE-Dose 1
Male	963 (91%)	600 (67%)	936 (89%)	531 (60%)	725 (69%)	363 (41%)	361 (34%)	114 (13%)
Female	1166 (95%)	860 (78%)	1157 (95%)	770 (70%)	981 (80%)	632 (57%)	505 (41%)	186 (17%)
	Any AE-Dose 2	Any AE-Dose 2	Local AE-Dose 2	Local AE-Dose 2	Systemic AE-Dose 2	Systemic AE-Dose 2	Other AE-Dose 2	Other AE-Dose 2
Male	725 (87%)	395 (63%)	707 (85%)	359 (57%)	496 (60%)	244 (39%)	225 (27%)	52 (8%)
Female	892 (93%)	573 (75%)	874 (91%)	524 (69%)	697 (72%)	394 (52%)	315 (33%)	97 (13%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
------(b)(4)-----

The gender effects of the treatment suggest higher solicited AE rates for the rMenB treatment group versus the comparator, regardless of race. Among gender categories, those identified as Caucasians appeared to have the highest solicited AE response rate in the rMenB treatment group for any AE, local AEs, and Systemic AEs, with rates of 97%, 96%, and 77%, respectively. Those identified as Hispanic or Asian appeared to have the lowest rates of any AE, local AEs, and Systemic AEs for the rMenB treatment group, as can be seen in the following table.

Table 8.5.3.1.b) Summary of Solicited Adverse Events by Race (Observed count and %)

Reaction	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Local AE-Dose 1	Local AE-Dose 1	Systemic AE-Dose 1	Systemic AE-Dose 1	Other AE-Dose 1	Other AE-Dose 1
Asian	43 (90%)	17 (71%)	39 (81%)	15 (63%)	15 (63%)	15 (63%)	14 (29%)	4 (17%)
Black	11 (92%)	6 (50%)	11 (92%)	4 (33%)	9 (75%)	5 (42%)	3 (25%)	0
Caucasian	512 (97%)	296 (74%)	504 (96%)	232 (58%)	408 (77%)	216 (54%)	191 (36%)	31 (8%)
Hispanic	1524 (92%)	1112 (73%)	1501 (91%)	1024 (67%)	1228	740 (49%)	648 (39%)	260 (17%)
Other	39 (98%)	29 (81%)	38 (95%)	26 (72%)	28 (70%)	22 (61%)	10 (25%)	5 (14%)
	Any AE-Dose 2	Any AE-Dose 2	Local AE-Dose 2	Local AE-Dose 2	Systemic AE-Dose 2	Systemic AE-Dose 2	Other AE-Dose 2	Other AE-Dose 2
Asian	41 (87%)	13 (59%)	41 (87%)	13 (59%)	28 (60%)	8 (36%)	9 (19%)	2 (9%)
Black	10 (83%)	7 (58%)	10 (83%)	6 (50%)	8 (67%)	5 (42%)	1 (8%)	0
Caucasian	482 (93%)	251 (66%)	471 (91%)	215 (56%)	331 (64%)	172 (45%)	162 (31%)	24 (6%)
Hispanic	1053 (89%)	675 (72%)	1028 (87%)	630 (67%)	806 (68%)	433 (46%)	358 (30%)	118 (13%)
Other	31 (86%)	31 (86%)	31 (86%)	19 (61%)	20 (56%)	20 (65%)	10 (28%)	5 (16%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
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There were a slightly higher percentage of subjects 18-25 years of age reporting any solicited AE, any solicited local AE, and any solicited systemic AEs compared with individuals 11 to <18 years of age, after each vaccination in both the rMenB+OMV NZ and control/placebo groups. Approximately 96% of subjects 18-25 years of age reported

any AE after dose 1 of the MenB product, while 93% of subjects 11 to <18 years of age reported any AE after dose 1 of the MenB product, with each age group reporting a rate of 74 and 73%, respectively, for the comparator treatment after dose 1. Similar rates and patterns are observed when considering the local AEs with slightly lower rates for the systemic AEs for both age groups, which can be seen in the following table.

