Application Type	Original Application
STN	125546/0
CBER Received Date	July 24, 2014
PDUFA Goal Date	March 24, 2015
Division / Office	DVRPA /OVRR
Priority Review	Yes, granted September 22, 2014
Reviewer Name	Anuja Rastogi, MD MHS
Review Completion Date / Stamped Date	January 23, 2015
Supervisory Concurrence	R. Douglas Pratt, MD MPH
Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Meningococcal Group B Vaccine
(Proposed) Trade Name	BEXSERO
Pharmacologic Class	Vaccine
Formulation (0.5mL dose)	50 mcg of each of the following *Neisseria meningitidis* recombinant proteins: Neisserial adhesion A (peptide 8 variant 2/3), Factor H binding protein (variant 1.1), Neisserial Heparin Binding Antigen (peptide 2). 25 mcg of Outer Membrane Vesicle (expressing outer membrane protein PorA P1.4) from *N. meningitidis* strain NZ98/254 Other components: 1.5 mg aluminum hydroxide, 10 mg sucrose; 3.125 mg NaCl; 0.776 mg histidine, water for injection: up to 0.5mL
Dosage Form and Route of Administration	Suspension for intramuscular injection in 0.5 mL single-dose prefilled syringes
Dosing Regimen	Two doses (0.5 mL each) administered at least 1 month apart
Indication and Intended Population	Active immunization to prevent invasive disease caused by *N.meningitidis* serogroup B individuals 10 through 25 years of age.
Orphan Designated	No

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GLOSSARY

ABCs	Active Bacterial Core surveillance (ABCs) program
AE	Adverse Event
ACIP	Advisory Committee on Immunization Practices
$Al(OH)_3$	Aluminum hydroxide
Bexsero	Proposed Trade Name for Meningococcal B Recombinant + OMV NZ
BIMO	FDA's Bioresearch Monitoring Program
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CSR	Clinical Study Report
DIS	Division of Inspections and Surveillance
fHbp	Factor H binding protein (outer membrane protein)
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
Hib-MenCY-TT	MenHibrix®, Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine (Glaxo Smith Kline Biologicals)
hSBA	Serum Bactericidal Activity (assay) using human complement
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
JEV	Japanese Encephalitis Vaccine
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY-CRM	Menveo®, Meningococcal (Groups A,C,Y and W-135) Polysaccharide CRM Conjugate Vaccine (Novartis Vaccines and Diagnostics, Inc.)
MenACWY-D	Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur, Inc.)
MenB	Meningococcal Serogroup B
MPSV4	Menomune®, Meningococcal Polysaccharide Vaccine Groups A,C,Y and W-135 Combined (Sanofi Pasteur, Inc.)
NadA	Neisserial adhesion A (outer membrane protein)
NHBA	Neisserial Heparin Binding Antigen (outer membrane protein)
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NVD	Novartis Vaccines and Diagnostics
NZ	New Zealand
OBE	Office of Biostatistics and Epidemiology
OMV	Outer Membrane Vesicle
OSE	Office of Surveillance and Epidemiology
PeRC	Pediatric Review Committee
PI	Package Insert
PMR	Post-marketing Requirement
PPS	Per Protocol Analysis Set
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy

rMenB	recombinant outer membrane proteins *N.meningitidis* serogroup B
rMenB+OMV	Meningococcal B Recombinant + OMV NZ Vaccine (Bexsero)[1]
SAE	Serious Adverse Event
SOC	MedDRA system organ class

1 During clinical development, the candidate vaccine (Bexsero) was referred to as rMenB+OMV.

1. EXECUTIVE SUMMARY

An original Biologics License Application (BLA) for candidate Meningococcal Group B vaccine, rMenB+OMV (Bexsero™) has been submitted by Novartis Vaccines and Diagnostics, Inc. with a proposed indication for the active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B for use in individuals 10 through 25 years of age.

N. meningitidis serogroup B is a significant cause of invasive disease, including bacterial meningitis and sepsis. According to the Centers for Disease Control and Prevention (CDC),[2] between 2005 and 2011 an estimated 800 to 1200 cases of meningococcal disease cases occurred annually in the United States (US), representing an incidence of 0.3 cases/100,000 population. Although the majority of reported cases were sporadic, outbreaks accounted for 108 cases (1.5%) of the 7,343 reported cases between 2005 and 2011. The CDC estimates that an average of 402 meningococcal disease cases due to serogroup B occurred annually between 2002 and 2011. In 2012, serogroup B was the most frequently reported serogroup causing meningococcal disease, with an estimated incidence rate of 0.06/100,000.[3] Between 2013 and 2014, there were 13 cases of serogroup B meningococcal disease associated with outbreaks at two US universities, including one fatality, highlighting an urgent public health need for a licensed vaccine in the US.

This public health need prompted FDA to assess existing data available from the international clinical development program of Bexsero, and determine if those data could support an expedited approval under the accelerated approval regulations [21 CFR 601.40]. These regulations authorize FDA to approve products for a serious or life-threatening condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. For products approved under accelerated approval, post-marketing confirmatory trials are required to verify and describe the anticipated clinical benefit. As the result of communications between FDA and Novartis Vaccines and Diagnostic, Inc., this original Biologics License Application was filed with data intended to support an accelerated approval.

The vaccine formulation for Bexsero includes 50 mcg of the following three recombinant outer membrane proteins: Neisserial adhesion A (NadA), Neisserial Heparin Binding Antigen (NHBA), and factor H binding protein (fHbp). In addition, 25 mcg of outer membrane vesicle (OMV) containing PorA P1.4 (immunodominant antigen in OMV from *N.meningitidis* strain NZ98/254) is included. The vaccine antigens are adsorbed on to aluminum hydroxide (1.5 mg).

The applicant has submitted data from nine clinical studies as part of this BLA which were conducted at over 200 study sites. The four main studies which provided the immunogenicity and/or safety data to support the intended indication in an adolescent and young adult population were conducted in Canada/Australia, United Kingdom (UK), Chile, and US/Poland. Two supportive studies are included in the application to provide additional safety data, and two other studies are included to provide lot-to-lot consistency data and dose selection data. Although these two latter studies were not conducted in the age group intended for licensure for this application, they provided important data to characterize the vaccine product. One additional extension study conducted in adolescents and young adults was also submitted.

Because of the diverse nature of meningococcal group B strains as well as the low incidence of disease and the sporadic and unpredictable nature of an outbreak, obtaining data to support effectiveness of a serogroup B vaccine is challenging. On April 7, 2011, the Vaccines and Related

2 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.
3 CDC. Active Bacterial Core Surveillance (ABCs) Report: *Neisseria meningitidis*, 2012

Biological Products Advisory Committee (VRBPAC) of the Center for Biologics Evaluation and Research (CBER), FDA met to discuss approaches to demonstrate effectiveness of meningococcal serogroup B vaccines. The consensus of the committee was that the primary mechanism of protection against meningococcal serogroup B disease is complement-mediated antibody-dependent killing of the bacterium. Thus, serum bactericidal antibody levels induced by the vaccine, as measured by serum bactericidal activity assays using human complement (hSBA assays), could be used as a measure of vaccine effectiveness. The committee acknowledged that the genetic diversity and range of the level of expression of surface proteins among meningococcal group B strains adds an additional challenge to ascertaining effectiveness of meningococcal serogroup B vaccines against the diverse population of circulating meningococcal serogroup B strains.

CBER determined that Bexsero met the criteria for Breakthrough Therapy designation and granted that designation on April 1, 2014. As noted above, public health concerns about meningococcal serogroup B disease in the US and recent outbreaks on college campuses, prompted CBER to consider licensing Bexsero under the accelerated approval regulations, 21 CFR 601 Subpart E. The Agency determined that the accelerated approval pathway was appropriate, basing approval on the ability of the vaccine to induce bactericidal antibodies, as measured by the hSBA assay, that are able to kill a panel of meningococcal group B strains that are representative of prevalent strains in the US. This panel consists of three strains, each of which expresses one antigen (fHbp, NadA, PorA P1.4) in common with the vaccine components. The breadth of coverage of Bexsero against diverse meningococcal group B strains will be confirmed in subsequent clinical studies that examine the ability of the vaccine to induce bactericidal antibodies against a larger panel of genetically diverse meningococcal serogroup B strains that represent disease isolates in the US.

During the IND review process for this product, CBER conducted extensive discussions with the applicant concerning design of clinical studies, appropriate serological end-points, and clinical serology methodology. The clinical trials supporting the current application were conducted prior to some of these discussions. Therefore, CBER requested additional analyses of modified immunogenicity endpoints which were considered more meaningful than those originally specified in the clinical trial protocols.

Immunogenicity Analyses:
Immunogenicity data from three main trials conducted in Canada/Australia, UK, and Chile among individuals 11 through 24 years of age were used to assess the effectiveness of Bexsero. The proportion of subjects who achieved $\geq$4-fold increase in serum bactericidal activity one month following the 2nd dose of Bexsero compared to baseline against test strain 5/99 (NadA) was similar across the 3 main studies used to assess vaccine effectiveness, ranging from 94%-99%. A $\geq$4-fold increase in hSBA against strain H44/76 (fHbp) was observed in 93-98% of subjects enrolled in the trials conducted in Canada/Australia and Chile, and in 79% subjects in the UK trial. The proportion of subjects who achieved $\geq$4-fold increase in hSBA against strain NZ98/254 (PorA P1.4 in OMV) was observed to be 39% in the Canadian/ Australian trial, 67% in the UK trial, and 83-85% in the Chilean trial.

The composite hSBA immune response generated to 3 out of 3 strains by Bexsero one month after the 2nd dose was 63% in the Canadian/Australian trial, 88% in the UK trial, and 90-94% in the Chilean trial. The composite response 11 month after the 2nd dose, which was evaluated in the UK trial, was 65%. Of note, pre-vaccination hSBA titers were higher among subjects in the studies conducted in Chile and the UK, compared to baseline titers among Canadian/Australian subjects. The hSBA responses observed across studies conducted in Canada/Australia, UK, and

Chile likely reflect differences of the meningococcal serogroup B epidemiology across geographic locations.

Overall, the immunogenicity data based on modified hSBA endpoints demonstrate that the vaccine is effective in generating bactericidal activity against 3 meningococcal serogroup B strains reasonably representative of prevalent strains in the US.

The reviewer recommends that the hSBA data from the Canadian/Australian study in adolescents 11 through 17 years of age be included in the package insert to provide effectiveness data on adolescents 10 years through 17 years of age, as the hSBA responses generated by participants in this trial are likely most representative of the responses in a North American population. The reviewer also recommends that hSBA titers from the UK study in young adults 18 through 24 years of age be included in labeling to provide effectiveness data on young adults 18 years through 25 years of age. The hSBA data collected from participants 11 through 17 years of age in the Chilean study are not considered most representative of expected responses in a US population and are not recommended for inclusion in the package insert because a higher proportion of Chilean subjects had measurable hSBA titers at the baseline and higher post-vaccination titers when compared with hSBA responses observed in the Canadian/Australian study. To support the effectiveness of the Bexsero for the intended population for licensure, 10 years through 25 years of age, the hSBA responses generated by subjects 11 years of age were extrapolated to individuals 10 years of age, and the hSBA responses generated by individuals 24 years of age is extrapolated to include individuals 25 years of age.

Safety Analyses:
Safety data were reviewed on 3,139 subjects enrolled in randomized clinical trials conducted in Canada, Australia, UK, Chile, US, Poland, Switzerland, Germany, and Italy. These subjects received at least one dose of Bexsero and provided post-vaccination safety data. Additional serious adverse event safety data were collected on 15,351 Bexsero recipients who participated in in vaccination campaigns sponsored by the CDC at 2 US universities. Common adverse reactions across trials included injection site pain, injection site erythema, myalgia, malaise, and headache. Unsolicited adverse events that were reported among 2% of subjects and were more frequently reported in Bexsero recipients than in control recipients were injection site pain, headache, and injection site induration unresolved 7 days after vaccination, and nasopharyngitis within 7 days of vaccination.

Review of the safety data from the clinical trials and the CDC vaccination campaigns, demonstrated that serious adverse events were rare following Bexsero vaccination. In the clinical trials, there was one case of juvenile arthritis that was considered by the reviewer to be temporally related to vaccination and for which no other etiology was identified; therefore a relationship to vaccination cannot be excluded. Based on review of the totality of safety data submitted as part of this BLA, there does not appear to be an increased risk for juvenile arthritis and/or other autoimmune conditions following Bexsero vaccination. One case of anaphylaxis was reported in the CDC vaccination campaigns which occurred within 30 minutes of the 1st Bexsero vaccination, and was considered related to vaccination by both the investigator and the reviewer. CDC analyses determined that the rate of anaphylaxis following Bexsero vaccination was no greater than the rates of anaphylaxis following other vaccines currently licensed in the US. There were 9 appendicitis cases reported in the Chilean study which had no control group, and an additional 9 cases were reported in the CDC vaccination campaigns. CBER analysis of the available data and background rates of appendicitis in an adolescent and young adult population demonstrated no increased risk for appendicitis following Bexsero vaccination.

Based on a thorough review of the safety data submitted, the reviewer concludes that both the nature and frequency of adverse events reported in subjects 10 through 25 years of age were consistent with events commonly observed following other vaccinations administered to adolescents and young adults in the US. The reviewer recommends that the reactogenicity rates for the US/Polish study which evaluated subjects 10 years through 25 years of age be included in the package insert.

Subgroup Demographic Analyses:
The studies submitted as part of the BLA were conducted in many countries across diverse populations. The four main trials were conducted in Canada/Australia, United Kingdom, Chile, and United States/Poland. The demographic characteristics and other baseline characteristics for each study therefore reflect the countries of enrollment.

The results of descriptive subpopulation immunogenicity analyses performed on small data sets which evaluated differences due to gender and racial origin of enrolled subjects were largely consistent with the overall immunogenicity findings. In the Canadian/Australian study a nominally higher hSBA response rate was noted in males (69%) than females (56%) against test strain NZ98/254. No gender differences in hSBA response against any of the three strains evaluated in the other main trials were observed.

The observed rates of adverse events across different demographic groups based on race, gender, and age were fairly comparable and consistent with overall safety findings.

Lot consistency:
The applicant satisfactorily demonstrated consistency of lot performance based on a comparison of hSBA GMTs of three different lots of Bexsero. Safety profiles across lots were consistent.

Concomitant vaccination
Safety and effectiveness of Bexsero when administered concomitantly with other vaccines recommended for use in adolescents in the US were not evaluated in the studies submitted as part of this application. The potential for interference with immune responses to other vaccines when co-administered with Bexsero was not evaluated in clinical studies.

Pediatric Assessment and Pediatric Research Equity Act
The applicant's Pediatric Study Plan (PSP) was presented to FDA's Pediatric Review Committee (PerC) on November 19, 2014. The safety and effectiveness of Bexsero has not been established in US children younger than 10 years of age. The applicant's plan for an assessment of Bexsero in pediatric individuals 0 to <6 weeks was waived because the candidate vaccine did not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used. The applicant's assessment in pediatric individuals 6 weeks to <10 years of age was deferred because the candidate vaccine was ready for approval for use in individuals in adults before pediatric studies in this age group are complete. The applicant's deferred studies include Study V72_57 to be conducted in infants ≥6 weeks of age in the US, Study V72_28 evaluating infants ≥2.5 months and children 2-10 years of age conducted outside of the US, and two additional completed studies evaluating infants ≥2 months of age conducted outside of the US. The committee agreed with the Pediatric Study Plan, including the partial waiver, partial deferral, and the review division's plans to extrapolate effectiveness to 10 years of age based on the available data.

Confirmatory Studies:
For the purpose of accelerated approval of Bexsero, the applicant has demonstrated that the candidate vaccine generates an immune response in adolescents/young adults as measured by serum bactericidal activity against three serogroup B test strains representative of prevalent strains in the United States. As required under accelerated approval regulations, the applicant must study the product further to verify and describe its clinical benefit. To meet this requirement, the applicant will demonstrate the effectiveness of Bexsero against an extended panel of serogroup B meningococcal strains, thus confirming that the vaccine can protect against diverse meningococcal strains prevalent in the United States. The applicant has confirmed that the requisite evaluations in randomized clinical trials to demonstrate breadth of coverage are ongoing and planned.

Clinical Reviewer Recommendation:
The totality of clinical data presented in this application supports approval of Bexsero candidate vaccine for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in adolescents and young adults 10 through 25 years of age.

2. BACKGROUND

2.1 Meningococcal Serogroup B: Vaccine Development and Disease Burden[4,5,6,7,8]

Introduction:
Neisseria meningitidis serogroup B is a significant cause of invasive disease, including bacterial meningitis and sepsis. The rates of all serogroup meningococcal disease have decreased over the past few decades due to cyclical trends in meningococcal disease incidence and a combination of environmental, organism, and host factors. In 2005, the first meningococcal serogroup A,C,W,Y quadrivalent conjugate vaccine was licensed by the FDA for use in individuals 11 through 55 years of age in the United States. The ACIP recommended routine use of the quadrivalent vaccine in adolescents 11 to 12 years of age at that time, and then expanded the recommendation to include all adolescents 11 through 18 years of age in 2007. As a result during 2009 and 2010, the incidence of serogroup C and Y meningococcal disease declined among adolescents, though not in other age groups for which vaccination was not recommended. In 2012, the CDC estimated incidence rate of meningococcal disease was 0.15 per 100,000 population, of which serogroup B had the highest estimated incidence rates (0.06/100,000).

Public Health Need:
Between 2013 and 2014, there were 9 cases of serogroup B meningococcal disease reported at Princeton University over a one year period and 4 cases reported over a one month period at University of California, Santa Barbara. In March 2014 a Drexel University student died from invasive meningococcal serogroup B infection due to the same strain circulating at Princeton University. Efforts to develop a meningococcal serogroup B vaccine in the US have spanned several decades. Due to the urgent public health need for a licensed serogroup B vaccine, FDA granted breakthrough therapy designation status in the spring of 2014 to -(b)(4)- candidate meningococcal serogroup B vaccines which were in late stage development, one of which is manufactured by Novartis Vaccines and Diagnostics, Inc., the subject of this original BLA

4 Pace D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. *Vaccine.* 2012 May 30;30 Suppl 2:B3-9.
5 CDC. Meningococcal Disease Chapter. *Pink Book*, 12th Ed. May 2012.
6 CDC. Active Bacterial Core Surveillance (ABCs) Report: *Neisseria meningitidis*, 2012.
7 Cohn AC, MacNeil JR, Harrison LH, et al. changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998-2007: implication for prevention of meningococcal diseases. *Clin Infec Dis.* 2010;50:184-91.
8 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.

review. This public health need played an important role in FDA adopting the Accelerated Approval licensure pathway for (b)(4) serogroup B vaccines.

Vaccine Development:
Meningococcal serogroup A,C,W,Y conjugate vaccines consist of purified polysaccharide antigens from the bacterial capsules of these four serogroups conjugated to a carrier protein. Vaccine development for serogroup B has proven to be difficult because the serogroup B capsular polysaccharide is identical to a widely distributed carbohydrate in human neurologic tissue (α [2,8] N-acetyl neuraminic acid or polysialic acid) and is therefore poorly immunogenic in humans, even when conjugated to carrier proteins. Serogroup B meningococcal sub-capsular antigen vaccines, including protein-containing outer membrane vesicle (OMV) vaccines have shown promise. Vaccines based on OMV have been effective in controlling epidemic disease caused by strains similar to the vaccine strain in Cuba, Brazil, Chile, (b)(4), and New Zealand. OMV vaccines have been effective in generating bactericidal antibody activity, but their narrow strain specificity limits their usefulness in the context of endemic disease caused by diverse strains.

Further research revealed other protein targets for bactericidal antibody activity, including conserved surface exposed outer membrane proteins of serogroup B strains which were identified as a result of genomic sequencing. The initial clinical development of candidate vaccine rMenB+OMV (Bexsero) included a single recombinant outer membrane protein antigen. Once safety was established for this initial formulation, two more recombinant proteins, aluminum hydroxide, and OMV containing PorA P1.4, the immunodominant antigen present in OMV from *N. meningitidis* strain NZ98/254 were included in the vaccine. The recombinant proteins included in the vaccine are factor H binding protein (fHbp), Neisserial adhesion A (NadA), and Neisserial Heparin Binding Antigen (NHBA). Antigenic diversity and variable expression of these protein antigens (fHbp, NadA, NHBA, PorA P1.4) by invading meningococci could result in varying levels of serologic protection against infection afforded by the vaccine. From a regulatory perspective, demonstration of vaccine effectiveness would require that meningococcal serogroup B protein vaccines are able to prevent disease caused by a broad spectrum of circulating meningococcal group B strains.

Licensure Pathway: Accelerated Approval
Consideration of licensure of rMenB+OMV vaccine under the accelerated approval regulations (21 CFR 601.41) was considered appropriate by CBER on the basis of the following:

- *Serious condition*: Invasive infection with serogroup B meningococcus, including meningococcemia and/or meningitis, is associated with significant morbidity and mortality, with an overall case-fatality rate of ~10%.
- *Meaningful advantage over available therapies*: At the time this regulatory approach was considered, no licensed meningococcal group B vaccine was available in the US
- *Demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit*: The relationship between serum bactericidal antibody and protection against meningococcal disease was established by Goldschneider et al.[9] As discussed at the April 2011 VRBPAC meeting, the committee supported the use of serum bactericidal activity with human complement (hSBA) to evaluate effectiveness of protein-based meningococcal B vaccines. However, antigenic diversity and variable expression of meningococcal surface proteins complicate the approach to infer effectiveness from

9 Goldschneider I, et al: Human immunity to meningococcus I. The role of humoral antibodies. J Exp Med. 1969 Jun 1;129(6):1307-26; and Human immunity to meningococcus II. Development of natural immunity. J Exp Med. 1969 Jun 1;129(6):1327-48.

immunogenicity. In applying the accelerated approval regulations, CBER considers hSBA against a panel of 3 test strains, each expressing an antigen contained in rMenB+OMV, as a serologic marker reasonably likely to predict protection against diverse meningococcal serogroup B strains prevalent in the United States.

As part of the accelerated approval pathway, the applicant is required to conduct confirmatory studies to demonstrate effectiveness of rMenB+OMV against an extended panel of serogroup B meningococcal strains, confirming that the vaccine can protect against a breadth of prevalent strains in the United States . The following studies will be conducted to meet this requirement::

- **V102_16 -** *A Phase 2b, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Effectiveness, Immunogenicity and Safety of Novartis Meningococcal (b)(4)- Vaccine Administered to Healthy Adolescents in the US.* The final report is anticipated to be submitted in the 1st quarter of 2016. The final data collected from this study will be used to inform the main confirmatory study listed below.
- **V72_72 -** *A Phase 3, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Effectiveness, Immunogenicity and Safety of Novartis Meningococcal serogroup B Vaccine Administered to Healthy Adolescents and Young Adults.* The final protocol is anticipated to be submitted 4th quarter 2015, and the final report is anticipated to be submitted 4th quarter 2018.

Epidemiology:
The incidence rates of meningococcal disease follow a cyclical pattern with peaks and troughs occurring in 5 to 8 year patterns. The incidence of meningococcal disease in the US has decreased in the past decade due to a combination of factors including environmental, organism, and host factors. After the introduction of meningococcal serogroup A,C,W,Y conjugate vaccine in 2005, there was a further reduction in the cases of invasive disease due to these serogroups. In 2012, the Active Bacterial Core surveillance (ABCs) program of the Centers for Disease Control and Prevention (CDC) estimated meningococcal disease rate was 0.15/100,000 (480 cases), and death rate was 0.02/100,000 (75 deaths) in the US. By serogroup, the estimated rates were as follows: serogroup B: 0.06/100,000; serogroup C: 0.03/100,000; and serogroup Y: 0.05/100,000. These rates do not include data from Oregon where an outbreak of serogroup B disease has been ongoing. When the Oregon cases are included, the rates for serogroup B disease were estimated to be 0.08/100,000 in 2012 in the US. In 2013 to 2014 at two US universities, there were 13 reported cases of invasive disease due to meningococcal serogroup B infection, which included one reported death.

Meningococcal Disease and Clinical Presentation:
Regardless of serogroup, invasive meningococcal disease including meningococcemia, meningitis, and pneumonia is associated with significant morbidity and mortality. *Neisseria meningitidis*, a gram negative endotoxin producing diplococcal bacteria exclusively infects humans. Transmission occurs by aerosolized droplet or contact with nasopharyngeal secretions from colonized individuals. Subsequent spread to the blood in colonized individuals can occur in <1% of individuals, of whom 50% develop meningitis. Common presenting clinical features include fever, neck stiffness, headache, altered mental status, myalgia, and vomiting. Petechial rash is seen initially in 50% of patients upon presentation, and can coalesce into the pathognomonic meningococcal purpuric and ecchymotic rash. Purpura fulminans is a severe complication, seen in 15-25% of bacteremic individuals, resulting in cutaneous hemorrhage and necrosis due to vascular thrombosis and disseminated intravascular coagulopathy. Other severe complications include disseminated intravascular coagulopathy, acute respiratory distress syndrome, coma, diabetes insipidus, and pericarditis.

Prognosis:
The course of meningococcal disease is wide-ranging, from an initial nonspecific febrile illness to a rapidly progressive fulminant infection with multi-organ involvement, sepsis, and possibly death within hours. Early diagnosis and intervention is an important prognostic factor, as classic meningococcal symptoms appear late. Early features suggesting sepsis include leg pain, cold extremities, and abnormal skin color (pallor/mottling). Long term sequelae occur in 11-19% of those who survive and include hearing loss, neurologic disability, loss of limbs, and/or other serious conditions associated with meningococcemia. Overall, the case fatality rate is 10-15%, regardless of early treatment initiation. In adults ≥65 years of age the case fatality rate is ~24%, and for those individuals with bacteremia, the fatality rate is ~40%.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication

As mentioned above, due to the variable clinical presentation, a high index of suspicion is required by the clinician early in the disease process to reduce both morbidity and mortality by providing treatment as early as possible. In the US, pharmacologic treatment of meningococcal disease is empiric therapy with a broad-spectrum antibiotic, such as a third generation cephalosporin. Yet as mentioned above, despite antibiotic treatment case fatality rates are high at 10-15%. Chemoprophylaxis is indicated for close contact of infected individuals, and includes people in the same household, roommates, or anyone with direct contact with the infected individual's oral secretions.

2.3 Safety and Effectiveness of Pharmacologically Related Products

Five meningococcal vaccines are licensed in the United States for the prevention of invasive meningococcal disease due to various serogroups.

Table 1: FDA Approved Meningococcal Vaccines

Vaccine (serogroup)	Components (type of vaccine)	Applicant	Year	Age Group	Dose
Menomune (ACWY)	MPSV4 (polysaccharide)	Sanofi Pasteur	1981	≥2yo	Single
Menactra (ACWY)	MenACWY-D (polysaccharide-protein conjugate)	Sanofi Pasteur	2005 2007 2011	11-55yo 2-10yo 9-23mo	Single Single 2-doses
Menveo (ACWY)	MenACWY-CRM (polysaccharide-protein conjugate)	Novartis	2010 2011 2013	11-55yo 2-10yo 2mo 7mo-23mo	Single Single 4-doses 2-doses
MenHibrix (CY)	Hib-MenCY-TT (polysaccharide-protein conjugate)	GlaxoSmithKline	2012	6wks-18mo	4-doses
Trumenba (B)	2 fHbp variants (lipidated protein)	Wyeth	2014	10-25 yo	3 doses (0-,2-,6-mo)

(See text below for table description)

Polysaccharide and Polysaccharide Protein Conjugate Vaccines:
The first meningococcal vaccine to be licensed in the US was Menomune® (MPSV4) in 1981 manufactured by Sanofi Pasteur. It is a meningococcal polysaccharide (ACWY) vaccine indicated for individuals ≥2 years old as a single dose. Subsequently, Menactra® (MenACWY-D) was the first conjugated quadrivalent meningococcal vaccine to be licensed in 2005 for use in individuals 11 – 55 years old as a single dose; in 2007 for children 2-10 years old as a single dose; and in 2011 for 9-23 month old infant/toddlers as a 2 dose series. Menveo® (MenACWY-CRM), manufactured by Novartis Vaccines and Diagnostics was the next conjugate quadrivalent (ACWY) meningococcal vaccine to be licensed in the US in 2010 for use in individuals 11-55 years old as a single dose; in 2011 for children 2-10 years old as a single dose; and in 2013 for infants 2 months old as a 4-dose series or infant/toddlers 7 through 23 months of age as a 2-dose series. MenHibrix®, manufactured by GlaxoSmithKline, is a meningococcal serogroups C and Y (polysaccharide) with *Haemophilus influenzae* type B (polyribosyl-ribitol-phosphate) conjugated to tetanus toxoid vaccine (Hib-MenCY-TT) that was licensed in 2012 for infants/toddlers 6 weeks to 18 months as a 4-dose series.

Sub-capsular Lipidated Protein Vaccine:
In October 2014, the first meningococcal group B vaccine, Trumenba® was licensed in the US for use in adolescents and young adults 10 through 25 years of age as a 3-dose series administered at 0-, 2-, and 6 months. Trumenba is composed of two recombinant lipidated factor H binding protein (fHbp) variants from meningococcal serogroup B. In clinical studies, the most common solicited adverse reactions were pain at the injection site (≥85%), fatigue (≥40%),

headache (≥35%), muscle pain (≥30%), and chills (≥15%). Adverse events reported more frequently in the treatment group than in the control group included injection site pain and headache. Serious adverse events were reported at similar rates across groups. Effectiveness of the vaccine was demonstrated based on serum bactericidal activity one month after the 3rd dose.

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

The candidate vaccine, under the trade name BEXSERO, has received market authorization in the European Union, Canada, and Australia. As of June 15, 2014, the applicant reports that there have been 220 spontaneous adverse event reports following Bexsero use, including 34 serious adverse events. There have been an estimated 100,000 individuals exposed to Bexsero based on the doses distributed. Based on voluntary reporting of adverse events, the applicant reports the following core safety information since introduction of Bexsero by system organ class (SOC):

- General disorders and administration site conditions: Blisters at or around the injection site.
- Immune System Disorders: Allergic reactions (including anaphylaxis), rash
- Nervous System Disorders: Syncope or vasovagal responses to injection

Due to separate meningococcal serogroup B outbreaks at two US universities in 2013, vaccination campaigns with Bexsero were conducted prior to licensure in the US under an Expanded Access IND granted by the FDA and sponsored by the CDC. Between 2013 and 2014, 15,351 students and staff at Princeton University and University of California Santa Barbara were vaccinated with two doses of Bexsero administered at least one month apart. Review of the safety findings from these campaigns are included as part of this memo and are provided in Section 8.4.

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

The following timeline includes a list of major regulatory activity associated with the submission of this BLA:

- March 2013: Meningococcal Serogroup B Outbreak
    - Beginning in March 2013 and spanning through March 2014, 9 cases of invasive disease due to meningococcal serogroup B infection were reported at or in association with Princeton University.
- November 2013: IND Expanded Access Authorization Granted
    - CBER granted the CDC expanded access authorization to distribute and vaccinate those individuals at increased risk for serogroup B meningococcal disease at Princeton University with rMenB+OMV (Bexsero). It was estimated that ~5760 individuals were at risk, and the prescribed dosing regimen was 2 doses administered at least one month apart. The vaccination campaign was initiated at Princeton University in December 2013 and resulted in 5520 individuals receiving at least one dose of Bexsero. A second outbreak of serogroup B meningococcal disease was reported in November 2013 over a one month period at UCSB (4 cases reported). CDC submitted a second protocol under the same IND in January 2014 to vaccinate ~19,872 individuals identified as at-risk at UCSB. The vaccination campaign at UCSB initiated in February 2014, and resulted in 9831 individuals receiving at least one dose of Bexsero.
- February 12, 2014: Clinical Development Status Update- Type C Meeting
    - The purpose of the meeting was for the applicant to provide CBER with an update on the status of their clinical development program for rMenB+OMV. The following items were discussed:

  - Priority Review Status: CBER confirmed that the submission of an application may qualify for priority review.
  - Accelerated Approval Licensure Pathway: CBER stated that the safety and immunogenicity data accrued to date in the clinical development program for the candidate vaccine may be adequate to support an application for licensure under FDA's accelerated approval licensure pathway (21 CFR 601.41)
  - hSBA meningococcal reference (test) strains to be used in the assay for the evaluation of the serum bactericidal immune response to the vaccine were confirmed. CBER requested additional analyses of existing immunogenicity data using modified clinical study endpoints.
  - Confirmatory studies required as part of the accelerated approval pathway: confirmatory studies would need to demonstrate a breadth of coverage of vaccine effectiveness against a panel of additional strains representative of circulating strains in the US.
  - Safety database for the adolescent and young adult indication being considered for accelerated approval was acceptable for filing an application.
- April 1, 2014: Breakthrough Therapy Designation Granted
  - CBER granted Breakthrough Designation status to rMenB+OMV because invasive meningococcal disease is a serious and life-threatening condition, and there is preliminary clinical evidence to indicate that the vaccine demonstrates substantial improvement on clinically significant endpoints over available therapies.
- May 27, 2014: Pre-BLA Meeting
  - During the Pre-BLA meeting the following major discussions occurred:
    - Review of proposed safety and immunogenicity to support licensure, including additional immunogenicity analyses based on existing data.
    - Accelerated Approval Confirmatory Studies proposed as follows:
      - Study V72_37 & Study V72_59: These studies will evaluate an ------(b)(4)---------- hSBA assay that would allow direct testing of a large number of disease isolates identified by the CDC as epidemiologically relevant in the US. The serogroup B strain qualification report for the ----------(b)(4)---------- hSBA assay was submitted to CBER on December 11, 2014 for review.
      - Study V102_16: This study will evaluate the applicant's candidate ----(b)(4)------ vaccine ----(b)(4)-------, which is a rMenB+OMV 'containing' vaccine. The interim data from this phase 2 study using ----------(b)(4)---------- hSBA ((b)(4)-hSBA) will be used to define the primary endpoint(s), determine sample size, and define study success criteria for the confirmatory trial (V72_72). The study will be conducted in individuals 10-18 years of age. The final study report is anticipated to be available 3rd quarter of 2016.
      - Study V72_72: The protocol for this confirmatory phase 3 trial is anticipated to be submitted in the 4th quarter 2015. CBER advised that the final study report data from study V102_16 will be required to determine study success criteria for this confirmatory trial.
- July 24, 2014: Original BLA Submitted BLA 125546/0
- September 22, 2014: Priority Review Status Granted (BLA 125546/0)
  - CBER granted Priority Review Status because the vaccine treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The review cycle was abbreviated to an 8 month time period.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA submission was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The 9 studies included for review in this application (V72_41, V72_29, V72P10, V72P10E1, V102_03, V72P13, V72P16, V72P5, and V72P4) were conducted in accordance with Good Clinical Practice (GCP) and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21CFR 50.25. In accordance with 21 CFR 312.120, the applicant provided the required elements to ensure that each study confirmed with GCP.

CBER's Division of Inspections and Surveillance (DIS) issued 6 high priority foreign inspections for three of the main trials, V72P10, V72_29, and V72_41. The clinical sites selected for inspection were based on the number of subjects enrolled at the site, previous inspectional history, number and types of adverse events, number and types of protocol deviations, and geographic locations. During the inspection of three sites in the Chilean study (sites 11, 14, and 41), it was determined that some clinical safety data appeared to be missing because they were not documented in the source documents (diary cards) issued to subjects. It was also noted that some subjects withdrew from the study due to adverse events which were recorded in the source documents only, but not in the case report forms. In response to these observations and noted patterns of missing solicited reaction data in the BLA, a revised analysis of reactogenicity data was requested. The inspection of the other two studies did not reveal any significant problems that would impact the data submitted. The four main clinical trials under review in this application were conducted in the following countries at 41 study sites: Canada, Australia, United Kingdom, Chile, US, and Poland. The four supportive clinical trials were conducted 160 sites in Italy, Germany, Austria, Finland, Czech Republic, Hungary, Chile, Argentina, and Switzerland.

3.3 Financial Disclosures

Covered clinical studies: There were 9 studies included for review in this application: V72_41, V72_29, V72P10, V72P10E1, V102_03, V72P13, V72P16, V72P5, and V72P4 (names of each trial are listed in the appropriate subsections of Section 6 of this review).		
Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 52 principal or coordinating investigators		
Number of investigators who are applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☒

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

4.1 Chemistry, Manufacturing, and Controls (CMC)

Review of manufacturing process development, in-process testing, release and stability testing were reviewed and found to be adequate to support licensure. Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

4.2 Assay Validation

The --(b)(4)-- potency test for the final drug product (immunogenicity test) and clinical serologic assays were adequate for licensure as determined by CBER assay review.

4.3 Nonclinical Pharmacology/Toxicology

In single and multiple dose intramuscular toxicity studies in rabbits, the product was well-tolerated. In the reproductive and developmental toxicity study revealed no significant reproductive and developmental effects in the rabbits. The CBER toxicology reviewer recommended a pregnancy category B, as proposed by the applicant.

4.4 Clinical Pharmacology

Vaccine Composition
With the development of new genomic technology, reverse vaccinology was used by the applicant to identify 350 genes from the meningococcal genome which could encode for surface exposed proteins. These antigens were evaluated for their ability to elicit serum bactericidal activity against panels of *N.meningitidis* serogroup B strains. The first recombinant outer membrane protein evaluated was NHBA, and subsequently other recombinant outer membrane proteins were added to the current rMenB+OMV formulation to improve the immune response against genetically distinct meningococcal B strains. The current vaccine formulation consists of the following components:

- 3 recombinant proteins: 50 micrograms (ug) each

  - NHBA (Neisserial Heparin Binding Antigen): antigen 287 fused to accessory protein 953 derived from *N. meningitidis* strains NZ98/254 (B:4:P1.7-2,4) and 2996, respectively
  - fHbp (Factor H binding protein): antigen 741 fused to the accessory protein 936 derived from *N. meningitidis* strains MC58 and 2996, respectively
  - NadA (Neisserial adhesion A): antigen 961c is a single recombinant protein derived from *N. meningitidis* strain 2996
- Outer Membrane Vesicle (OMV) containing PorA P1.4 (25 ug) which is the immunodominant antigen in OMV from *N. meningitidis* strain NZ98/254.[10]
- aluminum hydroxide (1.5 mg): each of the 4 components are adsorbed to aluminum hydroxide
- sodium chloride (3.125 mg); histidine (0.776 mg); and sucrose at pH 6.4-(b)(4) (10 mg)

Measures of Immunogenicity

The principle method to measure a functional immune response to meningococcal vaccines is the serum bactericidal activity (SBA) assay which measures functional antibody by determining the ability of sera to kill a target *N.meningitidis* strain via complement-mediated bacterial cell lysis. SBA involves incubating a bacterial cell suspension with sera (i.e., from a vaccinated individual) and an active complement source. Surviving bacteria are quantified, usually by colony counts, and compared to either the cell count prior to killing or a control in which the complement was heat inactivated. The source of complement is an important factor in the SBA assay, and either intrinsic or extrinsic sources have been used. Serum bactericidal activity using intrinsic complement was assessed in military recruits in a historic study conducted by Goldschneider, et al[11] in the 1960's to help establish the importance of bactericidal antibodies as a mechanism of protection against pathogenic meningococci during an outbreak of serogroup C meningitis. The use of SBA using intrinsic (or endogenous) complement provides a qualitative determination of bactericidal activity at a single dilution (historically 1:4). More typically, SBA using extrinsic (or exogenous) complement sources has been used to quantitatively determine serum bactericidal activity. This is performed by using 2-fold serially diluted heat inactivated test sera with an extrinsic source from rabbit or human sera. From a regulatory perspective, serum bactericidal activity measured using extrinsic human complement (hSBA) is viewed as a clinically meaningful endpoint, protection against invasive disease caused by meningococcal strains similar to the test strain used in the assay.

Serologic Marker of Protection

An approach to evaluate vaccines for the prevention of invasive group B meningococcal disease was discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held April 7, 2011.[12] The committee supported the use of hSBA as a serologic marker to evaluate the effectiveness of sub-capsular protein-based meningococcal vaccines. However, a limitation of this immune marker is that strain specificity and diversity of vaccine antigens restrict generalization of protection to only those bacterial strains similar to the test strains used in the hSBA assay. As a result, effectiveness against a single strain is not a meaningful measure of effectiveness in the context of the diverse meningococcal serogroup B strains circulating in the US.

10 The dose and identity of OMV antigen is the same as the one used in the applicant's New Zealand OMV vaccine which was effective against an epidemic of meningococcal B disease predominantly caused by the epidemic strain NZ98/254 in New Zealand

11 Goldschneider I, et al. Human Immunity to the meningococcus. I. The role of humoral antibodies. J Esp Med 1969;129:1307-1326.

12 FDA. Briefing Document: Approaches to Licensure of Meningococcal Vaccines for Prevention of Serogroup B Invasive Meningococcal Disease. Vaccines and Related Biological Products Advisory Committee. Rockville, Maryland. April 6-7 2011.

Demonstration of a protective hSBA response of a group B vaccine against all *N.meningitidis* strains that cause invasive disease is not possible as strains are diverse and evolve over time. Additionally, the incidence of serogroup B meningococcal disease in the US is not high enough to assess clinical effectiveness directly, and the number of distinct strains that would need to be tested in hSBA assays to adequately represent US endemic disease would be unfeasible using current hSBA methodologies. In addition, the immune response generated by infants, older children, and adults are different in magnitude, duration, and breadth of immune response. The correlation between hSBA seroresponse and vaccine effectiveness is supported when invasive disease is caused by the same strain that is used for vaccine preparation and serologic assessment in the relevant age cohort.

4.4.1 Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing of *N. meningitidis.* The effectiveness of rMenB+OMV was assessed by measuring serum bactericidal activity using human complement (hSBA).

Vaccination with rMenB+OMV leads to the production of antibodies directed against meningococcal proteins NHBA, NadA, fHbp, and PorA P1.4 (present in OMV). The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with rMenB+OMV is dependent on both the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

4.4.2 Human Pharmacodynamics

No pharmacodynamics studies were conducted as part of this BLA.

4.4.3 Human Pharmacokinetics

No pharmacokinetics studies were conducted as part of this BLA.

4.5 Statistical

CBER statistical reviewers concluded that the datasets and analyses provided in this application were adequate to assess the safety and effectiveness of the candidate vaccine.

4.6 Pharmacovigilance

The CBER Epidemiology/Pharmacovigilance reviewer did not identify any safety concerns that would require a post-marketing study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS). The reviewer recommended routine pharmacovigilance to monitor adverse events in accordance with 21 CFR 600.80 and agreed with the applicant's proposed Pharmacovigilance Plan (PVP). The reviewer also agreed to the applicant's proposal of a US based pregnancy registry for three years to monitor safety in women exposed to the candidate vaccine, rMenB+OMV during pregnancy.

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

5.1 Review Strategy-Accelerated Approval

Effectiveness/Immunogenicity Data Review Strategy:
CBER views Serum Bactericidal Activity using human complement (hSBA) titer against three meningococcal primary strains (H44/76, 5/99, NZ98/254) as a serologic marker predictive of clinical benefit of a meningococcal serogroup B vaccine for similar strains. As discussed during the Pre-BLA meeting for this application, immunogenicity data from each study is reviewed individually because of differences in study designs, demographic characteristics, epidemiologic characteristics of study populations, and hSBA testing methods/validations of individual laboratories. The immunogenicity data selected for review for the main trials is based upon modified endpoints (post-hoc analyses) that address the conditions for accelerated approval by providing data that show both of the following:

- individual components of the vaccine stimulate the production of bactericidal antibodies,
- individual subjects respond to multiple components (as a proxy for evaluating breadth of coverage)

Effectiveness for Accelerated Approval
CBER determined that the available immunogenicity data from completed clinical trials could be analyzed (post hoc) using end-points that address more definitively the criteria described above to support accelerated approval. These modified immunogenicity endpoints using revised LLOQ were based on the specific laboratory performing the assay and/or the indicator strain assessed [13]. These hSBA responses against three meningococcal serogroup B test strains are viewed as reasonably likely to predict clinical benefit of rMenB+OMV vaccine against more diverse strains causing invasive meningococcal disease. These strains and the associated vaccine antigen against which a functional immune response is measured include:

- H44/76 (fHbp)
- 5/99 (NadA)
- NZ98/254 (PorA P1.4)

The following hSBA measurements are viewed by CBER as clinically relevant to the evaluation of rMenB+OMV effectiveness for the 3 main studies (Studies V72_41, V72_29, and V72P10) included in the application:

1. the proportion of subjects with a ≥4-fold response (post-vaccination #2 compared to pre-vaccination #1) for each of 3 meningococcal B test strains (measuring the immunogenicity of the vaccine components), and
2. the proportion of subjects with a hSBA response ≥the lower limit of quantitation (LLOQ) to all of the test strains (composite response)

Studies assessed the proportion of subjects who achieved a 4-fold or greater increase in hSBA titer for each of the three strains), and the proportion of subjects with a titer greater than or equal to the lower limit of quantitation (LLOQ) of the assay for all three strains. The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified

13 CBER reviewed validation reports for the hSBA assays conducted at Novartis Vaccines ---(b)(4)--- laboratories and ----(b)(4)---------- laboratories in the context of their intended use. Due to the limitations of data submitted to support the LLOQ for either dilutional linearity or precision, CBER considered the hSBA assays to be adequately validated for LLOQ of either 8 or 16 depending on the laboratory that performed the assay and/or the indicator strain assessed as follows: for NVD ---(b)(4)--- laboratories- 8 for NZ98/254 strain and 16 for H44/76 and 5/99 strains; and for -----(b)(4)--------- laboratories- 8 for 5/99 strain and 16 for H44/76 and NZ98/254 strains.

Immunogenicity Data as Pre-Specified in Protocol
The pre-defined immunogenicity objectives other than lot consistency are considered supportive in the review of this application. Data from selected primary and/or secondary immunogenicity objectives are presented as background information. The immunogenicity data that do not contribute substantially to the evaluation of rMenB+OMV are not included in this review. Of note, during the clinical development of rMenB+OMV, a suitable indicator strain for vaccine antigen NHBA (287-953 antigen) was not available.