Table 8.5.3.1.c) Summary of Solicited Adverse Events by Age Group (Observed count and %)

Reaction	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Local AE-Dose 1	Local AE-Dose 1	Systemic AE-Dose 1	Systemic AE-Dose 1	Other AE-Dose 1	Other AE-Dose 1
11 to <18 years of age	1906 (93%)	1144 (73%)	1877 (92%)	1055 (67%)	1520 (74%)	758 (48%)	816 (40%)	266 (17%)
18-25 years of age	223 (96%)	316 (74%)	216 (93%)	246 (58%)	186 (80%)	237 (56%)	50 (21%)	34 (8%)
	Any AE-Dose 2	Any AE-Dose 2	Local AE-Dose 2	Local AE-Dose 2	Systemic AE-Dose 2	Systemic AE-Dose 2	Other AE-Dose 2	Other AE-Dose 2
11 to <18 years of age	1413 (90%)	704 (72%)	1385 (88%)	657 (67%)	1039 (66%)	452 (46%)	486 (31%)	126 (13%)
18-25 years of age	204 (90%)	264 (65%)	196 (87%)	226 (56%)	154 (68%)	186 (46%)	54 (24%)	23 (6%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

Unsolicited AEs

Unsolicited Adverse events were reported at a higher rate in the rMenB treatment group compared to the comparator, in general.

There was a slightly higher percentage of female subjects reporting unsolicited AEs compared with the male subjects after the initial dose of rMenB; reported rates were 27% and 16% for females and males, respectively, in the rMenB containing vaccine, compared to 15% and 10% for females and males, respectively, in the comparator group. Serious AEs were reported by too few subjects to allow a meaningful comparison by gender. The following table presents a summary of the observed AEs by gender and dose (for dose 1 and dose 2 only).

Table 8.5.3.2.a) Summary of Unsolicited Adverse Events within 30 days of Vaccine by Gender (Observed count and %) and Dose

Reaction	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Serious AE-Dose 1	Serious AE-Dose 1
Male	232 (16%)	162 (10%)	3 (<1%)	3 (<1%)
Female	442 (27%)	295 (15%)	11 (1%)	4 (<1%)
	Any AE-Dose 2	Any AE-Dose 2	Serious AE-Dose 2	Serious AE-Dose 2
Male	140 (12%)	94 (7%)	4 (<1%)	2 (<1%)
Female	231 (17%)	174 (11%)	2 (<1%)	5 (<1%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

Considering the unsolicited AEs, there appeared to be a slightly higher reporting rate of AEs for all racial groups when compared to the comparator treatment, with the highest reported unsolicited AEs within 30 days of vaccine administration after dose 1 of rMenB noted in Hispanic (24%), Other (21%), Caucasian (19%), and Asian (18%) individuals. These rates compare to unsolicited AE rates of 16%, 15%, 10%, and 10% for Hispanic, Other, Caucasian, and Asian individuals in the comparator group, respectively. Similar rates are noted for dose 2 of both the products. Serious AEs were reported by too few subjects to allow a meaningful comparison by race. The following table presents a summary of the observed AEs stratified by race based on dose (for dose 1 and dose 2 only).

Table 8.5.3.2.b) Summary of Unsolicited Adverse Events within 30 days of Vaccine by Race (Observed count and %)

Reaction	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Serious AE-Dose 1	Serious AE-Dose 1
Asian	18 (18%)	10 (10%)	1 (<1%)	0
Black	3 (11%)	5 (13%)	0	0
Caucasian	234 (19%)	188 (10%)	10 (<1%)	4 (<1%)
Hispanic	403 (24%)	239 (16%)	2 (<1%)	3 (<1%)
Other	16 (21%)	14 (15%)	1 (<2%)	0
	Any AE-Dose 2	Any AE-Dose 2	Serious AE-Dose 2	Serious AE-Dose 2
Asian	10 (11%)	9 (9%)	0	0
Black	2 (8%)	6 (16%)	0	0
Caucasian	161 (14%)	143 (8%)	4 (<1%)	5 (<1%)
Hispanic	195 (16%)	104 (11%)	2 (<1%)	1 (<1%)
Other	3 (4%)	6 (7%)	0	1 (<2%)

Source: Table created by reviewing statistician utilizing data and study information provided in: -----
----- (b)(4) -----

There was a slightly higher percentage of subjects 11 to <18 years of age reporting unsolicited AEs within 30 days of vaccine administration, compared with the individuals 18-25 years of age after the initial dose of rMenB; however, after the second dose of either product, AE rates were comparable. Serious AEs were reported by too few subjects to allow a meaningful comparison by age group. The following table presents a summary of the observed AEs by age and dose (for dose 1 and dose 2 only).