Safety Data Review Strategy:
For the 4 main studies included as part of this application, safety endpoints evaluated include the following:

- frequency of solicited injection site and systemic reactions for 7 days after each vaccination
- any unsolicited adverse event for 7 days after each vaccination (for Study V102_03 unsolicited AEs were followed until 1 month after the 2nd injection);
- Serious Adverse Events (SAEs), Medically Attended Adverse Events (MAAEs), and Adverse Events (AEs) leading to withdrawals for the entire study period. Total study duration varied as follows:
  - Study V72_41: 2 months
  - Studies V102_03, V72P4, & V72P5: 8 months
  - Studies V72_29 & V72P10: 12 months

Solicited Adverse Event Safety Data
Based on findings from FDA inspections conducted by BIMO during the review cycle, and patterns of missing solicited reaction data in the BLA, concerns arose regarding the methods used to collect solicited adverse event data when diary cards were lost. The inspections and review of the submitted data indicated that some of the solicited adverse event data were not obtained from protocol-specified source documents, but rather were collected by questioning of subjects several weeks or months after the 7-day post vaccination monitoring time period was completed, which could introduce recall bias. In addition, data entry for solicited adverse events based on distant recall was frequently incomplete, resulting in rate calculations for solicited events without reported outcomes using denominators that included counts of subjects with entries for any recalled event. Upon the request of CBER, the applicant submitted[14] a revised set of reactogenicity rates for the 4 main studies included in the application. These revised rates excluded solicited adverse event safety data not obtained from a source document. This was accomplished by a review of listings of protocol deviations and investigator comments suggesting that a diary card (source document) was lost and/or that solicited AEs data were obtained by retrospective recall by subjects. This information was compared to solicited AE listings in the clinical study reports indicating that data were either recorded with a value, or recorded as unknown, not done, or missing. In addition, the denominator for the reactogenicity rates was adjusted to account for missing source documents. The statistical approach taken by the applicant to obtain these revised solicited reactogenicity rates was acceptable to CBER. The revised rates for the 4 main studies are included as part of the safety data review for each study. The validity of reported unsolicited adverse events, SAEs, MAEEs, and AEs leading to withdrawal data is not affected by the inspection findings.

14 BLA 125546/Amendment 0.21 on 10/23/2014

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following amendments and modules the BLA were reviewed:

- Am 0.0: m5.3.5 Reports of Effectiveness and Safety Studies; m5.4 Literature references
- Am 0.2: m1.1 Forms; 1.2 Cover Letters; m1.3.3 Debarment Certification; m1.3.4 Financial Disclosure; 1.4.1 Letter of Authorization BB-IND15810; m1.9 Pediatric Administrative Information; m1.14 Labeling; m2.5 Clinical Overview; m2.7.3 Summary of Clinical Effectiveness
- Am 0.8: m1.9 Pediatric Administrative Information; m5.3.5 Reports of Effectiveness and Safety Studies; m5.3.5.3 ISE; m5.3.5.3 ISS
- Am 0.17: m1.11.3 Effectiveness Information Amendment-Immunogenicity
- Am 0.18: m1.11.4 Investigators and Enrollment per Study and Protocol Deviation per Site and Study
- Am 0.21m1.11.3 Effectiveness Information Amendment-Safety Data
- Am 0.22:m1.11.4 Multiple Module Information Amendments Clinical Trial Conduct and V102_02 Additional Information
- Am 0.25:m1.11.3 Effectiveness Information Amendment-Immunogenicity
- Am 0.34: m1.11.3 Effectiveness Information Amendment-SAE; m1.11.4 Multiple Module Information Amendment Pregnancy Register.

5.3 Table of Clinical Trials

Table 2: List of Clinical Trials

Study Number	Country	Description (relevance to US licensure)	Concomitant vaccines	Vaccination Schedule/ Population	Subjects receiving at least 1 dose rMenB+OMV
Main Trials for Effectiveness and/or Safety					
V72_41	Canada, Australia	Phase 3, multicenter study evaluate overall safety and immunogenicity, that associated with a comparison of two different OMV components manufactured at 2 sites	None	2 doses one month apart. Adolescents 11 through 17 years	342
V72_29	United Kingdom	Phase 3, multicenter study to evaluate safety and immunogenicity versus an active control	None	2 doses one month apart. Young adults 18 through 24 years	974

Study Number	Country	Description (relevance to US licensure)	Concomitant vaccines	Vaccination Schedule/ Population	Subjects receiving at least 1 dose rMenB+OMV
V72P10	Chile	Phase 2b, multi-center study to evaluate safety and immunogenicity, versus an aluminum hydroxide control for the 1st half of the study prior to the Month 6 visit. The study did not have a control group for entire time duration.	None	Multiple regimens evaluated: 1 dose, 2 doses, and 3 doses. Yet the review primarily focused on 2 dose regimens either 1 or 2 months apart. Adolescents 11 through 17 years	1622
V102_03	US, Poland	P2, multicenter study to evaluate safety of 2 doses of rMenB+OMV administered 2 months apart, versus an active control (dose of placebo followed by dose of Menveo)	None	2 doses two months apart. Adolescents and young adults 10 through 25 years of age.	120
Extension Study					
V72P10E1	Chile	Phase 2b, open label multicenter extension study to Study V72P10 to assess antibody persistence 18-24 months after the completion of the vaccination course in the first study. The extension study enrolled 666 subjects who had completed the Month 6 visit in Study V72P10, and enrolled 150 vaccine naïve subjects.	None	There were no vaccinations given, and study activities only included collection of 15 mL blood sample. Subjects were 13 to 19 years of age.	0
Manufacturing Lot-to-Lot Consistency and Dose Selection					
V72P13	Italy, Germany, Austria, Finland, Czech Republic	Phase 3 lot-to-lot consistency study	Infanrix-Hexa® (DTPa-HBV-IPV/Hib)- not licensed in the US; and Prevenar® (Pneumococcal 7-valent Conjugate Vaccine)- licensed in the US as Prevnar®	3 doses (2 mo, 4mo, 6 mo). Infants 2 months of age	2480

Study Number	Country	Description (relevance to US licensure)	Concomitant vaccines	Vaccination Schedule/ Population	Subjects receiving at least 1 dose rMenB+OMV
V72P16	Czech Republic, Hungary, Italy, Argentina, Chile	Phase 2 dose ranging study	Infanrix-Hexa® (DTPa-HBV-IPV/Hib)- not licensed in the US; and Prevenar® (Pneumococcal 7-valent Conjugate Vaccine)- licensed in the US as Prevnar®	3 doses (2mo, 3mo, 4mo). Infants 2 months of age.	367
Supportive Trials					
V72P5	Switzerland	Phase 1 study to evaluate safety in adults	None	3 dose series (each dose one month apart). Adults 18-40 years of age	28
V72P4	Germany, Italy	Phase 2 study to evaluate safety in adults at high risk	None	3 dose series (0, Month 2, Month 6). Adults 18-50 years of age.	53

5.4 Consultations

5.4.1 Advisory Committee Meeting

An advisory committee meeting was not convened during the review of this original BLA. An advisory committee meeting was held on April 7-8 2011 to discuss the approaches to licensure of meningococcal vaccines for the prevention of serogroup B invasive meningococcal disease.

5.4.2 External Consults/Collaborations

There were no external consultations or collaborations during the review of this application.

5.5 Literature Reviewed

The literature reviewed as part of the evaluation of this application is referenced throughout the memo as footnotes.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study V72_41

A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of rMenB+OMV Vaccine Formulated with OMV Manufactured at Two Different Sites in Healthy Adolescents Aged 11-17 Years.

6.1.1 Objectives

Primary:
Immunogenicity

- To demonstrate the equivalence of rMenB+OMV lot 1 (Rosia) and rMenB+OMV lot 2 (b)(4)- when administered to adolescents, as measured by hSBA GMTs against 3 *N. meningitidis* serogroup B test (reference) strains (H44/75, 5/99, and NZ98/254).

Safety

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

Reviewer Comment:

1. *This study provides a comparison of the OMV component of this vaccine manufactured at the (b)(4) site (original site) compared to the OMV manufactured at the Rosia site, which is the manufacturing site under review as part of this application.*
2. *Of note, for the 3 other main studies (V72_29, V72P10, and V102_03) included as part of this BLA, the OMV component was manufactured at the (b)(4) site. Only OMV manufactured at the (b)(4) site is contained in rMenB+OMV doses that have been distributed for use in other countries/regions where the vaccine is licensed for use, including Canada, Australia, and Europe.*
3. *Study objectives relevant to the evaluation of rMenB+OMV vaccine for the BLA are listed, and do not include all pre-specified study objectives.*
4. *As mentioned in Section 5.1 of this review, additional evaluations of the functional immune response (hSBA) to vaccination were specified by CBER and were used to assess effectiveness of the vaccine. For this study, these modified immunogenicity analyses were performed on data for both lots combined in order to assess the serum bactericidal activity.*
6. *Though the safety evaluations were assessed descriptively without a control group, these evaluations will be used help characterize the overall safety profile of the vaccine.*

6.1.2 Design Overview

Study V72_41 is a Phase 3 multicenter, observer-blind, randomized trial in adolescents 11-17 years of age to evaluate consistency of the immune response of 2 lots of rMenB+OMV formulated with OMV manufactured at two different sites: Rosia, or (b)(4) (both in (b)(4)).

Study Groups-each group received 2 doses[15] (one month apart) as follows (N=#enrolled):

- Lot 1-Rosia: Day 0, Month 1 (N=170)
- Lot 2-(b)(4): Day 0, Month 1 (N=174)

15 Each group received the same lot for each dose

All subjects had sera collected one month post-dose 2, while a subset of subjects (~50%) had an additional blood draw two weeks post-dose 2 at pre-selected sites who enrolled subjects willing to have this extra blood draw. The study was conducted at 13 study sites in Canada and Australia. Planned enrollment was for 320 subjects (160 subjects/group), and with a presumed 15% dropout rate, the immunogenicity analyses was anticipated to include 135 subjects per study group, while the safety analyses was to include only subjects who received at least one dose of study vaccine. The trial was partially blinded; therefore the study staff member (nurse or physician) whose responsibilities were vaccine preparation, administration, and accountability was unblinded. This unblinded staff was instructed not to reveal the study vaccines identity to the subject nor the staff member involved in monitoring the conduct of the trial, except in the case of emergency; and had no contact with the subject after vaccine administration. In addition each study site had an unblinded monitor who was responsible for reviewing randomization records and had no other role in the study. Specific instructions were provided for the appropriate processing, labeling and storage of samples during study visits which included blood draws.

6.1.3 Population

Subjects were eligible for participation in the study if they were healthy 11-17 years old and were able to given written assent and whose parents gave written informed consent, and were able to attend all scheduled visits. Subjects were excluded for participation if they had a history of serogroup B meningococcal vaccination, suspected or confirmed *N. meningitidis* disease, chronic or progressive disease, impairment of immunity (due to treatment or underlying condition), severe allergic reactions after prior vaccinations or hypersensitivity to any vaccine component, and/or any condition which was considered by the investigator to interfere with the evaluation of the study objectives. In addition, subjects were excluded if they had contact with an individual who had laboratory confirmed *N. meningitidis* disease within 60 days (of enrollment); significant illness and/or fever (temperature measured by axillary route of $\geq$38.0C) within 7 days; antibiotics within 72 hours; pregnancy/nursing mothers; females not using acceptable method of birth control for the 30 days prior to study entry through the 2 month duration of the study; receipt of blood or blood products within prior 90 days; receipt of any other vaccine within 30 days prior (60 days for live viral vaccines, 14 days for influenza vaccines); participation in another clinical trial within prior 90 days, or during study; and/or family/household members of staff.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The composition of rMenB+OMV includes the following components per 0.5 mL dose:

- *N. meningitidis* NadA (961c antigen): 50 micrograms (ug)
- *N. meningitidis* fHbp (936-741 antigen): 50 ug
- *N. meningitidis* NHBA (287-953 antigen): 50 ug
- OMV containing PorA P1.4 from *N. meningitidis* Strain NZ 98/254: 25 ug
- Aluminum hydroxide: 1.5 mg
- Sucrose: 10 mg (2%)
- NaCl: 3.125 mg
- Histidine: 0.776 mg
- Water for injection: up to 0.5mL

The vaccine was provided as an off-white opalescent suspension for injection in a single dose syringe, and 0.5mL was administered intramuscular in the deltoid region. The two lots of rMenB+OMV used in this study were as follows:

- Rosia- Lot number 101601, release date 28 July 2011

- (b)(4)- Lot number 090101, release date 27 July 2011

Both vaccine lots were used in both study site countries (Canada and Australia).

6.1.5 Directions for Use

See above

6.1.6 Sites and Centers

The study was conducted at 13 study sites: 6 sites in Australia with a total enrollment of 75 subjects, and 7 sites in Canada. The sites include the following (N=total enrolled subjects at the site)

Canada:

- Site 51: Dr. Paul Rheault, Medical Research, Inc, Sudbury Ontario (N=90)
- Site 52: Dr. Tai Araki, TASC[16] Research Services, Surrey British Columbia (N=51)
- Site 55: Dr. Anil Gupta, Albion Finch Medical Center, Etobicoke Ontario (N=30)
- Site 56: Dr. Kenneth Heaton, Devonshire Clinical Research Ind, Woodstock Ontario (N=30)
- Site 57: Dr, Sam Henein, SKDS Research Inc, Newmarket, Ontario (N=21)
- Site 58: Dr. Hartley Garfield, Hartley Garfield Medicine Professional Corporation (N=27)
- Site 59: Dr. Murdo Ferguson, Colchester Research, Truro Nova Scotia (N=20)

Australia:

- Site 01: Dr. Michael Nissen, Herston, QLD, Australia (N=17)
- Site 02: Dr. Helen Marshall, North Adelaide, SA, Australia (N=17)
- Site 03: Dr. Peter Richmond, Subiaco, WA, Australia (N=12)
- Site 04: Dr. Ferdinandus de Looze, Sherwood QLD, Australia (N=15)
- Site 06: Dr. Terry Nolan, Melbourne, VIC, Australia (N=14)

Reviewer Comment:
The majority of subjects were enrolled at sites in Canada: 269 subjects (~78%) out of 344 total subjects enrolled.

6.1.7 Surveillance/Monitoring

Schedule of Events: All subjects received 2 vaccinations (one month apart) and were followed for a total of 2 months. The following list includes the scheduled visits and telephone contacts with the subjects, including trial activity associated with each visit/contact:

- *Day 1-Visit 1:* Informed Consent; medical history; review of eligibility criteria; history directed physical examination with blood pressure, pulse, and heart/lung examination, temperature and urine pregnancy test; allocation of subject number; baseline blood sample given (20mL maximum); vaccination by unblinded vaccine administrator; 30 minutes safety observation; diary card provided and instruction on how to monitor solicited symptoms, including recording of axillary temperatures.

- *Day 4-Telephone Call (window Day 3-7):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian on how to record adverse events/concomitant medications on diary card.

16 This site closed in 2012, therefore all site documentation is with an independent archival facility.

- *Day 31-Visit 2 (window 28-35 days):* Diary card collected/reviewed, history directed PE with temperature and examination of injection site; review of ongoing eligibility criteria; urine pregnancy test, study vaccination by unblinded vaccine administrator, 30 minute safety observation, diary card provided and instructions given as above

- *Day 34-Telephone Call (window Day 32-37):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian on how to record adverse events/concomitant medications on diary card.

- *Day 45-Visit 2b for a subset of subjects with additional blood draw (window Day 43-47):* Review diary card, history directed PE, examination of injection site; evaluation of ongoing eligibility criteria; obtain sera (20 mL maximum); all subjects given a Memory Aid (to record SAEs, medically attended AEs, and prescription medications to treat these AEs) and instruction on how to complete the form.

- *Day 61-Visit 3 (window Day 58 to 65):* Diary card or Memory Aid collected/reviewed, history directed PE with examination of injection site; obtain sera (20 mL maximum); complete Trial Termination Form for subject.

Immunogenicity Assessments:

Blood samples were collected on Day 1 (pre-vaccination) and Day 61 (Visit 3- one month after 2nd dose) for all subjects, and on Day 45 (Visit 2b- 2weeks after 2nd dose) for a subset of subjects (160 subjects); maximum 20 mL blood collected. Sera were collected for hSBA using human serum as the source of exogenous complement, and -(b)(4)-. The primary measures of immunogenicity to demonstrate vaccine lot comparability were the hSBA GMT against each of the 3 serogroup B test (reference) strains: H44/76, 5/99, and NZ98/254.

Safety Assessments:

- *Immediate post-vaccination*: subjects were observed for the 30 minute post-vaccination after each vaccination dose.

- *Solicited Local, Systemic Reactions, Axillary Temperature*: collected for 7 days post-vaccination (including day of vaccination); frequencies and percentages of subjects experiencing each reaction was presented based on symptom severity.
    - *Local injection site reactions*: pain, erythema, induration, and swelling. Severity grading scale: none (0mm), 1 to <25mm, 25 to <50mm, 50 to <100mm, ≥100mm
    - *Systemic reactions*: nausea, fatigue, myalgia, arthralgia, headache, fever, and rash. Severity grading scale: 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.
    - *Temperature*: measured by axillary route Severity grading scale: <38.0; 38.0-38.4; 38.5-38.9; 39.0-39.4; 39.5-39.9; ≥40.0, If fever (T≥38.0) persists beyond Day 7, then it was reported as an AE.

- *All Unsolicited Adverse Events:* collected for 7 days post-vaccination (including day of vaccination), though all AEs regardless of severity were monitored until resolved.

- *Serious Adverse Events, Medically Attended AEs, AEs Leading to Withdrawal, Medications*: collected throughout the study, including all prescription medications and all antipyretic over the counter medications

Reviewer Comment: *Study activities were recorded on the relevant electronic Case Report Form, a sample of which was reviewed and included the appropriate components. A Data Monitoring Committee was not utilized in this study.*

6.1.8 Study Endpoints and Criteria for Study Success

Post-Hoc Modified Immunogenicity Analyses:

- the proportion of subjects with a ≥4-fold response (post-vaccination #2 compared to pre-vaccination #1) for each of 3 meningococcal B test strains, and
- the proportion of subjects with a hSBA response ≥the lower limit of quantitation (LLOQ) to all of the test strains (composite response)

Immunogenicity Endpoints:[17]
Primary:

- Based on the one month post dose 2 response, study success demonstrating consistency of manufacturing of two different lots of OMV was based on the two-sided 95% CI of the ratio of the hSBA GMTs (across the two study vaccine lots) for each of the 3 serogroup B test (reference) strains (H44/76, 5/99, and NZ98/254) were contained within the interval of 0.5 and 2.0.

  Reviewer Comment: *As mentioned in Section 5.1 of this review, additional evaluations of the functional immune response (hSBA) to vaccination were specified by CBER and were used to assess effectiveness of the vaccine. For this study, these modified immunogenicity analyses were performed on data for both lots combined in order to assess the serum bactericidal activity after OMV manufacturing lot consistency was established. The CBER specified post-hoc immunogenicity analyses are presented below.*

Safety Endpoints: (as described above in Section 6.1.7)

- Safety was assessed in a descriptive manner without statistical comparisons between vaccine groups.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Hypothesis and Statistical Methods for Primary Endpoints:
H_0: Null hypotheses of nonequivalence
H_1: Alternative hypotheses of equivalence (consistency)

- For the primary immunogenicity objective, the study would be considered a success if consistency of immune response (the alternative hypotheses) between the two lots is demonstrated for each of the 3 serogroup B test (reference) strains. Consistency was concluded, if one month after the 2nd vaccination, the two-sided 95% CI of the difference in means of $\log_{10}$ transformed hSBA was within the equivalence range (-0.301 to 0.301) for each of the 3 serogroup B test (reference) strains (H44/75, 5/99, and NZ98/254). This is equivalent to the statement that the two-sided 95% CI of the one month post-second ratio of GMTs (or GMCs) is within the equivalence range of 0.5 to 2.0.

17 The applicant calculated the two-sided 95% CI by exponentiating (base 10) the least squares means and the lower and upper limits of the 95% CI of the log $_{10}$ transformed titers (or concentrations). These were obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study center.

- The analyses for the primary safety objectives and the secondary immunogenicity objectives were descriptive without hypotheses testing.

Sample Size Calculations:

- With 135 evaluable subjects per lot (group) the overall power to demonstrate immunologic consistency between the two manufacturing lots was approximately 93.6%.

Significant Changes in the Conduct of the Study or Planned Analyses:

The final version of the protocol was Version 1.0, dated 30 June 2011. The changes to conduct of study were as follows:

- The target enrollment was 320 subjects, and a total of 344 subjects were enrolled, as sites were informed of study status as the trial reached close to the target enrollment. Sites were permitted to proceed with all pre-scheduled screening an enrollment visits, resulting in over – enrollment across the trial.
- Additional exploratory analyses were performed that were not specified in the analysis plan.

Reviewer Comment*: These additional exploratory analyses were not relevant for the purpose of determining lot comparability or in the evaluation of vaccine effectiveness and therefore are not included as part of this review.*

6.1.10 Study Population and Disposition

The first subject was enrolled on 30 August 2011, and the last subject completed the study on 01 December 2011. A total of 344 subjects were enrolled in the study, 170 in the Lot-1 Rosia group and 174 in the Lot-2 (b)(4) group.

6.1.10.1 Populations Enrolled/Analyzed

Analysis Sets:

- *All Enrolled Population*: all subjects who have signed an informed consent, undergone screening procedures, and were randomized
- *Full Analysis Set (FAS)/Modified Intention-to-treat (MITT) Population*: all subjects in the enrolled population who actually received a study vaccination, and provided at least one evaluable blood sample after baseline.
- *FAS/MITT, Immunogenicity*: all subjects in the FAS/MITT population who provided at least one evaluable serum sample after baseline and whose assay result was available for at least one strain
- *Per-Protocol Analysis Set, Immunogenicity (PPS):* A subset of subjects in the MITT Immunogenicity set who correctly received the vaccine, and provided evaluable serum samples at the relevant time points (for subjects in the immunogenicity subset), and had no major protocol violation as defined prior to unblinding.
    - A major deviation is defined as a protocol deviation that was considered to have a significant impact on the immunogenicity result of the subject.
- *Exposed Population:* all enrolled subjects who actually received a study vaccination
- *Safety Population*: all subjects in the Exposed Population who provided post vaccination safety data.

6.1.10.1.1 Demographics

The demographics for the study are shown in the following table:

Table 3: Study V72_41 Demographics

	Lot 1-Rosia N= 170	**Lot 2-(b)(4) N=174**
% Female	72 (42.0%)	82 (47.0%)
% Male	98 (58.0%)	92 (53.0%)
Age -Mean	13.6 ± 1.9 (years)	13.8 ± 1.8 (years)
Racial origin:	(%)	(%)
-Asian	17 (10%)	18 (10%)
-Black, Non-Hispanic	4 (2%)	1 (<1%)
-White, Non-Hispanic	134 (79%)	141 (81%)
-Native American/Alaskan	9 (5%)	6 (3%)
-Hawaiian/Pacific Islander	0	1
-Other	6 (4%)	7 (4%)
Weight	57.86±17.10 kg	57.37±16.23 kg
Height	162.6±10.9	162.3±11.0

Source: Adapted from BLA 125546/0, V72_41 Clinical Study Report, Table 11.2-1 on p.86 of 1537.

Reviewer Comment:

1. *The age range of all study participants was from 11 to 17 years of age, and median age of enrollment across both groups was 13.0 years.*
2. *Across groups 55% of subjects were male, and 45% were female. Lot 1-Rosia group had 58% males and 42% females, while Lot 2-(b)(4) had 53% males than 47% females. All other demographic characteristics appear to be well matched across groups.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Country-Specific Demographic Characteristics:

As mentioned above, ~78% of subjects (269 Canadian subjects/344 total subjects) were enrolled at sites in Canada. The following table provides the demographic characteristics for subjects enrolled at sites in Canada.

Table 4: Study V72_41 Demographics for Subjects enrolled at Canadian Sites:

	Lot 1-Rosia N= 133	**Lot 2-(b)(4) N=136**
% Female	62 (47.0%)	64 (47.0%)
% Male	71 (53.0%)	72 (53.0%)
Age -Mean	13.6 ± 1.9 (years)	13.8 ± 1.8 (years)
Racial origin:	(%)	(%)
-Asian	17 (13%)	17 (13%)
-Black, Non-Hispanic	4 (3%)	1 (<1%)
-White, Non-Hispanic	99 (74%)	104 (76%)
-Native American/Alaskan	9 (7%)	6 (4%)
-Hawaiian/Pacific Islander	0	1 (<1%)
-Other	4 (3%)	7 (5%)
Weight	58.95±17.52 kg	59.33±16.97 kg
Height	162.7±10.6	162.1±11.0

Source: Adapted from BLA 125546/0, V72_41 Clinical Study Report, Table 14.1.1.3.5 on p.139-140 of 1537

Reviewer Comment:

1. *The mean age for all subjects enrolled in Canadian sites was 13.8 ± 1.9 years, with a median age of 14.0 years. There were slightly more females enrolled than males, while other demographic characteristics across groups were equal.*
2. *Though not shown above, the racial distribution for Australian subjects was 96% white (non-Hispanic), 3% other; and 1% Asian. When compared to those enrolled at Australian sites, the racial origin of subjects enrolled at Canadian sites more closely approximates that of the US general population, though with a notable underrepresentation of Hispanic and Black subjects.*

6.1.10.1.3 Subject Disposition

The following table provides the number of subjects enrolled, vaccinated, and included in the populations selected for clinical analysis, in addition to the number of subjects discontinued for various cited reasons and who had at least one protocol deviation.

Table 5: Study V72_41 Disposition of Subjects

Population	**Lot 1-Rosia N= 170**	**Lot 2-(b)(4) N=174**	**Total N=344**
Enrolled (N)	170	174	344
Vaccinated Population	169 (99%)	173 (99%)	342 (99%)
Completed Protocol	168 (99%)	170 (98%)	
Subjects Discontinued (due to)	2 (1%)	4 (2%)	342 (99%)
-AE	0	1 (<1%)	1 (<1%)
-Protocol Noncompliance	-	-	-
-Lost to follow-up	-	-	-
-withdrawal of consent	2 (1%)	3 (2%)	5 (1%)
Vaccinated Population	169 (99%)	173 (99%)	342 (99%)
Safety Population	169 (99%)	173 (99%)	342 (99%)
MITT Population	168 (99%)	171 (98%)	339 (99%)
Protocol Deviations	66 (39%)	63 (36%)	129 (38%)
-Major Deviation	23 (14%)	26 (15%)	49 (14%)
-Minor Deviation	54 (32%)	52 (30%)	106 (31%)
Per Protocol Analysis Set	147 (86%)	152 (87%)	299 (87%)
-Subjects excluded from PPS Analysis	23 (14%)	22(13%)	45 (13%)

Source: Adapted from BLA 125546/0, V72_41 Clinical Study Report: Table 14.1.1.2; Table 14.1.1.1, Table 14.1.1.7

Reviewer Comment*: There were 342 subjects who received at least one dose of rMenB+OMV, and there were 338 subjects who received 2 doses of rMenB+OMV, 1 month apart.*

Protocol Deviations:

As mentioned in the table above, there were 129 subjects with a protocol deviation, including 66 subjects in the Lot 1-Rosia group, and 62 in the Lot 2-(b)(4) group. Of these, 49 subjects had any major deviation (23 subjects in Lot 1-Rosia group, and 26 subjects in Lot 2-(b)(4) group). The most frequently cited reasons for a major protocol deviation were the following (% of subjects enrolled in Lot 1 vs Lot 2):

- Vaccination dose #2 outside the allowed window (8%, 6%)
- Subject received an excluded concomitant medication (4%, 3%)
- Subject with treatment not according to original protocol (2%, 2%)

There were 54 subjects in Lot 1- Rosia group and 52 subjects in Lot 2-(b)(4) group who had any minor protocol deviation. The most common reasons cited were as follows (% of subjects enrolled in Lot1 vs Lot2)

- Day 4 call not done according to protocol/not done-Vaccination 2 (14%, 10%)
- Day 4 call not done according to protocol/not done-Vaccination 1 (14%, 6%)
- Day 4 call out of window-Vaccination 1 (5%, 5%)
- Blood draw at Visit 3 outside the protocol window (4%, 6%)

Exclusions from the PPS Analyses Set:

There were a total of 45 subjects excluded from the PPS Analysis Set, including 23 from Lot 1-Rosia and 22 subjects from Lot 2-(b)(4). The reasons for these exclusions are presented below:

Table 6: Study V72_41 Subjects Excluded from Per Protocol Immunogenicity Analyses Set

Reason for Exclusion	**Lot 1-Rosia N= 170**	**Lot 2-(b)(4) N=174**
Enrolled (N)	170	174
Vaccinated Population	169 (99%)	173 (99%)
Completed Protocol	168 (99%)	170 (98%)
Per Protocol Analysis Set	147 (86%)	152 (87%)
Subjects excluded from PPS Analysis	23 (14%)	22(13%)
Reason for Exclusion		
Vaccination 2 outside of allowed window (27-34 days)	14 (8%)	10 (6%)
Subjects received excluded concomitant medication	7 (4%)	6 (3%)
Subjects with treatment not according to original random back-up list	3 (2%)	3 (2%)
Subjects withdrawal of consent	2 (1%)	4(2%)
Subject did not receive vaccination 2	1(<1%)	3(<2%)
No blood draw at Visit 2b and 3	1(<1%)	1 (<1%)
No blood draw at Visit 3	1 (<1%)	1 (<1%)
No lab result at Visit 2b and 3	1 (<1%)	1 (<1%)
No lab result at Visit 3	1 (<1%)	1 (<1%)
Subject did not receive vaccination at all	1 (<1%)	1 (<1%)
Blood draw at visit 3 outside analysis window (23-55 days)	0	1 (<1%)
No blood draw	0	1 (<1%)
No lab results at all	0	1 (<1%)

Source: Adapted from BLA 125546/0, V72_41 Clinical Study Report: Table 14.1.1.8 on pa. 189-190 of 1537.

***Reviewer Comment**:*

The majority of subject excluded from the immunogenicity analyses due to a protocol deviation were enrolled at a Canadian study site. The following two Canadian sites had the highest rates of exclusion as follows:

- *Site #51 (PI- Dr Paul Rheault) had 15 subjects (16.6%) excluded from the total enrolled at this site (90 subjects enrolled);*

- *Site #52 (Dr Tai Araki) had 11 subjects (21.6%) excluded from the total enrolled at this site (51 subjects enrolled).*

There does not appear to be an imbalance across groups (Lot 1-Rosia versus Lot 2–(b)(4)).

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses Supporting Accelerated Approval (Post-hoc)

As discussed in Section 5.1, CBER has selected specific hSBA measurements using three meningococcal serogroup B test strains (H44/76, 5/99, NZ98/254) as serologic markers likely to predict clinical benefit of rMenB+OMV vaccine in the context of accelerated approval. These hSBA measurements include the proportion of subjects with a ≥4-fold response after the 2nd dose for each of the 3 serogroup B test strains; and the proportion of subjects with hSBA response ≥ LLOQ to all test strains as a composite response.

Reviewer Comment*: Since lots manufactured at both sites were comparable based on GMT evaluations, the data for both lots were combined to evaluate vaccine effectiveness using CBER selected hSBA criteria.*

Proportion of Subjects with ≥4-fold Response

The table below provides the percentage of subjects with greater than or equal to a 4-fold rise one month after the 2nd dose when measured against each of the meningococcal test strains for both the lots combined.

Table 7: Study V72_41 Percentage of Subjects with ≥4-Fold Rise[a] One Month Post Dose-2, PPS

% [95%CI] of Subjects with ≥4-Fold Response	
Strain (Antigen)	**1 mo. PD#2 (N=298-299)**
H44/76 (fHbp)	98% [95, 99]
5/99 (NadA)	99% [98,100]
NZ98/254 (PorA P1.4)	39% [33,44]

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/3/2014. Table corresponds to Table 3.2.3-1 of ISE submitted under BLA 125546/0. PPS:Per Protocol Analysis Set. 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. Two doses were administered one month apart: (0,1) schedule.

[a] Four-fold rise is defined as postvaccination hSBA ≥1:16 for subjects with prevaccination hSBA <1:4, a post vaccination titer at least 4-fold the LLOQ for subjects with prevaccination hSBA ≥1:4 but <LLOQ; and a postvaccination 4-fold rise for subjects with pre-vaccination hSBA ≥LLOQ. LLOQ is defined as 16 for strain H44/76; 16 for strain 5/99, and 8 for strain NZ98/254.

Reviewer Comment*: The percentage of subjects who achieved a 4-fold hSBA immune response against NZ98/254 strain was low when compared to the other 2 test strains.*

Proportion of Subjects with hSBA Response ≥ LLOQ to All Test Strains as a Composite Response
The percentage of subjects with hSBA response ≥ LLOQ at baseline and one month after the 2nd dose (1 month PD#2) is provided in the table below for both the lots combined.

Table 8: Study V72_41 Percentage of Subjects with hSBA Response ≥ LLOQ[a] One Month Post Dose-2, PPS

	% [95%CI] of Subjects with hSBA ≥LLOQ	
Strain (Antigen)	**Baseline N=299**	**1 mo. PD#2 N=298**
H44/76 (fHbp)	0%	98% [96,99]
5/99 (NadA)	2% [1,5]	100% [99,100]
NZ98/254 (PorA P1.4)	1% [0,3]	63% [57,69]

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/3/2014. Table corresponds to Table 3.2.1-1 of ISE submitted under BLA 125546/0. PPS:Per Protocol Analysis Set. 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. Two doses were administered one month apart: (0,1) schedule.
[a]LLOQ is defined as 16 for strain H44/76; 16 for strain 5/99, and 8 for strain NZ98/254.

***Reviewer Comment**:*

1. *The percentage of subjects with hSBA immune response ≥LLOQ is lower against test strain NZ98/254 when compared to the other two test strains. As noted the baseline measurements were similar across each test strain.*
2. *In supplemental analyses[18]not shown above, the percentage of subjects with hSBA response one month after the 2nd dose evaluated by gender were similar when measured against H44/76 and 5/99 test strains, but were different for NZ98/254 strain: 69% [95% CI: 62,76] of males compared to 56% [95% CI: 47,64] of females who achieved this response. As noted, there is minimal overlap of the 95% confidence intervals. This difference across genders in hSBA response based on CBER specified criteria was not observed in the 3 other pivotal trials.*

Based on the per protocol analysis set, the proportion of subjects at baseline with hSBA response ≥ LLOQ to 3 out of 3 test strains was 0 for Lot 1-Rosia group, Lot 2-(b)(4) group, and for both lots combined. The composite response for percentage of subjects with 1 month after the 2nd dose was as follows for each lot evaluated and for both lots combined:

- Lot 1-Rosia 1 month post dose 2 (N=147): 59% [51,67]
- Lot 2-(b)(4) 1 month post dose 2 (N=151): 66% [58,74]
- Combined Lots:
  - Baseline (N=299): 0
  - 1 month post dose 2 (N=298): 63% [57,68]

Reviewer Comment:
The composite response for both lots combined was 63% to 3 out of 3 test strains one month after the 2nd dose. Though the composite response was nominally higher in the Lot 2-(b)(4) group (66%) than the Lot 1-Rosia group (59%), the 95% confidence intervals for these responses are broadly overlapping.

18 Source: BLA 125546/0.17 submitted 10/3/2014- Information Amendment-Immunogenicity Data (Table Q3-1d).

6.1.11.2 Analyses of OMV Lot Consistency Endpoints

Ratio of hSBA Antibody Responses for Lot 1-Rosia to Lot 2-(b)(4) (1 month Post Dose-2)-PPS
The study's primary analyses evaluated the one month post dose-2 immune response, based on the two-sided 95% CI of the ratio of the hSBA GMTs across vaccine lots (Lot 1-Rosia to Lot 2-(b)(4)) for each of the 3 serogroup B test (reference) strains (H44/76, 5/99, and NZ98/254). Study success was determined if these ratios were contained within the interval of 0.5 and 2.0. The ratio of hSBA GMTs for Lot1-Rosia to Lot-2 (b)(4) [2-sided 95% CI] is as follows by strain for the Per Protocol Population:

- H44/76: 1 [0.82, 1.23]
- 5/99: 0.92 [0.77, 1.1]
- NZ98/254: 0.81 [0.6, 1.09]

6.1.11.3 Subpopulation Analyses

Please see reviewer comment below in Section 6.1.11.4.

6.1.11.4 Dropouts and/or Discontinuations

Missing values were left out of analyses.

6.1.12 Safety Analyses

6.1.12.1 Methods

The Safety Population, subjects who received at least one dose of rMenB+OMV was comprised of 342 subjects, 169 subjects in Lot1-Rosia and 173 subjects in Lot 2-(b)(4). Two subjects were excluded from this analysis because they did not receive any vaccination. There were 338 subjects who received two doses of rMenB+OMV, 1 month apart.

As mentioned in Section 6.1.7 above, safety data collection included immediate AEs within 30 minutes of vaccination; solicited local/systemic AEs and all unsolicited AEs for 7 days post-vaccination; SAEs, MAAEs, and AEs leading to withdrawal throughout the study. A diary card was used to collect both solicited unsolicited AEs for the 7 day post-vaccination time period, and Memory Aide was provided to record SAEs, MAAEs, AEs leading to withdrawal, and prescription medications to treat these AEs. Diary cards and memory aids were collected at follow-up visits, including final study visit on Day 61.

6.1.12.2 Overview of Adverse Events

Solicited Adverse Events:
Rates of solicited reactions were similar across the two different lot groups. The rates of any local solicited reaction were 96% in the Lot1-Rosia group compared to 98% in the Lot 2-(b)(4) group. The most common local reaction was pain, seen in 96% of subjects in the Lot1-Rosia group and 98% of Lot 2-(b)(4) group after any vaccination, while severe pain was seen in 14% and 17% of subjects, respectively. Erythema was seen in ~65% of subjects in both groups, with only 1 subject in each group reporting severe erythema. Swelling was seen in 43-47% of subjects in both groups, with only 1 subject in Lot 1-Rosia reporting severe swelling.

Though the rates of any systemic reactions were higher in the Lot2-(b)(4) group, the rates of severe systemic reactions were similarly low across groups. The most common systemic reaction across groups was myalgia seen in 59% of Lot 1-Rosia group and 68% of Lot 2-(b)(4) group, while severe myalgia was seen in ~8% of subjects across both groups. Other common systemic reactions included headache (44-51%); fatigue (44-49%); and nausea (29-32%) of subjects. The rates of severe symptoms for these reactions were low (2-6%) across both groups. The majority of

subjects did not report a fever (95%-97%), as defined by temperature <38C; and there were no severe fevers reported (T≥40C). Approximately half of all subjects reported using an analgesic (49-52% of subjects), and ~14% of subjects reported staying home after vaccination.

> ***Reviewer Comment****: The rates of adverse reactions across groups were similar, and did not indicate that there were any differences in the reactogenicity profile of each OMV lot. The most common solicited AEs reported for both groups were injection site pain, injection site erythema, myalgia, headache and fatigue. Reports of fever were generally low for this study population, though almost half of subjects reported use of an analgesic after vaccination. Interpretation of the rates of adverse events is limited in the absence of an inactive comparator.*

Revised Solicited Adverse Event Rates:
As discussed in Section 5.1, the rates of solicited adverse events which exclude data that appeared to be obtained by subject recall several weeks or months after the 7-day post vaccination monitoring period when the source document appeared to be missing were assessed and provided in response to CBER request. The revised rates are presented for both rMenB+OMV groups combined by dose. The applicant notes that for this study the collection of solicited AEs data that were obtained by retrospective recall was neither explicitly prohibited nor permitted by study documents. The applicant estimates that the proportion of solicited AEs data not obtained from a source document was low (0.33%). By dose, 2.04% of solicited AE data after the 1st dose of rMenB+OMV was considered to be obtained by retrospective recall, and 1.47% of solicited AE data after the 2nd dose was considered to be recalled.

Table 9: Study V72_41 Revised Reactogenicity Rates: % of All Subjects (both rMenB+OMV groups combined) with Any & *Severe* Solicited Local & Systemic Adverse Events for 7 Days Post-vaccination, by dose

		Dose 1	Dose 2
		Bexsero N=316-337 *N=315-337*	**Bexsero** N=322-337 *N=322-337*
Local Adverse Events			
Pain	Any *Severe*	96 *11*	90 *9*
Erythema	Any *>100 mm*	43 *<1*	44 *<1*
Induration	Any *>100 mm*	26 *0*	26 *0*
Swelling	Any *>100 mm*	26 *0*	29 *<1*
Systemic Adverse Events			
Fatigue	Any *Severe*	N/A *N/A*	N/A *N/A*
Nausea	Any *Severe*	18 *1*	20 *1*
Myalgia	Any *Severe*	56 *4*	37 *3*
Arthralgia	Any *Severe*	15 *0*	13 *1*
Headache	Any *Severe*	35 *2*	34 *2*
Fever	≥38°C 38.0-38.9°C 39.0-39.9°C *≥40°C*	3 3 <1 *0*	2 1 <1 *0*

Source: Adapted from BLA 125546/0.21 (Information Amendment-Safety Data submitted 10/23/2014) Table 6-3.
Abbreviation: N/A = not applicable as the reaction was not collected.

Reviewer Comment*: Subject recall of solicited AE data at a time point several weeks or months after the 7-day post vaccination time period was low, and did not significantly impact the overall solicited AE safety data findings for this study.*

Unsolicited Adverse Events:
Across both study groups, 39% of subjects reported at least one adverse event during the entire study period, including 40% of Lot1-Rosia recipients, and 38% in Lots 2-(b)(4) recipients. Similar percentages of subjects across groups reported an AE as possibly or probably related to vaccination, including 20% of Lot1-Rosia subjects and 22% of Lot 2-(b)(4) recipients.

The most frequently reported AE by MedDRA preferred term was injection site pain, seen in 10 subjects (6%) in Lot 1-Rosia group and 12 subjects (7%) in Lot 2-(b)(4) group, all of which were considered at least possibly related to vaccination. Other common AEs considered at least

possibly related to vaccination were injection site induration (2% Lot 1-Rosia, 4% Lot 2-(b)(4)) and myalgia (3% Lot1-Rosia, 3% Lot 2-(b)(4)). Other common AEs reported by subjects were upper respiratory infections (5% Lot 1-Rosia, 2% Lot 2-(b)(4)), half of which were considered at least possibly related to vaccination, and nasopharyngitis (2% Lot 1-Rosia, 4% Lot 2-(b)(4)) none of which were considered related to vaccination. Overall the types and rates of unsolicited adverse events were similar across groups.

6.1.12.3 Deaths

There were no deaths during the study.

6.1.12.4 Nonfatal Serious Adverse Events

There were no SAEs reported over the study period.

> ***Reviewer Comment:*** *Of note this study was conducted over a short time interval of two months.*

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no pregnancies reported in this study. Please see Section 8 for an overview of AESI across all studies.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

AE leading to Study Withdrawal or Delay in Vaccination

One subject in the Lot 2-(b)(4) group withdrew due to infectious mononucleosis on Study Day 14 which was not considered related to vaccination. There were no withdrawals due to an AE in the Lot 1-Rosia group. There were 4 additional subjects who had reported an AE leading to vaccination delay: 2 in the Lot 1-Rosia group and 2 in the Lot 2-(b)(4) group. The 2 AEs in the Lot 1-Rosia group included a toenail bed infection on Study Day 20 not considered related to vaccination; and myalgia with pain in arm on Study Day 1 considered possibly related to vaccination. Both subjects required non-prescription medications and recovered. The 2 AEs in the Lot 2-(b)(4) group included acute sinusitis on Study Day 14; and asthma on Study Day 30. Both AEs were considered not related to vaccination, and both subjects required prescription medications and recovered.

6.1.13 Study Summary and Conclusions

The applicant evaluated two lots of rMenB+OMV which differed by the manufacturing site of the OMV component. Two doses of each lot were administered one month apart and data were collected until one month after the 2nd dose. The applicant's primary study objective was to evaluate the comparability of the OMV lot manufactured at the new site in Rosia, compared to the OMV lot manufactured at the original site in (b)(4). Based on a comparison of hSBA GMTs across lots, the study met its pre-specified success criteria and both OMV lots are considered to be equivalent.

Although there was no control group, an analyses for both lots combined was assessed to characterize the effectiveness and safety of the vaccine. For both lots combined, immune responses as measured by CBER specified hSBA measurement 1 month after the 2nd dose against H44/76 and 5/99 strains was 98%-99%, and 39% against NZ98/2545 strain. The reviewer

recommends that the hSBA data generated by Canadian/Australian study participants be included in the package insert as the responses are likely more representative of the responses in a North American population.

The overall safety profile was similar across both lots and common solicited reactions included injection site pain/erythema, myalgia, headache and fatigue. The rates of severe reactions were low, except for severe injection site pain which was reported by 9-11% of subjects. The reactogenicity profile of rMenB+OMV in 11 year to 17 year old participants in this study appears to be comparable to the rates observed following other vaccinations administered to this age group in the US. The rates of unsolicited AE and SAEs were low during the study, though the follow-up time period was only 1 month after the 2nd dose. The overall safety profiles of each lot were comparable and the reactogenicity data demonstrated similar trends as observed in other studies.

6.2 Trial #2: Study V72_29

A Phase 3 Observer-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Effect of Neisseria Meningococcal B Recombinant and MenACWY-CRM (Menveo®) Conjugate Vaccines on Pharyngeal Carriage of Neisseria Meningitidis in Young Adults (18-24 years old).

6.2.1 Objectives

The study's secondary objectives pertaining to individuals 18-24 years of age who received rMenB+OMV are listed below.

Immunogenicity

- To explore the immunogenicity of rMenB+OMV and MenACWY-CRM (Menveo®) vaccine administered to healthy young adults, by evaluation of serum bactericidal activity using human complement (hSBA) response rates at one month after 2 doses of rMenB+OMV, and two months after a 1 dose of MenACWY-CRM (Menveo®) vaccine.

Safety

- To evaluate the safety and tolerability of 2 doses of rMenB+OMV vaccine, given one month apart, and a single dose of MenACWY-CRM (Menveo®) conjugate vaccine

***Reviewer Comment**:*

1. *As specified in Section 5.1 of this review, CBER has selected modified immunogenicity hSBA endpoints to characterize the effectiveness of the vaccine as part of the accelerated approval regulatory pathway for this BLA. The reviewer notes that the primary objective for this study evaluated the pharyngeal carriage prevalence of virulent sequence types of N. meningitidis group B at one month following the 2nd dose of rMenB+OMV, compared to the control group receiving Japanese Encephalitis Vaccine (JEV) Ixiaro®. The final clinical study report states in its results section that there was no significant difference between the rMenB+OMV and the control group in the prevalence of carriage of N. meningitidis group B virulent sequence types at one month after the 2nd vaccination. The data associated with the primary endpoint pertaining to pharyngeal carriage were not considered relevant to the demonstration of effectiveness of the vaccine as part of the accelerated approval regulatory pathway for this application, and therefore were not evaluated as part of this application.*
2. *For this study, the reviewer will evaluate and present only safety and immunogenicity data pertaining to rMenB+OMV vaccination.*

6.2.2 Design Overview

Study V72_29 is a Phase 3 multi-center, observer blind randomized trial evaluating the effect of rMenB+OMV on meningococcal carriage rates in university students (18-24 years old) in the United Kingdom (UK) compared to two active comparators.