Table 8.5.3.2.c) Summary of Unsolicited Adverse Events within 30 days of Vaccine by Age Group (Observed count and %)

Reaction	rMenB	Comparator	rMenB	Comparator
	Any AE-Dose 1	Any AE-Dose 1	Serious AE-Dose 1	Serious AE-Dose 1
11 to <18 years of age	514 (25%)	250 (16%)	2 (<1%)	3 (<1%)
18 to 25 years of age	160 (16%)	207 (10%)	12 (<1%)	4 (<1%)
	Any AE-Dose 2	Any AE-Dose 2	Serious AE-Dose 2	Serious AE-Dose 2
11 to <18 years of age	265 (17%)	109 (11%)	2 (<1%)	3 (<1%)
18 to 25 years of age	106 (11%)	159 (8%)	4 (<1%)	4 (<1%)

Source: Table created by reviewing statistician utilizing data and study information provided in-----
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Overall, the observed AEs were fairly comparable between different demographic dispositions, with solicited AEs noted by 80%-90% of individuals and unsolicited AEs noted by 10%-25% of individuals for dose 1 and fewer AEs noted after dose 2 for all demographic groups.

8.5.4 Product-Disease Interactions

There are no data regarding product-disease interactions provided within this submission.

8.5.5 Product-Product Interactions

There are no data regarding product-product interactions provided within this submission.

8.5.6 Human Carcinogenicity

There are no data regarding human carcinogenicity of this product provided within this submission.

8.5.7 Immunogenicity (Safety)

Not applicable.

8.6 Safety Conclusions

Based on the observed safety data, this product frequently causes local AEs that are often associated with vaccines. The data reviewed support the general conclusion that the episodes of severe or serious AEs associated with Bexsero® were typically self-limiting and resolved

by study completion. Additional details can be seen in the medical officer's and epidemiologist's reviews.

9. ADDITIONAL STATISTICAL ISSUES

No additional statistical issues were noted during the examination and re-analysis of the safety data provided by the applicant.

9.1 Special Populations

No special populations were examined in any studies submitted within this BLA.

9.1.1 Human Reproduction and Pregnancy Data

There are limited data regarding human reproduction or pregnancy provided within this submission. Pregnancy was an exclusion criterion in all the clinical trials. However, 19 pregnancies were reported during the 12-month overall study period in study V72P10; all occurred after at least 1 dose of rMenB+OMV NZ. Nine pregnancies (of which 1 was during pregnancy screening prior to enrollment) were reported in the 12-month overall study period of study V72_29, of which 3 were in the rMenB+OMV NZ group, with 2 occurring after at least 1 dose of vaccine. Two pregnancies occurred in the 8-month overall duration of study V102_03, 1 of which was in the rMenB+OMV NZ group and occurred after at least 1 dose of vaccine. No pregnancies were reported during the 2-month study duration in study V72_41. As of June 27, 2014, overall 5 pregnancies were reported in the CDC-immunization campaigns at the University of Princeton and UC Santa Barbara.

9.1.2 Use during Lactation

There are no data provided in this submission regarding the use of this product in lactating individuals.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of this product was not evaluated in pediatric individuals younger than 10 years of age. The safety data collected on pediatric subjects 10 to 18 year of age have been described previously within this review.

9.1.4 Immunocompromised Patients

There are no data regarding individuals with compromised immunity provided within this submission, particularly since immunocompromised subjects were generally excluded from the studies (particularly the Phase II/III randomized controlled clinical studies).

9.1.5 Geriatric Use

There are no data regarding geriatric use in individuals older than 65 years of age provided within any studies submitted by the applicant.

9.2 Aspect(s) of the Statistical Evaluation Not Previously Covered

The reviewer has no additional comments.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The data from the studies provided in this submission appear to support the applicant's conjecture that the Bexsero® MenB vaccine is safe and effective in the prevention of MenB caused by *Neisseria meningitidis*.

10.2 Conclusions and Recommendations

Based on the data submitted and reviewed, Novartis's Bexsero® vaccine appears to be safe for the prevention of meningococcal group B disease. Based on the solicited and unsolicited adverse events observed during the various Phase II/III studies, as well as the open label study of students from UC Santa Barbara and Princeton University, this vaccine appears to have an acceptable safety profile, consisting of generally self-limiting adverse events that are typically mild or moderate in severity. Although up to 10% of subjects did experience a variety of severe adverse events, this rate is common in vaccines and is comparable to licensed meningitis vaccines, including Menveo®, Menactra®, and Trumenba®. Thus, the vaccine appears to be safe for subjects 10-25 years of age, based on the statistical analyses performed and data examined by the reviewing statistician.