Study Groups: each group received two doses (one month apart) as follows (N=#enrolled):

- rMenB+OMV: Day 0, Month 1 (N=979)
- MenACWY+CRM (Menveo®)[19] at Day 1, followed by Placebo containing Aluminum hydroxide at Month 1 (N=988)
- Japanese Encaphalitis Vaccine (JEV), Ixiaro®[20]: Day 0, Month 1 (N=987*)*

Planned enrollment was for 3000 subjects between the ages of 18-24 years at 10 study sites in the UK, with a randomization ratio of 1:1:1 across the 3 study groups. Subjects were assigned by the investigator a 6-digit number after signing the informed consent form and confirming eligibility. The subject number corresponded to a vaccination group in the randomization list produced by the applicant using a validated system that automates the random assignment of treatment arms to randomization number in the specified 1:1:1 ratio.

Subjects participated for 12 months, which included two vaccination visits on Day 1 and Month 1. A subset of ~200 subjects/group were enrolled in the 'immunogenicity subset', who had 20mL of sera collected at baseline and at one month post-dose 2 (Month 2); three months post-dose 2 (Month 4); 5 months post-dose 2 (Month 6); and 11 months post-dose 2 (Month 12).

All subjects received "Diary Card-1" to record all serious adverse events (SAEs); medically attended AEs (MAAEs), and prescription medications to treat adverse events (AEs) throughout the study. In addition subjects in the 'immunogenicity subset' had an additional "Diary Card-2" to record solicited local and systemic reactions; all AEs; prescription medications for these AEs; and all over the counter antipyretic medications for 7 days after each vaccine dose administration.

The applicant specified 'immunogenicity subset' had the following scheduled study activities:

- sera collected for the evaluation of serum bactericidal activity throughout the study
- solicited reactogenicity and unsolicited safety data collected after each vaccination by two different diary cards as follows:
  - 1st diary card to assess serious adverse events and medically attended adverse events
  - 2nd diary card to assess 7 day post-vaccination reactogenicity

There were ~200 subjects from each group (~600 subjects) enrolled into the immunogenicity subset from Site 1 (Royal Hallamshire Hospital, Sheffield, UK).

6.2.3 Population

Subjects were eligible for participation if they were healthy 18-24 years of age who provided informed consent, were available for all scheduled visits. Subjects were excluded for participation if they had a history of serogroup B meningococcal vaccination, suspected or confirmed *N. meningitidis* disease, chronic or progressive disease, impairment of immunity (due to treatment or underlying condition), severe allergic reactions after prior vaccinations or hypersensitivity to any vaccine component, and/or any condition which was considered by the investigator to interfere with the evaluation of the study objectives. In addition, subjects were excluded if they had contact with individual with laboratory confirmed case of *N. meningitidis*

19 Menveo®, manufactured by Novartis Vaccines and Diagnostics, Inc.
20 Ixiaro®, manufactured by Intercell, Vienna, Austria.

within 60 days (of enrollment); significant illness within 7 days and/or fever (temperature measured by axillary route of ≥38.0C) within the previous day; antibiotics within 72 hours; pregnancy/nursing mothers; females not using acceptable method of birth control for the 30 days prior to study entry through the 12 month duration of the study; receipt of blood or blood products within prior 90 days; prior administration of JEV (Ixiaro); receipt of a meningococcal C or meningococcal ACWY vaccine within 30 days of Visit 1; participation in another clinical trial within prior 90 days, or during study; and/or family/household members of staff.

6.2.4 Study Treatments or Agents Mandated by the Protocol

There were three vaccine treatment groups: rMenB +OMV; MenACWY-CRM (Menveo®) and placebo (aluminum hydroxide); Japanese Encephalitis vaccine (JEV).

1. rMenB+OMV: please see Section 6.1.4 of this review for vaccine description;
    - Lot number: 090101V
    - Dose 0.5mL, intramuscular (IM) in deltoid region
2. MenACWY-CRM, Menveo®
    - Dose 0.5 mL, IM in deltoid region
3. Placebo:
    - Lot number: X38D23N1C
    - Dose 0.5mL, IM in deltoid region
    - Each dose contained the following:
        - Aluminum hydroxide:1.5mg
        - NaCl: 3.12-3.62mg
        - Histidine: 10mM
        - Water for injection: up to 0.5mL
4. Japanese Encephalitis Vaccine, Ixiaro®:
    - Dose 0.5mL,IM in deltoid region

6.2.5 Directions for Use

See above

6.2.6 Sites and Centers

The study was conducted at 10 study sites at universities across the United Kingdom as follows (N= number of subjects enrolled at each site):

- Site 01: Dr. Robert Read, Royal Hallamshire Hospital, Sheffield, UK (N=822 total enrolled, which included 585 subjects enrolled in the immunogenicity subset)
- Site 02: Dr. Paul Heath, St. Georges, University of London, London, UK (N=153)
- Site 03: Dr. David Turner, Cripps Health Centre, University Park, Nottingham, UK (N=318)
- Site 04: Dr. Andrew Pollard, University of Oxford, Oxford, UK (N=260)
- Site 05: Dr. David Chadwick, The James Cook University Hospital, Middlesbrough, UK (N=128)
- Site 06: Dr. David Baxter, University of Manchester, Manchester UK (N=261)
- Site 07: Dr. Stephen Gordan, Royal Liverpool and Broad Green University Hospital Trust, Liverpool, UK (N=499)
- Site 08: Dr. Saul Fraust, University of Southampton, Division of Immunology and Infectious Disease, Southampton, UK (N=312)
- Site 09: Dr. Adam Finn, University of Bristol, Bristol, UK (N=207)
- Site 10: Dr. David Lewis, University of Surrey, Surrey, UK (N=8)

6.2.7 Surveillance/Monitoring

Schedule of Events: All subjects received 2 vaccinations (one month apart) and were followed for a total of 12 months. The following list includes the scheduled visits and telephone contacts with the subjects, including trial activity associated with each visit/contact:

- *Day 1-Visit 1:* Informed Consent; medical history/concomitant medications; questionnaire (review of eligibility criteria); history directed physical examination with blood pressure, pulse, and heart/lung examination; urine pregnancy test; allocation of subject number; pharyngeal swab; baseline blood sample given (20mL maximum); vaccination; 30 minutes safety observation; diary card-1 provided to all subjects; diary card-2 provided to 'immunogenicity subset' subjects; instruction provided on how to complete both, and if applicable how to monitor solicited symptoms, including recording of oral temperatures.

- *Month 1 (Day 31)-Visit 2 (window Day 24 to 45):* Diary cards-1 and -2 collected/reviewed SAEs/MAAEs collected; history directed PE with oral temperature and examination of injection site; urine pregnancy test; concomitant medications; questionnaire; pharyngeal swab; study vaccination; 30 minute safety observation, diary cards-1 and -2 provided and instructions given as above

- *Month 2 (Day 61)-Visit 3 (window Day 47 to 89):* Diary cards-1 and -2 collected/reviewed SAEs/MAAEs collected; history directed PE with oral temperature and examination of injection site; concomitant medications; questionnaire; pharyngeal swab, blood sample given (20mL maximum); diary card-1 provided and instructions given as above

- *Month 4 (Day 121)-Visit 4 (window Day 107 to 135) and Month 6 (Day 181)-Visit 5 (window Day 153 to 209):* Diary card-1 reviewed; SAEs/MAAEs collected; concomitant medications; questionnaire; pharyngeal swab; blood draw; diary card-1 provided and instructions given as above

- *Month 12 (Day 361)-Visit 6 (window Day 333 to 389):* Diary card-1 reviewed; SAEs/MAAEs collected; concomitant medications; questionnaire; pharyngeal swab; blood draw; study vaccination (Menveo given to those subjects in rMenB+OMV and JEV groups); study termination.

Immunogenicity Assessments:

The immunogenicity of rMenB+OMV and Menveo were evaluated by measuring serum bactericidal activity using human complement (hSBA) on sera collected on Day 1 (pre-vaccination) and Months 2, 4, 6, and 12 for subjects in the '*immunogenicity subset'* only, ~20% of enrolled subjects (592 subjects). The primary measure of immunogenicity for subjects receiving rMenB+OMV was hSBA against meningococcal B (MenB) strains, including 3 serogroup B test (reference) strains: H44/76, 5/99, and NZ98/254 performed at ----------(b)(4)----------. Subject's receiving Menveo had hSBA testing done for serogroup Y; and for serogroup C for samples collected at baseline, Months 2, 6, and 12 months. In addition, a sample of 50 subjects who received Menveo had hSBA testing done for MenB strains. Testing of serogroup A or W was not done, as a substantial proportion of A or W carriage was not present in the study.

Safety Assessments:

- *Immediate post-vaccination*: subjects were observed for the 30 minute post-vaccination after each vaccination dose for signs and symptoms of anaphylaxis

- *Solicited Local, Systemic Reactions, Oral Temperature for 'immunogenicity subset' subjects only*: collected for 7 days post-vaccination (including day of vaccination); frequencies and percentages of subjects experiencing each reaction was presented based on symptom severity.
    - *Local injection site reactions*: pain, erythema, induration, and swelling. Severity grading scale: none (0mm), 1 to <10mm; 11 to ≤25mm; 26mm to ≤50mm; 51mm to ≤100mm; >100mm (severe local reactions)
    - *Systemic reactions*: chills, nausea, malaise, myalgia, arthralgia, headache, fever, and rash. Severity grading scale: 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.
    - *Temperature*: measured by oral route; severity grading scale: <38.0; 38.0-38.4; 38.5-38.9; 39.0-39.4; 39.5-39.9; ≥40.0; 40.5-40.9; ≥41, If fever (T≥38.0) persists beyond Day 7, then it was reported as an AE.

- *All Unsolicited Adverse Events/All prescription and antipyretic medications for 'immunogenicity subset' subjects only:* collected for 7 days post-vaccination (including day of vaccination),

- *Serious Adverse Events, Medically Attended AEs, AEs Leading to Withdrawal,* collected throughout the study

Reviewer Comment*: The applicant recorded study activities on the relevant electronic Case Report Form, a sample of which was reviewed and included the appropriate components. A Data Monitoring Committee was not utilized in this study.*

6.2.8 Study Endpoints and Criteria for Study Success

Reviewer Comment*: As mentioned above, the review of Study V72_29 will focus on the components which are relevant to the indication being sought under this BLA. The endpoints listed below pertain to the evaluation of immunogenicity and safety of two doses of rMenB+OMV vaccination in the study population. The study's primary endpoints pertaining to pharyngeal carriage rates were not reviewed.*

Post-Hoc Modified Immunogenicity Analyses:

- *the proportion of subjects with a ≥4-fold response (post-vaccination #2 compared to pre-vaccination #1) for each of 3 meningococcal B test strains, and*
- *the proportion of subjects with a hSBA response ≥the lower limit of quantitation (LLOQ) to all of the test strains (composite response)*

Immunogenicity Endpoint[21]

At 1 month, 3 months, 5 months, and 11 months post-dose 2 the hSBA immune responses against MenB test strains were analyzed using the cut-off hSBA ≥1:4, as per the threshold defined by the lab which conducted the assay.

21 hSBA titers at each visit were logarithmically transformed (base $_{10}$) and summarized by *N.meningitidis* serogroup B strain and vaccine group.

Safety Endpoint: (as described in Section 6.2.7 above)

- All subjects who received at least one vaccination dose, and provided some safety data were considered for the safety analyses.
- Safety variables assessed included, the
    - Safety population: all immediate reactions, SAEs, MAAEs, and AEs leading to withdrawal
    - 'Immunologic subset:' Solicited AEs and all AEs

6.2.9 Statistical Considerations & Statistical Analysis Plan

Reviewer Comment: *Hypothesis testing for the primary endpoint in this study evaluated the rate of pharyngeal carriage of virulent sequence types of N. meningitidis Group B one month after the 2nd dose. This analysis is not relevant to this application, and therefore is not presented. Safety testing is only descriptive.*

Missing Data:

The applicant handled missing data differently for safety and immunogenicity analyses as follows:

- Safety: Safety evaluations, included solicited and unsolicited adverse events were divided into discrete intervals. If observations were missing within a prespecified interval, then the following algorithm was applied:
    - If observations were missing for less than 20% of subjects (ie, without any AE records for the respective time interval), then no further action was necessary. The safety sets pertaining to the interval will be analyzed.
    - If observations were missing for 20% or more of subjects, the "missing mechanism" was to be analyzed with vaccine group as a categorical variable and newly created variable describing the missing information as dependent variable (1= AE record present; 0= AE record not present).
        - If the effect of the missing observation was
            - not significant ($p<0.05$), then 'missing as completely random' (MCAR) was to be assumed and no further action was required.
            - significant ($p>0.05\%$), then 'missing at random' (MAR) was to be assumed (missing mechanism was conditional on treatment group).

- Immunogenicity: Missing immunogenicity data were considered as missing completely at random (MCAR), therefore no imputation methods were used. Analyses of immunogenicity data were done on the FAS and PPS.

Significant Changes in the Conduct of the Study or Planned Analyses:

The final version of the protocol was Version 4.0, Amendment 3, dated 24 Aug 2011. The major changes made to the protocol were as follows:

- Addition of a dose of Menveo at the 12 month visit for subjects enrolled in the rMenB+OMV and control JEV groups,
- Exclusion of subjects who had a prior dose of JEV,
- Prior receipt of a meningococcal C or ACWY vaccine within 30 days of Visit 1,
- An interim analysis was added to support a regulatory submission,
- Subjects planning to travel to Japanese Encephalitis or meningococcal endemic areas during the 6 month period between Visit 5 and 6 were unblinded so that they could obtain the appropriate preventive vaccinations. These subjects were allowed to remain in the trial,

- The immunogenicity endpoint against MenB test (reference) strains was changed to ≥1:4 as per the threshold defined by the lab which was conducting the assay (b)(4). The protocol initially specified a cut-off of ≥1:5 as per the Novartis Serology laboratory.

  Reviewer Comment: *In Section 9.8 of the V72_29 CSR (Changes in the Conduct of the Study or Planned Analyses), the applicant states that subjects potentially traveling to Japanese Encephalitis or meningococcal endemic areas were unblinded between Visit 5 (Month 6) and Visit 6 (Month 12) in order to obtain the appropriate preventive vaccinations, if required. During the review cycle CBER requested clarification on this unblinding procedure prior to trial completion. The applicant submitted the following information response to the BLA under Amendment 0.22 on 10/30/2014:*
  - *Proportion of subjects across groups who were unblinded:*
    - *rMenB+OMV: 9 of 979 subjects*
    - *Menveo/Placebo: 9 of 988 subjects*
    - *JEV: 4 out of 987 subjects*
  - *Steps taken to reduce bias in the assessment of long-term safety:*
    - *The applicant states that the benefit of retaining these unblinded subjects was judged to be greater than the risk of bias that unblinding might have introduced during the safety review at the final Visit 6 (Month 12) for these subjects.*

  Based on the applicant's response, the proportion of subjects who were unblinded appears to have been low, and unlikely impacted study findings.

Changes to Study Conduct:

- 40 subjects at two sites (Site 5 and Site 7) were administered JEV that was not authorized for use by the applicant. No adverse safety findings were apparent. The appropriate ethics committee review and monitoring of all 10 sites was undertaken. The subjects who were affected were given written notification after unblinding that they may not be protected against JE if they were to travel to endemic areas.
- 12 subjects at 3 sites (Sites 1, 4, and 6) were not re-consented with the revised informed consent which included an update that those subjects randomized to the Menveo group would not receive this vaccination at the 12 month visit.

  Reviewer Comment*: The reviewer notes that none of these subjects were included in the immunogenicity subset analyses.*

6.2.10 Study Population and Disposition

The first subject was enrolled on 21 September 2010, and the last subject completed the study on 21 January 2012. A total of 2968 subjects were enrolled in the study, including 979 in the rMenB+OMV group; 988 in the Menveo group; and 987 in the control JEV group[22].

6.2.10.1 Populations Enrolled/Analyzed

Analysis Sets:

- *All Enrolled Population*: all subjects who have signed an informed consent, undergone screening procedures, and were randomized
- *Modified Intention-to-treat (MITT) Population*: all subjects in the enrolled population who actually received a study vaccination, and

22 There were 14 subjects who were not randomized

  - *For Immunogenicity Subset*: provided at least one evaluable blood sample after baseline and whose assay result was available for at least one serogroup
- *Per-Protocol Analysis Set (PPS):* A subset of subjects in the MITT pharyngeal carriage population or immunogenicity subset who correctly received the vaccine, and had no major protocol violations, and
  - *For Immunogenicity subset:* provided evaluable samples at the relevant time points (for subjects in the immunogenicity subset); and a major violation is one that had a significant impact on the immunogenicity result of the subject
- *Exposed Population:* all enrolled subjects who actually received a study vaccination
- *Safety Population*: all subjects in the Exposed Population who provided post vaccination safety data.

6.2.10.1.1 Demographics

The demographic characteristics for all subjects enrolled are shown in the following table:

Table 10: Study V72_29 Demographics Characteristics of All Enrolled Subjects

	rMenB+OMV N= 979	**Menveo/Placebo N=988**	**Ixiaro N=987**
% Female	516 (53%)	533 (54%)	547 (55%)
% Male	463 (47%)	455 (46%)	440 (45%)
Age –Mean (years)	19.9 ± 1.6	19.9±1.6	19.8±1.6
Racial origin:	(%)	(%)	(%)
-Asian	60 (6%)	49(5%)	52 (5%)
-Black, Non-Hispanic	19 (2%)	14 (1%)	19 (2%)
-White, Non-Hispanic	860 (88%)	876 (89%)	866 (88%)
-Hispanic	3 (<1%)	3(<1%)	3 (<1%)
-Other	37 (4%)	45(5%)	47 (5%)
Weight	69.66±13.22 kg	68.76±13.43	69.18±13.5 kg
Height	172.6±9.4	172.5±9.4	172.0±9.4

Source: Adapted from BLA 125546/0, V72_29 Clinical Study Report, Table 11.2-1 on p.147 of 8504. Menveo:MenACWY+CRM; *Placebo containing aluminum hydroxide. Ixiaro: Japanese Encephalitis Vaccine

Reviewer Comment:

The age range of all study participants was from 18-24 years of age, and the mean age for enrolled subjects was 19.9±1.6 years. There were more females enrolled, which was relatively consistent across groups. The large majority of subjects enrolled were Caucasian, ~88% of subjects, followed by Asian subjects (5%), and then Black subjects (2%). Other demographic characteristics were also similar across groups. The demographic profile of subjects enrolled in this study conducted in the U.K are different than that of overall demographic profile of US individuals 18-24 years of age.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The immunogenicity subset included all subjects who had received a vaccination, and had at least one evaluable sera post-vaccination sample. For this study, reactogenicity and immunogenicity data were only collected from the immunogenicity subset of subjects. Additionally, only subjects randomized to the immunogenicity subset had reactogenicity data collected. The following table provides an overview of the demographic characteristics of these subjects.

Table 11: Study V72_29 Demographic Characteristics of MITT-Immunogenicity Subset

	rMenB+OMV N= 192	**Menveo/Placebo N=192**	**Ixiaro N=197**
% Female	101(53%)	94 (49%)	111 (56%)
% Male	91 (47%)	98 (51%)	86 (44%)
Age –Mean (years)	20.2 ± 1.7	20.2±1.5	20.2±1.7
Racial origin:	(%)	(%)	(%)
-Asian	10 (5%)	11(6%)	11 (6%)
-Black, Non-Hispanic	3 (2%)	5 (3%)	2 (1%)
-White, Non-Hispanic	177 (92%)	165 (86%)	170 (86%)
-Hispanic	1 (<1%)	2(<1%)	1 (<1%)
-Other	1 (<1%)	9(5%)	13 (7%)
Weight	68.81±13.09 kg	68.63±14.43	67.54±13.64 kg
Height	172.7±9.3	173.6±10.1	171.7±9.7

Source: Adapted from BLA 125546/0, V72_29 Clinical Study Report, Table 11.2-2 on p.148 of 8504. Menveo®:MenACWY+CRM; *Placebo containing aluminum hydroxide. Ixiaro®: Japanese Encephalitis Vaccine

Reviewer Comment*: Compared to the demographic characteristics of 'all enrolled subjects', subjects in the 'immunogenicity subset' were slightly older, with a mean age of 20.2 years, but otherwise the two analyses populations were similar. The overall demographic characteristics were similar across groups; therefore randomization was adequate overall for the immunogenicity subset analysis population.*

6.2.10.1.3 Subject Disposition

There were 2968 subjects enrolled in the study, of which 14 were not randomized and 502 subjects withdrew early, leaving 2466 subjects (83% of all subjects) who completed the study. There were 592 subjects enrolled in the immunogenicity subset. The following table provides the number of subjects enrolled, vaccinated, and included in the analyses populations, in addition to the number of subjects discontinued for various cited reasons.

Table 12: Study V72_29 Disposition of Subjects-Enrolled Population

Population	**rMenB+OMV N= 979**	**Menveo/Placebo* N=988**	**Ixiaro N=987**	**Total N=2968**
Enrolled (N)	979	988	987	2968
Vaccinated Population*	974	984	985	2943
Completed Protocol	796 (81%)	844 (85%)	826 (84%)	2466 (83%)
Subjects Discontinued (due to)	183 (19%)	144 (15%)	161 (16%)	502 (17%)
-SAE	-	-	-	
-AE	11 (1%)	8 (<1%)	3 (<1%)	22(<1%)
-Protocol Deviation	5 (<1%)	5 (<1%)	6 (<1%)	17 (<1%)
-Lost to follow-up	124 (13%)	98 (10%)	123 (12%)	345 (12%)
-Withdrawal of consent	38 (4%)	31 (3%)	28 (3%)	99 (3%)
-Unable to classify	2 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
Vaccinated Population*	974 (99%)	984 (100%)	985 (100%)	2943
Safety Population	974 (99%)	984 (100%)	985 (100%)	2943 (99%)
Safety Subset-Solicited AEs	185 (19%)	176 (18%)	182 (18%)	543 (18%)
Enrolled-Immunogenicity Subset	196 (20%)	198 (20%)	198 (20%)	585 (20%)
MITT-Immunogenicity Subset	193 (20%)	194 (20%)	198 (20%)	585(20%)
PPS-Imm Subset- 1mo PD#1	161 (16%)	164 (17%)	167 (17%)	492 (17%)
PPS-Imm Subset- 1mo PD#2	151 (15%)	159 (16%)	150(15%)	460 (15%)

Source: Adapted from BLA 125546/0, V72_29 Clinical Study Report, Table 10.1-1 on p.134 of 8504; Table 14.1.1.1.
Menveo®:MenACWY+CRM; *Placebo containing aluminum hydroxide. Ixiaro®: Japanese Encephalitis Vaccine
N= enrolled; *randomized, and received at least vaccination #1 and included in safety population ('exposed'); For explanation of analyses populations see text in Section 6.2.10.1 above. PPS Imm Subset: per protocol population immunogenicity subset; PD#1 = post dose 1; PD#2= post dose 2.

There were 974 subjects who received at least one dose of rMenB+OMV, and there were 932 subjects who received 2 doses of rMenB+OMV, 1 month apart. The MITT immunogenicity subset included 193 subjects, while the PPS immunogenicity subsets included 161 subjects (1 mo PD#1); 151 subjects (1mo. PD#2); and 137 subjects (11 month PD#2).

***Reviewer Comment**:*

1. *The percentage of subjects who withdrew early from the study was similar across groups (15-19%), and the most frequent cited reason across groups was lost to follow-up.*
2. *Per CBER request,[23] the applicant clarified that there were 59 subjects excluded from the PPS-immunogenicity subset at 11 months after the 2nd dose. The leading reason for exclusion was that the 2nd vaccination was outside the time window. The demographic characteristics across groups were similar for this analysis.*

23 Source: BLA 125545/Am 0.25 (submitted 11/10/2014).

Protocol Deviations:
The PPS immunogenicity subset included all subjects in the MITT immunogenicity subset who correctly received the study vaccinations, provided evaluable serum samples within protocol-specified visit windows, and had no major protocol deviations. The following table provides a list of major protocol deviations across groups for the immunogenicity subset. The most frequently cited reason for a major protocol deviation was that the 2nd vaccination was out of the protocol-specified window.

Table 13: Study V72_29 Major Protocol Deviations-Immunogenicity Subset Population

	rMenB+OMV N= 192	**Menveo/Placebo* N=192**	**Ixiaro N=197**
Subjects with Major Protocol Deviation	74 (38%)	65 (33%)	73 (37%)
Protocol Deviation reason:			
-2nd vac. outside window	23 (12%)	21 (11%)	23 (12%)
-3rd vac. outside window	6 (3%)	0	11 (6%)
-blood draw outside window (for all blood draws: Visits 1-6)	44 (23%)*	34 (18%)	40 (20%)
-no blood draw (for all blood draws: Visits 1-6)	25(13%)**	27 (14%)	10 (5%)
-MenC given within 30 days of study start	5 (3%)	5 (3%)	7 (4%)
-no re-consent	2 (1%)	3(2%)	3(2%)
-no vaccination at all	3 (2%)	2 (1%)	0
-received excluded concomitant medication	0	2 (1%)	1 (<1%)
-vaccination prior to blood draw at Visit 1	1 (<1%)	0	0

Source: Adapted from BLA 125546/0, V72_29 Clinical Study Report, Table 10.2-2 on p.141 of 8504. Menveo®:MenACWY+CRM; *Placebo containing aluminum hydroxide.Ixiaro®-: Japanese Encephalitis Vaccine. By visit, the 3%-8% of subjects had blood draws outside of the appropriate visit windows. **By visit, 0-6% of subjects had no blood draw at any given visit.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses Supporting Accelerated Approval (Post-hoc)

As discussed in Section 5.1, CBER has selected specific hSBA measurements against three meningococcal serogroup B test strains (H44/76, 5/99, NZ98/254) as serologic markers likely to predict clinical benefit of rMenB+OMV vaccine in the context of accelerated approval. These hSBA measurements include the proportion of subjects with a ≥4-fold response after the 2nd dose for each of the 3 serogroup B test strains; and the proportion of subjects with hSBA response ≥ LLOQ to all test strains as a composite response.

Proportion of Subjects with ≥4-fold Response
The table below provides the percentage of subjects with a four-fold rise one month after the 2nd dose when measured against each of the meningococcal test strains for rMenB+OMV recipients based on the PPS population[24].

[24] The most common reason subjects were excluded from the PPS following the 2nd vaccination dose was because 2nd vaccination was outside the time window. The demographic characteristics of the rMenB+OMV group and Menveo/Placebo group in the PPS were similar.

Table 14: Study V72_29 Percentage of Subjects with ≥4-Fold Rise[a] One Month Post Dose-2, PPS

% [95%CI] of Subjects with ≥4-Fold Response	
Strain (Antigen)	**1 mo. PD#2**
H44/76 (fHbp)	78% [71, 85] N=148
5/99 (NadA)	94% [89,97] N=147
NZ98/254 (PorA P1.4)	67% [58,74] N=147

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/3/2014. Table corresponds to Table 3.2.3-1 of ISE submitted under BLA 125546/0. PPS- Per Protocol Analysis for immunogenicity subset analysis population. 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. Two doses were administered one month apart: (0,1) schedule. [a] Four-fold rise is defined as postvaccination hSBA ≥1:16 for subjects with prevaccination hSBA <1:4, a post vaccination titer at least 4-fold the LLOQ for subjects with prevaccination hSBA ≥1:4 but <LLOQ; and a postvaccination four-fold rise for subjects with pre-vaccination hSBA ≥LLOQ. Study V72_29: LLOQ is defined as 16 for strain H44/76; 8 for strain 5/99, and 16 for strain NZ98/254.

Reviewer Comment:

1. *The proportion of subjects with ≥4-fold rise in hSBA immune response was highest against 5/99 strain (94%), and lowest against NZ98/254 strain (67%).*

Proportion of Subjects with hSBA Response ≥ LLOQ to All Test Strains as a Composite Response

The percentage of subjects with hSBA response ≥ LLOQ at baseline and one month after the 2nd dose (1moPD#2) is provided in the table below for rMenB+OMV recipients.

Table 15: Study V72_29 Percentage of Subjects with hSBA Response ≥LLOQ[a] One Month Post Dose-2, PPS

	% [95%CI] of Subjects with hSBA ≥LLOQ	
Strain (Antigen)	**Baseline N=151**	**1 mo. PD#2 N=148**
H44/76 (fHbp)	45% [37,53]	100% [98,100]
5/99 (NadA)	48%[40,56]	99% [96,100]
NZ98/254 (PorA P1.4)	30% [23,38]	88% [81,93]

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/03/2014. Table corresponds to Table 3.2.1-1 of ISE submitted under BLA 125546/0. PPS-Per Protocol Analyses for immunogenicity subset analysis population. 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. Two doses were administered one month apart: (0,1) schedule. [a] Study V72_29: LLOQ is defined as 16 for strain H44/76; 8 for strain 5/99, and 16 for strain NZ98/254.

Reviewer Comment:

1. *The percentage of UK subjects with baseline hSBA titers ≥ LLOQ was 30%-48%, which is higher than was observed in the Canadian/Australian study at baseline (0-2%).*
2. *The percentage of subjects who achieved a hSBA response ≥ LLOQ one month after the 2nd dose was 99% to 100% for H44/76 and 5/99 strains, and 88% for NZ98/254 strain.*

Based on the PPS, the composite response for percentage of subjects [95% CI] with hSBA ≥ LLOQ to 3 out of 3 test strains by time point were as follows:

- Baseline(N=186): 24% [18,30]
- 1 month post dose-2 (N=147): 88% [82,93]
- 11 months post dose-2(N=136): 66% [58,72]

Reviewer Comment*:*

1. *The composite response for the percentage of subjects with hSBA response ≥ LLOQ 1 month after 2nd dose to 3 out of 3 test strains was 88%, and the response 11 months after the 2nd dose was 66%. As a comparison, 63% of subjects in the Canadian/Australian study generated this response 1 month after the 2nd dose to 3 out of 3 test strains. Of note, the proportion of subjects at baseline with a composite response (hSBA ≥ LLOQ to 3 out of 3 test strains) observed in the UK study was 23% compared with the baseline composite response in the Canadian/Australian study which was 0.*

6.2.11.2 Analyses of Study Immunogenicity Endpoints

Percentage of subjects with hSBA >1:4 – MITT Immunogenicity Subset:

The percentage of subjects with hSBA titer ≥1:4 to each *N.meningitidis* serogroup B test strain at 1 month, 3 months, 5 months, and 11 months post-dose 2 was evaluated by the applicant as one of the study's secondary objectives. The results [95% CI] are provided for each vaccine group by MenB strain at time points post dose-2 (PD#2) for the MITT Immunogenicity Subset in the table below.

Table 16: Study V72_29 Percentage of Subjects with hSBA ≥1:4 [95%CI] Against MenB Test Strains at Various Time Points Post Dose-2 -MITT Immunogenicity Subset

	rMenB+OMV N=193			**Menveo/Placebo* N=49**			**Control-JEV N=50**		
Strain:	*H44/76*	*5/99*	*NZ98/254*	*H44/76*	*5/99*	*NZ98/254*	*H44/76*	*5/99*	*NZ98/254*
Baseline	69% [62,75]	60% [53,67]	57% [50,64]	71% [57,83]	45% [31,60]	53% [38,67]	62% [47,75]	54% [39,68]	38% [25,53]
1 mo. PD#2	100% [98,100]	100% [98,100]	99% [97,100]	76% [60,87]	40% [26,56]	53% [38,68]	63% [47,76]	58% [43,72]	44% [25,59]
3 mo. PD#2	99% [97,100]	99% [97,100]	93% [88,96]	73% [56,85]	40% [25,57]	48% [32,64]	65% [50,79]	54% [39,69]	48% [33,63]
5 mo. PD#2	100% [98,100]	99% [97,100]	91% [85,94]	74% [59,86]	49% [33,65]	58% [42,73]	67% [51,80]	53% [38,68]	42% [28,58]
11 mo PD#2	95% [91,98]	97% [94,99]	85% [79,90]	76% [60,88]	51% [35,67]	66% [49,80]	70% [54,82]	63% [48,77]	43% (29,59]

Source: Adapted from BLA 125546/0, V72_29 Clinical Study Report, Table 11.4.1-26 on p.190 of 8504. MenB: meningococcal group B. PD#2: post dose-2. Menveo®:MenACWY+CRM; *Placebo containing aluminum hydroxide. Ixiaro®-: Japanese Encephalitis Vaccine.

Reviewer Comment: *The reviewer notes that 1:4 titer is below the LLOQ determined by review of the submitted validations. The 1:4 titer is considered the limit of detection (LOD), and while not considered quantitative, the baseline data show that the majority of subjects were seropositive, i.e., above the LOD (1:4 titer).*

6.2.11.3 Subpopulation Analyses

Please see Section 7.1.2 of this review memo for commentary on subpopulation analyses based on gender and racial origin differences of enrolled subjects.

6.2.11.4 Dropouts and/or Discontinuations

See Section 6.2.9 above for an explanation of how missing data were handled. Missing immunogenicity values were considered as missing completely at random, and therefore were not considered informative. Imputation methods were not used.

6.2.12 Safety Analyses

6.2.12.1 Methods

The Safety Population was comprised of 2943 subjects (99% of enrolled subjects): 974 subjects (99%) in rMenB+OMV group; 984 subjects (100%) in Menveo/placebo (aluminum hydroxide-saline) group; and 985 subjects (100%) in Control (JEV) group. As prespecified in the protocol, the Safety Subset Population for Solicited AEs included those subjects enrolled in the *immunogenicity subset*, as described in Section 6.2.7 above. This included ~18% of subjects across groups: 185 subjects (19%) in rMenB+OMV group; 176 subjects (18%) in Menveo/placebo group; and 182 subjects (18%) in the Control (JEV) group. There were 932 subjects who received 2 doses of rMenB+OMV, 1 month apart; and 956 subjects who received 1 dose of Menveo followed by placebo; and 947 subjects who received 2 doses of JEV.

Safety data collection included immediate AEs within 30 minutes of vaccination; solicited local/systemic AEs and all unsolicited AEs for 7 days post-vaccination; SAEs, MAAEs, and AEs leading to withdrawal throughout the study. A diary card was used to collect both solicited unsolicited AEs for the 7 day post-vaccination time period, and Memory Aide was provided to record SAEs, MAAEs, AEs, and prescription medications to treat these AEs. There were two types of diary cards given to subjects: 'diary card-1' to all subjects to collect SAES, MAAEs, and AEs leading to withdrawal; and 'diary card-2' to subjects in the immunogenicity subset to collect solicited AE safety data. Diary card-1 was given to each subject after vaccination, and collected one month later. Diary card-2 was given at each visit and reviewed at the subsequent visit, including at the last visit at Month 12.

6.2.12.2 Overview of Adverse Events

Solicited Adverse Events:

The majority of subjects in the rMenB+OMV group reported a solicited adverse event, including 98% of subjects after the 1st vaccination and 94% of subjects after the 2nd vaccination, which was higher than both comparator groups (77-79% after 1st, and 66-74% after 2nd). The rates of solicited local and systemic AEs by group were as follows by dose:

- rMenB+OMV: 1st (local 95% & systemic 85%); 2nd (local 90% & systemic 72%)
- Menveo/Placebo: 1st (local 62% & systemic 75%); 2nd (local 70% & systemic 50%)
- Control JEV: 1st (local 61% & systemic 61%); 2nd (local 51% & systemic 50%)

The most common local reaction for rMenB+OMV recipients was pain at the injection site, seen in 93% of subjects after the 1st dose and 88% of subjects after the 2nd dose. For both doses, the rates of severe pain were 8%. The rates of pain in the comparator group were lower, seen overall in 40-63% of subjects, with very few reports of severe pain. The most common systemic reaction for rMenB+OMV recipients was myalgia (75% after 1st & 69% after 2nd); headache (29% after 1st & 21% after 2nd); and malaise (18% after 1st & 22% after 2nd). The rates of these systemic AEs for the two comparator groups were 35-50% for myalgia; 11-30% for headache; and 11-20% for malaise. Severe myalgia was reported in 7% of rMenB+OMV subjects, though very few subjects reported severe symptoms for the other solicited AEs (1-2%). Fever (T≥38.0C) was reported in few subjects across groups as follows by dose:

- rMenB+OMV: 1% after 1st; 3% after 2nd
- Menveo/Placebo: 2% after 1st; 1% after 2nd
- Control JEV: 3% after 1st; 1% after 2nd

There were no reports of severe fever (T≥40C) in any group. The rates of prophylactic antipyretic use prior to the 1st dose were 4% in rMenB+OMV group and 1% in the two comparator groups. The rates of use increased prior to the 2nd dose as follows: 9% in rMenB+OMV group; 3% in

Menveo/Placebo group; and it remained the same in the Control JEV group (1%). The rates of therapeutic antipyretic use in the rMenB+OMV group were high 19-21% after either dose compared to 5-9% for the two comparator groups.

Reviewer Comment: *The most common solicited reactions reported for rMenB+OMV recipients were injection site pain and myalgia. Reports of fever were generally low for this study population, though ~20% of subjects reported use of therapeutic antipyretic after vaccination with rMenB+OMV. In addition the rates of prophylactic antipyretic use increased prior to the 2nd vaccination to 9%, compared to 4% prior to the 1st dose.*

Revised Solicited Adverse Event Rates:
As discussed in Section 5.1, the rates of solicited adverse events which exclude data that appeared to be obtained by subject recall several weeks or months after the 7-day post vaccination monitoring period when the source document appeared to be missing were assessed and provided in response to CBER request. The applicant notes that for this study the collection of solicited AEs data that were obtained by retrospective recall was neither explicitly prohibited nor permitted by study documents. The applicant estimates that the proportion of solicited AEs data not obtained from a source document was low (0.1%= 106/101,010). By dose, 3.62% of solicited AE data after the 1st dose of rMenB+OMV was considered to be obtained by retrospective recall, and 1.57% of solicited AE data after the 2nd dose was considered to be recalled. After the 1st dose of Menveo or Control-JEV, ~5% of solicited AE data were considered recalled, and after the 2nd dose of either comparator group ~1-2% of solicited AE data were considered recalled. The following table provides a revised set of reactogenicity rates for each group by dose.

Table 17: Study V72_29 Revised Reactogenicity Rates: % of Subjects with Any & *Severe* Solicited Local & Systemic Adverse Events for 7 Days Post-vaccination, by group & dose

		Dose 1			Dose 2		
		Bexsero	**Menveo**	**JEV**	**Bexsero**	**$Al(OH)_3$ placebo**	**JEV**
		N=183-190 *N=183-190*	N=182-186 *N=181-175*	N=187-190 *N=187-190*	N=177-183 *N=177-183*	N=171-175 *N=171-175*	N=177-180 *N=177-180*
Local Adverse Events							
Pain	Any	93	50	46	89	63	39
	Severe	*8*	*0*	*0*	*8*	*2*	*0*
Erythema	Any	39	25	25	40	19	19
	>100 mm	*1*	*0*	*0*	*2*	*0*	*0*
Induration	Any	26	14	7	23	11	6
	>100 mm	*1*	*0*	*0*	*0*	*0*	*0*
Swelling	Any	25	10	5	27	9	6
	>100 mm	*1*	*0*	*0*	*0*	*1*	*0*
Systemic Adverse Events							
Malaise	Any	17	15	20	22	11	13
	Severe	*1*	*1*	*2*	*2*	*1*	*1*
Nausea	Any	13	10	7	10	5	7
	Severe	*1*	*0*	*1*	*1*	*0*	*1*
Myalgia	Any	75	42	50	70	47	36
	Severe	*6*	*1*	*2*	*7*	*1*	*0*
Arthralgia	Any	12	8	10	13	9	8
	Severe	*1*	*1*	*0*	*1*	*1*	*0*
Headache	Any	28	25	30	21	11	23
	Severe	*1*	*0*	*1*	*2*	*1*	*2*
Fever	≥38°C	1	2	3	2	1	1
	38.0-38.9°C	1	2	3	2	1	1
	39.0-39.9°C	0	0	0	1	0	0
	≥40°C	*0*	*0*	*0*	*0*	*0*	*0*

Source: Adapted from BLA 125546/0.21 (Information Amendment-Safety Data submitted 10/23/2014) Table 6-2.
$Al(OH)_3$ placebo: placebo contained aluminum hydroxide

***Reviewer Comment**: The rates of reported events listed above in the revised reactogenicity rates table for Study V72_29 are very similar to the rates provided in the CSR. The revised analysis did not significantly impact the overall solicited AE safety data findings for this study.*

Unsolicited Adverse Events
Based on the safety population, any difference noted in the rates of unsolicited adverse events during the initial 7-day post-vaccination time period appeared to dissipate over the duration of the study.

- 40% (386 subjects) of rMenB+OMV group
- 35% (344 subjects) of Menveo group
- 39% (380 subjects) of the Control (JEV) group

- 7-day post-vaccination time period:
  - 12% (121 subjects) of rMenB+OMV group
  - 7% (70 subjects) of Menveo group
  - 9% (90 subjects) of Control (JEV) group

While the overall rates of AEs that were reported as possibly related to vaccination were generally low, 7% of subjects in the rMenB+OMV group attributed an AE as possibly related to vaccination, compared to 4% in each of the other groups.

By MedRA preferred term, the most common AEs seen across groups were tonsillitis (3% across groups); urinary tract infections (2-3% across groups); and lower respiratory tract infections (1-2 % across groups), none of these were reported as severe.

The most common system organ class (SOC) cited for unsolicited AEs was within the 'Infections and Infestations,' seen in 17-18% of all subjects. Only ~1% of subjects in each group reported these AEs as at least possibly related to vaccination. Yet, 56 (6%) subjects in the rMenB+OMV group reported an AE classified under the SOC 'General Disorders and Administration Site Conditions,' of which 41 considered the AE as at least possibly related to vaccination. This is in contrast to the comparator groups, in which 3% of subjects (27 in the Menveo group; and 29 in the Control group) reported an AE in this category.

6.2.12.3 Deaths

No deaths were reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events

A serious adverse event was reported as follows in each group:

- 3% (31 subjects) of rMenB+OMV group
- 3% (26 subjects) of Menveo group
- 2% (20 subjects) of Control (JEV) group

The majority of SAEs in the rMenB+OMV were classified under the SOC of "Infections & Infestations" or "Injury & Poisoning." There was one SAE involving an ectopic pregnancy in a subject who received rMenB+OMV, which is discussed below in Section 6.12.5. There were 3 SAEs in the rMenB+OMV group that were considered at least possibly related to vaccination and included the following cases:

- Subject #09/0147: Acute thyroiditis. 20 year old female with a past medical history significant for weight loss, headaches, and exhaustion, and multiple food allergies reported 'non-serious' flu like symptoms 18 days after 1st vaccination with rMenB+OMV, and was treated with unspecified analgesics. A few days later she was hospitalized with a diagnosis of acute thyroiditis and subsequently withdrawn early from the study and did not receive her 2nd vaccination dose. In the opinion of the investigator, the SAE was considered probably related to study vaccination.
- Subject# 02/00248: Tremor. 20 years old male with no significant past medical history developed fine tremor 18 days after receiving the 1st dose of rMenB+OMV that was

diagnosed as tremors of moderate intensity by his general practitioner ~2 weeks later. No treatment was given, and the subject was given the 2nd dose of rMenB+OMV one week later without worsening of symptoms. This adverse event was considered a SAE by the PI because it resulted in persistent or significant disability at the time of last report, and was considered by the investigator to be possibly related to vaccination.

- Subject#07/0067: Dyspnea. 21 years old female with a past medical history significant for polycystic ovary syndrome developed non-serious paresthesia of both feet up to the knees on the day of 1st vaccination with rMenB+OMV. The next day, she developed chest pain/discomfort and shortness of breath, and was hospitalized. Her vital signs, physical exam, X-Ray, ECG, and complete blood count were reported as normal, and she was diagnosed with dyspnea of mild intensity and discharged the following day without any specific treatment. The symptoms continued and a subsequent full work-up was also negative. Her symptoms resolved 6 days from onset without specific treatment. The subject was withdrawn from the study due to these events. The investigator considered the SAE as possibly related to vaccination.

The following serious adverse event was not considered related to vaccination:

- Subject #08/0110: Appendicitis: 22 year old male developed appendicitis symptoms 15 days after the 2nd rMenB+OMV dose, which required hospitalization for appendectomy.. The subject recovered, and the investigator did not consider this AE related to vaccination.

***Reviewer Comment**:*

1. *Based on the narrative provided, Subject #09/0147 had weight loss and fatigue prior to vaccination, which are common symptoms associated with thyroid disease (thyrotoxicosis or hyperthyroidism). Though it is not possible to completely rule out an association with vaccination, it is unlikely that rMenB+OMV vaccination is causally associated with the onset of this subject's thyroid disease when considering her past medical history.*
2. *Subject #02/00248 developed tremors 18 days after the 1st vaccination, which did not worsen after receiving her 2nd dose. In the opinion of this reviewer, it is unlikely that there is a causal relationship with rMenB+OMV vaccination.*
3. *Subject#07/0067 developed dyspnea symptoms closely following vaccination. Yet subsequent clinical, radiologic, and laboratory evaluations did not document any abnormal findings and no treatments were administered, suggesting an unclear clinical diagnosis, and making causation of such symptoms difficult to attribute to vaccination. Therefore, in the opinion of this reviewer it is unlikely that this SAE is related to vaccination.*
4. *There were a total of 5 cases of appendicitis reported in this study, including 1 case observed in the rMenB+OMV group; 3 cases reported in the Menveo group; and 1 case reported in the JEV group. Based on a comparison of the rates of appendicitis across study groups, the rate observed in the rMenB+OMV is not elevated. The reviewer does not consider the case of appendicitis in the rMenB+OMV recipient to be related to vaccination.*

6.2.12.5 Adverse Events of Special Interest (AESI)

The following 3 subjects randomized to the rMenB+OMV group reported pregnancies during the study:

- Subject #09/0014 (rMenB+OMV): Ectopic Pregnancy/SAE. 18 yo female had received two doses of rMenB+OMV, and reported painless vaginal bleeding 57 days after her last dose. Symptoms continued for 25 days at which time she was hospitalized, and determined to have an ectopic pregnancy requiring surgical partial removal of her right

fallopian tube. The subject completely recovered, and this SAE was not considered related to vaccination by the investigator. The subject did not receive any further vaccinations.

- Subject #08/0045 (rMenB+OMV): Pregnancy. 19 yo female had received two doses of rMenB+OMV. Pregnancy was confirmed, and the subject had a therapeutic abortion.
- Subject 06/0249: Pregnancy. 23 yo female received one dose of rMenB+OMV (12/14/2010). The subject confirmed a pregnancy on 12/29/2010, and received no further vaccinations as the pregnancy was considered a protocol violation. The subject delivered a single baby on ---(b)(6)---.

Reviewer Comment: *There were no reported congenital malformations or anomalies for this study. For subject #09/0014, it is unclear if the ectopic pregnancy was related to vaccination.*

Please see Section 8 for an overview of AESI across all studies.

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

There were 26 subjects who were prematurely withdrawn from the study due to an AE as follows:

- 12 subjects in rMenB+OMV group (1%)
  - AEs considered probably/possibly related to vaccination:
    - Subject #07/0033: injection site rash on day of 1st vaccination, recovered
    - Subject #07/0291: urticarial 9 days after 1st vaccination, recovered
    - Subject #07/0342: muscular weakness 29 days after 1st vaccination, AE persisted
    - Subject #08/0209: arm swelling/pain on day of 1st vaccination, recovered
    - Subject #07/0067: dyspnea/paraesthesia (see SAE section above), beginning within one day of the first vaccination, recovered
    - Subject #09/0147: acute thyroiditis (see SAE section above) 18 days after 1st vaccination, SAE persisted
- 9 subjects in the Menveo group (1%):
  - AEs considered probably/possibly related to vaccination:
    - Subject #02/0137: chills/headache/fever on day of 1st vaccination, recovered
    - Subject #05/0116: injection site reaction (swelling/pain) on day of 1st vaccination, recovered
    - Subject #07/0018: vertigo 8 days after 1st vaccination, recovered
    - Subject #07/0044: urticarial 6 days after 1st vaccination, recovered
    - Subject#07/0325: mygalgia/pruritus/rash on day of 1st vaccination, recovered
    - Subject#08/0030: headache/blurred vision 3 days after 1st vaccination, headache resolved, though blurred vision resolution is unknown
- 5 subjects in the Control (JEV) group (1%):
  - AEs considered probably/possibly related to vaccination:
    - Subject# 05/0112: asthma, 45 days after 2nd vaccination, recovered
    - Subject# 07/0034: trigeminal neuralgia 2 days after 1st vaccination, recovered
    - Subject#10/0003: migraine 2 days after 1st vaccination, recovered

Reviewer Comment: *The percentages of subjects in each group with withdrawals due to an AE were similar, and an equal number of subjects (6 subjects/group) in the rMenB+OMV and Menveo groups had an AE that was considered possibly/probably related to vaccination. The majority of these in the rMenB+OMV group were related to injection site pain/rash/swelling.*

6.2.13 Study Summary and Conclusions

Study V72_29 was designed based on the anticipated high rates of meningococcal carriage in university students in the UK 18-24 years of age. The applicant evaluated two doses of rMenB+OMV administered one month apart, compared to two active control groups: placebo/Menveo and JEV. In the context of accelerated approval, only immunogenicity and safety data through 12 months were evaluated.

Based on the modified immunogenicity hSBA analyses, the percentage of rMenB+OMV recipients 1 month after the 2nd dose with at least a 4-fold response (rise) in hSBA titers when compared to baseline was 94% against 5/99 strain; 79% against H44/76 strain; and 67% against NZ98/254 strain. The composite response for the percentage of subjects with hSBA response ≥LLOQ 1 month after the 2nd dose to 3 out of 3 test strains was 88%, and the response 11 months after the 2nd dose was 66%. The immune response generated in this study supports effectiveness of rMenB+OMV in young adults 18 years through 24 years of age under the accelerated approval regulations. The reviewer recommends that hSBA titers from this study conducted in individuals 18 through 24 years of age be included in labeling to provide data on young adults 18 through 25 years of age not represented in the Canadian/Australian study. The relatively high response rates observed in the UK study are likely more representative of populations with similar characteristics, including higher baseline titers and an older population.

Common solicited reactions include solicited injection site pain (89-93%) and myalgia (70-75%) which were seen at higher rates than the two comparator groups. The rates of severe pain and myalgia were 6-8% across doses. The rates of unsolicited adverse events in the 1st week after any vaccination were higher in the rMenB+OMV group, but appeared to be more similar across groups throughout the duration of the study. One reported serious adverse event of acute thyroiditis was considered by the reviewer to not be causally related to vaccination. The overall safety profile of this vaccine does not demonstrate any serious safety concerns following vaccination.

6.3 Trial #3: Study V72P10 and V72P10E1

Primary Study V72P10: A Phase 2b/3, Multi-Center, Observer-Blind, Controlled Study of the Safety, Tolerability and Immunogenicity of Meningococcal B Recombinant Vaccine Administered to Healthy Adolescents Aged 11-17 years According to Different Vaccination Schedules.

Extension Study V72P10E1: A Phase 2b/3, Multi-Center, Extension Study of V72P10 to Assess Antibody Persistence at 18 Months after the Completion of the Vaccination Course in Study V72P10

Reviewer Comment:

1. *The review of the primary study will focus on the safety and immunogenicity of 2-dose regimens, though safety data pertaining to unsolicited AEs and SAEs across all groups for the entire 12 month study period will be included. As part of this BLA submission, the applicant has included Extension Study V72P10E1, which includes antibody persistence*

data following the last dose of rMenB+OMV evaluated in Study V72P10. The reviewer will only present relevant antibody persistence data from the extension study, and notes that the time interval after the last vaccination varies between groups from 18 months to 24 months, thus making direct comparisons across study groups difficult.

6.3.1 Objectives

Primary Study V72P10:

- To assess the immunogenicity, safety and tolerability of one, two, or three doses of rMenB+OMV in healthy adolescents, by evaluation of serum bactericidal activity using human complement (hSBA) response at one month after the last rMenB+OMV dose.

Extension Study V72P10E:

- To explore antibody persistence at 18 months after the completion of the vaccination course in subjects enrolled in the V72P10 study.

6.3.2 Design Overview

Study V72P10 is an observer-blind, multi-center, randomized, partially placebo-controlled trial in adolescents between the ages of 11 and 17 years divided into two parts. The 1st part of the study was placebo (aluminum hydroxide-saline) controlled through Month 6, and included 5 treatment groups as follows:

Study Groups through Month 2[25] (N=#enrolled):

- Group 1 (1 dose): Day 0-dose 1(N=375)
- Group 2 (2 doses): Day 0-dose 1; Month 1-dose 2 (N=375)
- Group 3 (2 doses): Day 0-dose 1; Month 2-dose 2 (N=380)
- Group 4 (3 doses): Day 0-dose 1; Month 1-dose 2; Month 2-dose 3 (N= 373)
- Group 5 (Placebo): Day 0-placebo; Month 1-placebo; Month 2-placebo (N=128)

In the 2nd part of the study from Month 6 through Month 12 (study termination), there are 8 treatment groups without a placebo control group. The above mentioned groups are subdivided based on the administration of an additional dose of rMenB+OMV at Month 6 to a subset of subjects; including to all subjects in the placebo group (Group 5). As a result, multiple 3-dose schedules are evaluated, in addition to a 2-dose schedule separated by six months.

Study Groups through Month 12 (N=#enrolled):

- Group 1a: Day 0-dose 1; Month 6-dose 2 (N=128)
- Group 1b: Day 0-dose 1; Month 6-placebo (N=247)
- Group 2a: Day 0-dose 1; Month 1-dose 2; Month 6-dose 3 (N=128)
- Group 2b: Day 0-dose 1; Month 1-dose 2; Month 6-placebo (N=247)
- Group 3a: Day 0-dose 1; Month 2-dose 2; Month 6-dose 3 (N=127)
- Group 3b: Day 0-dose 1; Month 2-dose 2; Month 6-placebo (N=253)
- Group 4: Day 0-dose 1; Month 1-dose 2; Month 2-dose 3; Month 6-placebo (N=373)
- Group 5a: Day 0-placebo; Month 1-placebo; Month 2-placebo; Month 6-dose 1 (N=119)

Reviewer Comment:

25 In Groups 1-4: At the Month 1 or 2 Visit when rMenB+OMV dose is not given, then placebo control is administered.

1. *At the Month 6 visit (Visit 5), 119 of the 128 subjects who had received placebo on Day 0 received rMenB+OMV. Therefore, for Visits 1-4 there were 128 control subjects, and from visits 1-7 there were 0 control subjects.*
2. *The reviewer will evaluate the immunogenicity data and solicited safety data for the two dose regimens administered to subjects in Groups 2, 3, and 4.*

V72P10E1 Study was a Phase 2b/3, open-label, multicenter extension study of Study V72P10 conducted in healthy adolescents between the ages of 13 to 19 years of age who had completed a vaccination course in the parent study. The purpose of the study was to assess antibody persistence at 18 months after the last dose of either placebo or rMenB+OMV at Month 6. The study enrolled a new group consisting of 150 vaccine-naïve subjects. Vaccine naïve is defined as those subjects who had never received rMenB+OMV or other experimental MenB vaccines. Study activities included a single study visit for the collection of 15 mL of blood. No vaccinations were given during the study, though subjects were offered outside of the study period, a dose of hepatitis A vaccine if they had not previously received it.

Reviewer Comment:

1. *The reviewer notes that subjects in V72P10 Extension Study, who were previously enrolled in the parent study, retained the same unique 6-digit number, while naïve controls were assigned new 6-digit numbers with the 3rd digit assignment of "6", indicating 'naïve-control' status. During the review cycle, CBER requested for clarification on whether laboratory personnel performing the hSBA assays for the Extension Study were blinded to the identification codes. The applicant responded to this Information Request under Amendment 0.22 (10/30/2014) to the BLA. The samples were centrally received by the applicant in ----------(b)(4)----------) for registration and aliquoting. These sample aliquots with the original label code were then sent in boxes to ----------(b)(4)---------- for testing. The applicant states that though the laboratory personnel were not blinded to the identification codes, the operational procedures followed for testing did not include any information pertaining to the sample label codes, and that testing occured in a randomized fashion determined by how samples were sent by (b)(4). Based on this response, laboratory personnel appear to have been blinded to sample group assignment.*

6.3.3 Population

Subjects were eligible for participation in the study if they were healthy 11-17 years old and were able to given written assent and whose parents gave written informed consent, and were able to attend all scheduled visits. Subjects were excluded for participation if they had a history serogroup B meningococcal vaccination, suspected or confirmed *N. meningitidis* disease, chronic or progressive disease, impairment of immunity (due to treatment or underlying condition), severe allergic reactions after prior vaccinations or hypersensitivity to any vaccine component, and/or any condition which was considered by the investigator to interfere with the evaluation of the study objectives. In addition, subjects were excluded if they had contact with individual with laboratory confirmed case of *N. meningitidis* within 60 days (of enrollment); significant illness and/or fever (temperature measured by axillary route of $\geq$38.0C) within 7 days; antibiotics within 6 days; pregnancy/nursing mothers; females not using acceptable method of birth control for 2 months prior to study entry through the 7 month duration of the study; receipt of blood or blood products within prior 90 days; receipt of any other vaccine within 30 days prior (60 days for live viral vaccines, 14 days for influenza vaccines); participation in another clinical trial within prior 90 days, or during study; and/or family/household members of staff.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The study evaluated rMenB +OMV versus a placebo control group.

1. rMenB+OMV: please see Section 6.1.4 of this review for vaccine description;
    - Lot number: X38D27N1
    - Dose: 0.5mL in pre-filled syringe, intramuscular (IM) in deltoid region of non-dominant arm
2. Placebo:
    - Lots number: X38D23N1
    - Dose: 0.5mL in pre-filled syringe, intramuscular (IM) in deltoid region of non-dominant arm
    - Each dose contained the following
        - Aluminum hydroxide: 1.5mg
        - Sodium Chloride: 3.12mg
        - Sucrose: 10mg
        - Histidine: 10mM (0.776 mg)
        - Water for injection (up to 0.5mL)

6.3.5 Directions for Use

See above.

6.3.6 Sites and Centers

The primary study was conducted in Chile at 10 sites as follows (N=total subjects enrolled) by Principal Investigator:

Dr. Maria Elena Santolaya:

- Site 11: Complejo Educacional Eduardo Cuevas Valdes, Santiago de Chile (N=182)
- Site 12*: Colegio San Jose De Lo Barnechea, Santiago de Chile (N=132)
- Site 13*: Centro de Salud Lo Barnechea, Santiago de Chile (N=168)
- Site 14: Colegio Parroguial Santa Rosa de Lo Barnechea, Santiago de Chile (N=181)
- Site 15: Liceo Carmela Carvajal de Prat, Santiago de Chile (N=202)
  **Subjects enrolled at Site 12 were transferred to Site 14; and those enrolled at Site 13 were transferred to Site 11 during the course of the study. Data from the Sites 12 and 13 were analyzed as part of the latter sites.*

Dr. Miguel O-Ryan:

- Site 41: Colegio Antonio Hermida Fabres, Santiago de Chile (N=181)
- Site 42: Centro Educacional Eduardo de La Barra, Santiago de Chile (N=170)
- Site 43: Liceo Jose Victorino Lastarria, Santiago de Chile (N=191)

Dr. Alma Munoz:

- Site 51: Centro para Vacunas en Desarrollo, Santiago de Chile (N=112)

Dr. Rodrigo Vergara:

- Site 61: Universidad de Valparasio, Valparaiso (N=112)

Extension Study V72P10E1 was conducted at the previously used sites listed in the parent study, and new sites. Due to logistical reasons some of the subjects from the parent study were not enrolled at the same study site in the extension study, though the PI was the same. The sites were as follows:

Dr. Maria Elena Santalaya

- Site 16: Hospital Luis Calvo Mackenna, Santiago de Chile (N=190)
- Site 17: Centro de Salud Lo Barnechea, Santiago de Chile (N=257)

Dr. Miguel O'Ryan
- Site 04: Microbiology and Micology Prog Faculty Medicine University of Chile, Santiago de Chile (N=34)
- Site 43: Liceo Jose Victorino Lastarria, Santiago de Chile (N=242)
-

Dr. Alma Munoz
- Site 51: Centro para Vacuna en Desarrollo, Santiago de Chile (N=46)

Dr. Rodrigo Vergara
- Site 61: Universidad de Valpraiso, Santiago de Chile (N=48)

6.3.7 Surveillance/Monitoring

Schedule of Events: The following list includes the scheduled visits/telephone contacts during the study.

- *Day 1-Visit 1:* Informed Consent; medical history; review of eligibility criteria; history directed physical examination with blood pressure, pulse, and heart/lung examination, temperature and urine pregnancy test; allocation of subject number; baseline blood sample given (15mL maximum); vaccination by unblinded vaccine administrator; 30 minutes safety observation; 'Diary Card A' provided and instruction on how to monitor solicited symptoms, including recording of axillary temperatures (thermometer provided).

- *Day 3-Telephone Call (window Day 2-6):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian on how to record adverse events/concomitant medications on diary card.

- *Month 1 (Day 31)-Visit 2 (window 27-38 days):* 'Diary Card A' collected/reviewed, history, brief physical assessment, determine ongoing eligibility; urine pregnancy test; blood sample (15mL); study vaccination by unblinded vaccine administrator, 30 minute safety observation, 'Diary Card A' provided and instructions given as above

- *Day 34-Telephone Call (window Day 33-37):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian on how to record adverse events/concomitant medications on diary card.

- *Month 2 (Day 61)-Visit 3 (window Day 57-68):* 'Diary Card A' collected/reviewed, history, brief physical assessment, determine ongoing eligibility; urine pregnancy test; blood sample (15mL); study vaccination by unblinded vaccine administrator, 30 minute safety observation, 'Diary Card A' provided and instructions given as above

- *Day 64-Telephone Call (window Day 63-67*): Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian on how to record adverse events/concomitant medications on diary card.

- *Month 3 (Day 91)-Visit 4 (window Day 87-98):* 'Diary Card A' collected/reviewed; blood sample (15mL); 'Diary Card B' provided to monitor MAAEs/SAEs, and concomitant medications, and instructions given as above

- *Month 6 (Day 181)-Visit 5 (window Day 167-195):* 'Diary Card B' collected/reviewed, history, brief physical assessment, determine ongoing eligibility; urine pregnancy test; blood

sample (15mL); study vaccination by unblinded vaccine administrator; 30 minute safety observation; 'Diary Card A' provided and instructions given as above

- *Month 7 (Day 211)-Visit 6 (window Day 207-218):* 'Diary Card A' collected/reviewed; assess all AEs/SAEs, and concomitant medications; blood sample (15mL); 'follow-up diary' card provided and instructions given as above.

- *Month 12 (Day 361)-Visit 12 (window Day 354-375):* Physical examination; 'Follow-up Diary Card' collected/reviewed; assess AEs/SAEs, and concomitant medications; study termination.

Immunogenicity Assessments:

Sera were collected for hSBA testing which was performed at the Meningococcal Reference Unit of the ----------(b)(4)----------. Sera was collected from subjects at Day 1, and Months 1, 2,3, 6, and 7.

Safety Assessments:

- *Immediate post-vaccination*: subjects were observed for the 30 minute post-vaccination after each vaccination dose.

- *Solicited Local, Systemic Reactions, Axillary Temperature*: collected for 7 days post-vaccination (including day of vaccination); frequencies and percentages of subjects experiencing each reaction was presented based on symptom severity.
    - *Local injection site reactions*: pain, erythema, induration, and swelling. Severity grading scale: none (0mm), >0-10mm, >10-25mm, >25-50mm, >50-100mm, >100mm.
    - *Systemic reactions*: nausea, malaise, myalgia, arthralgia, headache. Severity grading scale: none, mild, moderate, and severe.
    - *Temperature*: measured by axillary route. Severity grading scale: <38.0; 38.0-38.4; 38.5-38.9; 39.0-39.9; ≥40.0.

- *All Unsolicited Adverse Events:* collected for 7 days post-vaccination (including day of vaccination), though all AEs regardless of severity were monitored until resolved. Severity graded based on limitation of normal daily activity as follows:
    - Mild-no limitation;
    - Moderate-some limitation
    - Severe-unable to perform

- *Serious Adverse Events, Medically Attended AEs, AEs Leading to Withdrawal, Medications*: collected throughout the study, including all prescription medications and all antipyretic over the counter medications.

- *Safety Monitoring following Subject Withdrawal*: For subjects who withdrew from the study and whose consent had not been withdrawn, all efforts were made to collect safety information through 6 months after the last study vaccination using the follow-up diary cards. If the diary card was not brought to or sent to the clinic, then the safety information was collected by telephone. In the CRF the source of the safety data (diary card or telephone contact) was documented in the 'comments' section of the CRF. If consent was withdrawn, then safety follow-up information was not collected. Withdrawn subjects were not replaced. Adverse events leading to withdrawal were documented in the appropriate CRF.

Data Monitoring Committee (DMC): an independent, external DMC was used to monitor safety data at scheduled assessments. The DMC was to convene for any fatal SAE or possibly related SAE within 5 days of notification, and to then make an overall assessment on whether the study should be halted.

6.3.8 Study Endpoints and Criteria for Study Success

The main analyses for Primary Study V72P10 was performed on immunogenicity and safety data pertaining to the primary vaccinations through Month 3 (Visit 4) for the 1st part of the study. For the 2nd part of the study, the applicant performed follow-up analyses following the additional vaccination dose at Month 6 and subsequent safety follow-up through Month 12.

> ***Reviewer Comment:*** *The reviewer will present data primarily pertaining to the evaluation of a 2-dose series.*

Post-Hoc Modified Immunogenicity Analyses:

- the proportion of subjects with a ≥4-fold response (post-vaccination #2 compared to pre-vaccination #1) for each of 3 meningococcal B test strains, and
- the proportion of subjects with a hSBA response ≥the lower limit of quantitation (LLOQ) to all of the test strains (composite response)

Immunogenicity Endpoints:
For each meningococcal B test (reference) strain evaluated (H44/76, 5/99, and NZ98/254), the following was evaluated at baseline, Months 1, 2, and 3 for the 1st part of the study; and at Months 6 and 7 for the 2nd part of the study:

- percentage of subjects with a titer ≥1:4; ≥1:8

*Safety Endpoints: (*as described in Section 6.3.7 above)

- All subjects who received at least one vaccination dose, and provided some safety data were considered for the safety analyses.
- Safety variables assessed included
  - Local and systemic solicited reactions during the 7 days following each injection, and by severity, and by group
  - All immediate reactions, SAEs, MAAEs, and AEs leading to withdrawal

The main analysis for Extension Study V72P10E1 was the percentage of subjects hSBA titers ≥1:4 at 18 months after the Month 6 visit in Study V72P10. Therefore the time interval from the last vaccination ranged from ~18 months to 24 months.

> ***Reviewer Comment:*** *The modified immunogenicity endpoints used to assess effectiveness, including the proportion of subjects with a ≥4-fold rise one month post 2nd-vaccination using revised LLOQ criteria were not applied to this Extension Study. Therefore the antibody persistence data from this study will be reported but will not be used to demonstrate long-term effectiveness of the vaccine.*

6.3.9 Statistical Considerations & Statistical Analysis Plan

> ***Reviewer Comment****: Hypothesis testing was not pre-specified by the applicant*.

Significant Changes in the Conduct of the Study or Planned Analyses:

The final version of the protocol was Version 7.0, dated 13 April 2010. There were 5 protocol amendments to the original protocol which was initially issued in November 2007. The major changes to the protocol include the following:

- Establishment of an external safety Data Monitoring Committee (DMC) with a role to provide safety oversight, including halting the study if needed based on review of SAEs and accumulating safety data (Am 1, July 2008)
- Monitoring of medically attended fever for 7 days after vaccination; and prophylactic use of analgesics and antipyretics (Am 2, Aug. 2008). Of note: as this change was implemented after site training had occurred, the information provided in the BLA was insufficient to distinguish prophylactic use from therapeutic use of analgesics/antipyretics in the data presented.
- A final study visit replaced a final study phone contact to increase the reliability of safety data monitoring following the 6 month dose vaccination (Am 2, Aug. 2008)
- Details of safety follow-up after a subject withdraws were explained (Am 3, Sept. 2009)

6.3.10 Study Population and Disposition

The first subject was enrolled on 05 June 2008, and the last subject completed the study on 16 December 2010. A total of 1622 subjects received at least one dose of rMenB+OMV in this study.

6.3.10.1 Populations Enrolled/Analyzed

Analysis Sets:

- *All Enrolled Population*: all subjects who were enrolled in this study, (not necessarily randomized). No analyses used this population.
- *Full Analysis Set (FAS)/Modified Intention-to-treat (MITT) Population, Immunogenicity*: all subjects in the enrolled population who actually received a study vaccination, and provided one evaluable serum sample after baseline. Subjects were analyzed as randomized in the ITT analysis.
- *Per-Protocol Analysis Set (PPS), Immunogenicity:* A subset of subjects in the FAS/MITT population who correctly received all vaccine doses; and provided evaluable serum samples at the relevant time points, and had no major protocol violations as defined prior to unblinding.
- *Exposed Population:* all enrolled subjects who actually received a study vaccination
- *Safety Population*: all subjects who received study vaccination and provided post-baseline safety data.

Reviewer Comment*: The applicant defines a major protocol deviation as a deviation that had a significant impact on the immunogenicity result of the study, and was defined prior to unblinding.*

As mentioned above, the study design included primary doses administered on Day 0, Month 1 and/or Month 2. The applicant's main immunogenicity analysis was through one month after the last primary dose, ie Visit 4 sera collection at Month 3. In addition, the applicant main safety analysis was until Visit 4. The follow-up analysis of the study included immunogenicity data collected after the additional dose administered at Month 6; and safety data collected 6 months after each subjects last dose of either rMenB+OMV or placebo.

Reviewer Comment*: The reviewer will evaluate immunogenicity data from enrollment through one month after the 2nd dose (administered at either Month 1 or Month 2); and safety data through the entire study period.*

6.3.10.1.1 Demographics

The demographic characteristics of those subjects who received 2 doses of rMenB+OMV at least 1 month apart (Groups 2 and 3) compared to the placebo control group (Group 5) prior to the Month 6 vaccination are shown in the following table.

Table 18: Study V72P10 Demographics for 2-Dose Vaccination Schedules Compared to Placebo -Enrolled Population

	Group 2 (0,1mo) N=375	**Group 3 (0, 2mo) N=380**	**Group 5 Placebo N=128**
% Female	214 (57%)	211 (56%)	66 (52%)
% Male	161 (43%)	169 (44%)	62 (48%)
Age –Mean (years)	13.9 ± 1.9	13.7±1.9	13.8±2.0
Racial origin:	(%)	(%)	(%)
-Asian	0	0	0
-Hispanic	357 (100%)	376 (99%)	128 (100%)
-Other	0	4 (<1%)	0
Weight	56.39±13.17 kg	56.14±11.7	56.24±13.1 kg
Height	157.6±9.7	158.0±9.4	158.4±9.8

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 11.2-2 on p.86 of 10829.

Reviewer Comment:

The age range of all study participants was from 11-17 years of age, and the mean age for enrolled subjects was 13.8±1.9 years. Across all groups there were more females enrolled than males (overall 56% females versus 44% males), with all other demographic characteristics similar across groups. In addition, the study was conducted in Chile; therefore ~all subjects were Hispanic.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.3.10.1.3 Subject Disposition

The following table provides subject disposition for the 1st part of the study for the two dose series and the placebo group prior to the Month 6 vaccination. In addition subject disposition for all subjects in total is provided for the same time period.

Table 19: Study V72P10 Disposition of Subjects for 2-Dose Vaccination Schedules Compared to Placebo -Enrolled Population

	Group 2 (0,1mo) N=375	**Group 3 (0, 2mo) N=380**	**Group 5 Placebo N=128**	**Total (Groups 1-5) N=1631**
Enrolled (N)	375	380	128	1631
Completed Vaccinations at Day 0, Month 1, & Month 2	337 (90%)	333 (88%)	119 (93%)	1432 (88%)
Premature Withdrawal due to:	38 (10%)	47 (12%)	9 (7%)	199 (12%)
-AE	0	0	0	1
-Withdrawal of consent	32 (9%)	37 (10%)	8 (6%)	156 (10%)
-Protocol Deviation	5 (1%)	1 (<1%)	1 (<1%)	14 (<1%)
-Lost to follow-up	1 (<1%)	6 (2%)	0	21 (1%)
-Unable to classify	0	0	0	1
-Administrative reason	0	3 (<1%)	0	5 (<1%)
Safety Population	375 (100%)	380 (100%)	128 (100%)	1622 (100%)
MITT Population	356 (95%)	347 (91%)	124 (97%)	1521 (93%)
PPS-Primary Point*	330 (88%)	320 (84%)	108 (84%)	1396 (86%)
PPS-Imm - 1mo PD#1	344 (92%)	342 (90%)	115 (90%)	-
PPS-Imm - 1mo PD#2	330 (88%)	320 (84%)	108 (84%)	-

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 10.1-1 on p. 77 of 10829; Table 11.1-1 on p.84 of 10829; Table 12.1-1 p127 of 10829. N= enrolled; for explanation of analyses populations see text in Section 6.3.10.1 above. *: defined as one month after last dose of rMenB+OMV in treatment groups; and one month after last placebo dose in control group; PD#1 = post dose 1; PD#2= post dose 2.

***Reviewer Comment**: There were 1622 subjects who received at least one dose of rMenB+OMV, and there were 810 subjects who received 2 doses of rMenB+OMV, 1 or 2 months apart, which includes those subjects in Groups 2 and 3, in addition to Group 4 (only through 2nd dose).*

Protocol Deviations:
The following tables provided a list of the major protocol deviations for the 2-dose schedule compared to the placebo group prior to the Month 6 vaccination.

Table 20: Study V72P10 Summary of Protocol Deviations for 2-Dose Vaccination Schedules Compared to Placebo-Enrolled Population.

	Group 2 (0,1mo) N=375	**Group 3 (0, 2mo) N=380**	**Group 5 Placebo N=128**
Major Protocol Deviation*	49 (13%)	44 (12%)	21 (16%)
-1st BD outside window	1 (<1%)	0	0
-2nd BD outside window	12 (3%)	5 (1%)	9 (7%)
-2nd Vac. Outside window	11 (3%)	5 (1%)	8 (6%)
-3rd BD outside window	10 (3%)	11 (3%)	4 (3%)
-3rd Vac. outside window	10 (3%)	11 (3%)	2 (2%)
-4th BD outside window	7 (2%)	6 (2%)	3 (2%)
-5th BD outside window	24 (6%)	21(6%)	11(9%)
-Withdrawal criteria	0	0	0
Minor Protocol Deviation**	244 (65%)	251 (66%)	75 (59%)
-5th BD outside window	217 (58%)	209 (55%)	68 (53%)
-Diary Card Lost	3 (<1%)	3 (<1%)	0

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 10.2-1 on p.81-82 of 10829. BD: blood draw; * blood draws/vaccinations outside window of -7/+25 for Visits 4 & 6; and -7/+14 for other visits are considered major deviations. ** blood draws and vaccinations outside the window of -4/+7 are categorized as minor deviations.

Reviewer Comment:

1. *As described in the two tables above, Groups 2, 3, and 5 had similar characteristics in regard to analyses populations, subject disposition, and types/rates of protocol deviations.*
2. *In Table 10.2-1 of the CSR, 14 diary cards were reportedly lost across all 5 study groups from Visit 1 to Visit 5 (Month 6). These lost diary cards were considered minor protocol deviations. Yet upon review of the 'Comments' dataset, 211 subjects were found to have the term 'lost diary card' in the 'Comments' column. Upon CBER request, the applicant provided a clarification to the BLA under Am 0.21 (submitted 10/23/2014). The source of the protocol deviations for the CSR was provided by the applicant's 'Protocol Deviations Tracker' which was confirmed by site monitors. Reference to 211 subjects with lost diary cards was obtained by 'free-text' written by investigators at study sites, which was transcribed into the 'Comments' Case Report Form (CRF). This free-text data in the Comments CRF was not considered valid data from a source document, and therefore was not incorporated into the final analysis of protocol deviations. The applicant acknowledged the difference in the number of lost diary cards reported in the CSR compared to that found by review of the dataset. During the review cycle, CBER raised concerns about these lost diary cards, and the potential for solicited adverse event data obtained by subject recall of these data several weeks or months after the 7-day post vaccination monitoring period which could introduce recall bias. As a result, the applicant provided an assessment of the potential for subject recall of these data by accounting for lost diary cards (source documents) noted in the protocol deviations*

listings and in the 'Comments' datasets. This assessment is discussed in Section 5.1 (Review Strategy).

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses Supporting Accelerated Approval (Post-hoc)

As discussed in Section 5.1, an additional set of analyses were conducted by the applicant using specific hSBA measurements against three validated meningococcal serogroup B test strains (H44/76, 5/99, NZ98/254). These immunologic endpoints were considered by CBER as likely to predict clinical benefit of rMenB+OMV vaccine in the context of accelerated approval. These hSBA measurements were 1) the proportion of subjects with a ≥4-fold response after the 2nd dose for each of the 3 serogroup B test strains; and 2) the proportion of subjects with hSBA response ≥ LLOQ to all test strains as a composite response. Of note, ≥4-fold response as defined above with revised criteria for LLOQ will be presented in place of the protocol specified 4-fold response study endpoint.

Proportion of Subjects with ≥4-fold Response

The table below provides the percentage of subjects with a four-fold rise one month after the 2nd dose when measured against each of the meningococcal test strains. The table presents data following 2 doses of rMenB+OMV administered 1 month apart and 2 months apart. This data is descriptive without hypothesis testing.

Table 21: Study V72P10 Percentage of Subjects with ≥4-Fold Rise[a] One Month Post Dose-2, PPS

% [95%CI] of Subjects with >4-Fold Response		
Strain (Antigen)	**(0,1) schedule N=636-637 1 mo. PD#2**	**(0,2) schedule N=319-320 1 mo. PD#2**
H44/76 (fHbp)	93% [90,95]	93% [89,95]
5/99 (NadA)	98% [97,99]	98% [95,99]
NZ98/254 (PorA P1.4)	83% [80,86]	85% [81,89]

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/3/2014. Table corresponds to Table 3.2.3-1 of ISE submitted under BLA 125546/0. MITT- Modified Intention to Treat for immunogenicity subset analysis population.. 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. (0,1) schedule: two doses one month apart; (0,2) schedule: 2 doses two months apart.

[a] Four-fold rise is defined as postvaccination hSBA ≥1:16 for subjects with prevaccination hSBA <1:4, a post vaccination titer at least 4-fold the LLOQ for subjects with prevaccination hSBA ≥1:4 but <LLOQ; and a postvaccination four-fold rise for subjects with pre-vaccination hSBA ≥LLOQ. Study V72P10: LLOQ is defined as 16 for strain H44/76; 8 for strain 5/99, and 16 for strain NZ98/254.

Proportion of Subjects with hSBA Response ≥ LLOQ to All Test Strains as a Composite Response
The percentage of subjects with hSBA response ≥ LLOQ at baseline and one month after the 2nd dose (1moPD#2) is provided in the table below for 2 doses of rMenB+OMV administered either 1 month apart or 2 months apart.

Table 22: Study V72P10 Percentage of Subjects with hSBA Response ≥ LLOQ[a] One Month Post Dose-2, PPS

	% [95%CI] of Subjects with hSBA ≥LLOQ			
Strain (Antigen)	**(0,1) schedule**		**(0,2) schedule**	
	Baseline N=678	**1 mo. PD#2 N=637-638**	**Baseline N=342**	**1 mo. PD#2 N=319-320**
H44/76 (fHbp)	23% [20,27]	98% [96,99]	22% [18,27]	98% [96,99]
5/99 (NadA)	22% [18,25]	100%[99,100]	23% [18,27]	99% [98,100]
NZ98/254 (PorA P1.4)	18% [15,21]	92% [89,94]	19% [15,23]	95% [92, 97]

Source: Adapted from BLA 125546/0.17, Information Amendment-Immunogenicity Data submitted 10/03/2014. Table corresponds to Table 3.2.1-1 of ISE submitted under BLA 125546/0. MITT- Modified Intention to Treat for immunogenicity subset analysis population . 95% CI: 95% confidence interval. 1 mo.PD#2: one month after the 2nd dose. (0,1) schedule: two doses one month apart. (0,2) schedule: 2 doses two months apart..

[a] Study V72P10: LLOQ is defined as 16 for strain H44/76; 8 for strain 5/99, and 16 for strain NZ98/254.

Based on the per protocol analysis set, the composite response for percentage of subjects with hSBA response ≥ LLOQ to 3 out of 3 test strains at baseline and 1 month after the last dose is presented below. As a comparison, data is presented for the composite hSBA response one month after 2 doses of rMenB+OMV (administered 1 or 2 months apart); and for the composite hSBA response one month after the 3rd dose of rMenB+OMV administered on a (0, 1, 2) schedule.

- (0,1) schedule: 8% [6,11] baseline (N=677); 90% [87,92] 1 mo.PD#2 (N=637)
- (0,2) schedule: 8% [5,11] baseline (N=342); 94% [91,97] 1 mo.PD#2 (N=319)
- (0,1,2) schedule: 6% [4,9] baseline (N=333); 95% [92,97] 1mo.PD#3 (N=302)

Reviewer Comment: *The composite hSBA immune response generated to 3 out of 3 strains by rMenB+OMV recipients 1 month after the administration of 2 doses was 90-94%. The hSBA responses observed to two doses administered either one or two months apart are similar, and a 3 dose series when each dose is administered one month apart does not result in a meaningful increase over the hSBA response generated after either 2 dose series. Therefore the data supports a 2 dose series administered either one or two months apart.*

6.3.11.2 Analyses of Study Immunogenicity Endpoints

Primary Study V72P10: Percentage of subjects with hSBA >1:4 – PPS

For each meningococcal B test (reference) strain evaluated (H44/76, 5/99, and NZ98/254), the percentage of subjects who achieved a titer of ≥1:4 one month after the last dose in the series are provided below.

Table 23: Study V72P10 Percentage [95% CI] of Subjects with hSBA ≥1:4 *One Month after Last Dose in Series-PPS*

	Strain	***H44/76***	***5/99***	***NZ98/254***
One-Dose Series				
(0) N=335	*Baseline*	45% [40,51]	37% [32,42]	37% [32,42]
	1mo post last dose	92% [89,95]	97% [94,98] N=334	93% [89,95] N=334
Two-Dose Series				
(0,1) N=344	*Baseline*	39% [34,44]	30% [25-35]	34% [29,39]
	1mo post last dose	100% [99,100] N=330	100% [99,100] N=330	100% [98,100] N=330
(0,2) N=342	*Baseline*	44% [38,49]	35% [30,40]	36% [31,41]
	1mo post last dose	100% [99,100] N=319	99% [98,100] N=320	100% [99,100] N=319
(0,6) N=112	*Baseline*	42% [33,52]	29% [20,38]	32% [24,42]
	1mo post last dose	100% [96,100] N=86	99% [94,100] N=86	100% [96,100] N=86
Three-Dose Series				
(0,1,2) N=334	*Baseline*	46% [41,52]	36% [30,41]	33% [28,38]
	1mo post last dose	100% [98,100] N=303	100% [99,100] N=303	99% [97,100] N=302
(0,1,6) N=113	*Baseline*	41% [32,50]	28% [20,38]	33% [24,42]
	1mo post last dose	100% [96, 100] N=95	100% [96,100] N=95	100% [96,100] N=95
(0,2,6) N=110	*Baseline*	37% [28,47]	30% [22,39]	34% [25,43]
	1mo post last dose	100% [96,100] N=91	100% [96,100] N=91	100% [96,100] N=91

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 11.4.1.1-1 on p.90 of 10829 and Table 11.4.1.1-2 on p.91-92 of 10829. Numbers in parenthesis indicate Day 0, Month 1, Month 2, or Month 6.

Reviewer Comment: *Although the protocol-specified endpoint used a threshold titer (hSBA titer= 1:4) below the validated quantitative range of the assay, these data show that, prior to vaccination, a substantial proportion of subjects were seropositive. Also, the high proportion of subjects with titers ≥1:4 one month after the last dose following either 2 or 3 doses suggests this may not be a discriminatory end-point for examining the difference between a 2 dose regimen and a 3 dose regimen.*

Extension Study V72P10E:Percentage of Subjects with hSBA >1:4 at 24 Month Visit -MITT
~18 months after completion of the Month 6 Visit in the Primary Study V72P10, a subset of subjects were enrolled in to the Extension Study for assessment of antibody persistence. The time interval from the last vaccination varied for each group from 18 months to 24 months. The proportion of subjects who demonstrated hSBA titer ≥1:4 is shown below.

Table 24: Study V72P10E1 Percentage [95%CI] of Subjects with hSBA ≥1:4 *at Month 24 (18 to 24 months after last dose) -MITT*

Strain	***H44/76***	***5/99***	***NZ98/254***
One-Dose Series			
(0)	73% [63,81] N=95	65% [55,75] N=95	62% [52,72] N=95
Two-Dose Series			
(0,1)	82% [74,89] N=102	93% [86,97] N=102	75% [65,83] N=102
(0,2)	81% [72,88] N=106	95% [89,98] N=106	75% [66,83] N=106
(0,6)	84% [70,93] N=49	94% [83,99] N=49	86% [73,94] N=49
Three-Dose Series			
(0,1,2)	83% [76,89] N=153	96% [92,99] N=153	86% [79,91] N=153
(0,1,6)	92% [82, 98] N=53	98% [90,100] N=53	98% [90,100] N=53
(0,2,6)	86% [74,94] N=57	100% [94,100] N=57	96% [88,100] N=57

Source: Adapted from BLA 125546/0, V72P10E1 Clinical Study Report, Table 11.4.1.1-1 p.65 of 1590.

Reviewer Comment: *As discussed earlier, the modified immunogenicity endpoints used to assess vaccine effectiveness, including the proportion of subjects with a ≥4-fold rise one month post 2nd-vaccination using revised LLOQ criteria were not applied to this extension study. The hSBA data presented above is therefore interpreted with caution, and will not be used to demonstrate long-term effectiveness of the vaccine.*

6.3.11.3 Subpopulation Analyses

Please see Section 7.1.2 of this review memo for commentary on subpopulation analyses based on gender and racial origin differences of enrolled subjects.

6.3.11.4 Dropouts and/or Discontinuations

Missing data were not imputed. Missing values were regarded as completely missing at random and left out of the analyses.

6.3.12 Safety Analyses

6.3.12.1 Methods

As prespecified in the protocol, the Safety Population included all subjects who received a study vaccination and provided post-baseline safety data The Safety Population was comprised of 1622 subjects. By schedule, the safety population included the following by schedule/number of doses through study termination (Month 12 visit):

- One dose series:
  - (Day 0 only): 247 subjects
  - (Month 6 only): 128 subjects[26]
- Two-dose series:
  - (0,1): 247 subjects
  - (0,2): 253 subjects
  - (0,6): 128 subjects
- Three-dose series:
  - (0,1,2): 373 subjects
  - (0,1,6): 128 subjects
  - (0,2,6): 127 subjects

There were 1622 subjects who received at least 1 dose of rMenB+OMV, of which 748 subjects who received 2 doses of rMenB+OMV 1 or 2 months apart.

Safety data collection included immediate AEs within 30 minutes of vaccination; solicited local/systemic AEs and all unsolicited AEs for 7 days post-vaccination; SAEs, MAAEs, and AEs leading to withdrawal throughout the study. Three different types of diary cards (Diary Card A, Diary Card B, Follow-up Diary Card) were dispensed depending on the visit and type of data to be collected, as described in Section 6.3.7 above. Each diary card was collected and reviewed at the subsequent visit.

6.3.12.2 Overview of Adverse Events

Solicited Adverse Events:
The majority of subjects who received rMenB+OMV at a visit reported a solicited adverse event during the 7 day post-vaccination time period. The following 'any' solicited reactions were reported most frequently across all groups by visit:

- *Day 0 Visit (1st dose of rMenB+OMV):* injection site pain in 89-93%; injection site erythema 52-56%; malaise in 55-58%; myalgia in 44-47%; headache in 42-50%; fever (T≥38.0C) in 2-4% of subjects
- *Month 1 Visit (2nd dose of rMenB+OMV):* injection site pain in 86-87%; injection site erythema 52-53%; malaise in 49-54%; myalgia in 39-41%; headache in 43-45%; fever (T≥38.0C) 3-5%% of subjects
- *Month 2 Visit (2nd dose of rMenB+OMV):* injection site pain 78-84%; injection site erythema 48-49%; malaise in 44-47%; myalgia in 36-41%; headache in 37-42%; fever (T≥38.0C) in 4-5% of subjects
- *Month 6 Visit (2nd or 3rd dose of rMenB+OMV):* injection site pain in 75-78%; injection site erythema 44-46%; malaise in 44-49%; myalgia in 36-42% of subjects; headache in 25-38%; fever (T≥38.0C) in 3-5% of subjects
- *Month 6 Visit –Group 5a only[27] (1st dose of rMenB+OMV following 3 prior doses of placebo):* Subjects at Month 6 received 3 doses of placebo prior to receiving the 1st dose of rMenB+OMV at Month 6. Injection site pain was reported by 74% of subjects; malaise was reported by 39% of subjects; and fever (T≥38.0C) was reported by 8% of subjects When compared to Day 0 (1st dose of rMenB+OMV), the rates at Month 6 (1st dose after 3 prior doses of placebo) are generally lower. For example, for injection site pain the rates at Day 0 (1st dose) were 89-93% and for malaise the rates at Day 0 (1st dose) were 55-58%.

26 There were 9 subjects in Group 5a (Month 6 dose only) who received placebo only, therefore of the 1631 subjects enrolled there were 1622 subjects who received at least one dose of rMenB+OMV.
27 Group 5a: Day 0-*placebo*; Month 1-*placebo*; Month 2-*placebo*; Month 6-*dose 1*.

Solicited AEs reported as 'severe' were most frequently reported for injection site pain, malaise, myalgia and headache. These rates of severe reactions appear to slightly increase after receiving prior doses of rMenB+OMV. The reported rates by visit are as follows:

- severe injection site pain: 15-19% of subjects after Day 0 visit; 13-14% after Month 1 visit; 13-17% after Month 2 visit; 25-27% after Month 6 visit (after receiving prior doses of rMenB+OMV); 22% after Month 6 visit (Group 5a-receiving prior doses of placebo only)
- severe malaise: 6-9% after Day 0 visit; 6-8% after Month 1 visit; 5-7% after Month 2 visit; 9-12% after Month 6 visit (after receiving prior doses of rMenB+OMV); 2% after Month 6 visit (Group 5a-receiving prior doses of placebo only)
- severe myalgia: 6-7% after Day 0 visit; 6% after Month 1 visit; 5-6% after Month 2 visit; 6-9% after Month 6 visit (after receiving prior doses of rMenB+OMV); 5% after Month 6 visit (Group 5a-receiving prior doses of placebo only)
- severe headache: 4-6% after Day 0 visit; 5-6% after Month 1 visit; 5% after Month 2 visit; 7-8% after Month 6 visit (after receiving prior doses of rMenB+OMV); 3% after Month 6 visit (Group 5a-receiving prior doses of placebo only)

The use of oral analgesic and antipyretic medications was similar at each visit and was as follows by visit, respectively:

- *Day 0 Visit (1st dose of rMenB+OMV):*24-36% & 2-6%
- *Month 1 Visit (2nd dose of rMenB+OMV):*23-32% & 3-6%
- *Month 2 Visit (2nd dose of rMenB+OMV):* 25-27% & 4-5%
- *Month 6 Visit (2nd or 3rd dose of rMenB+OMV):* 24-27% & 3-7%
- *Month 6 Visit –Group 5a only (1st dose of rMenB+OMV):*24% & 2%

Reviewer Comment: *The most common solicited reactions for the 1st dose (at Day 0 or Month 6) were injection site pain and malaise. For the 2nd dose (at either Month 1 or Month 2) the most common reactions reported were also injection site pain and malaise, with slightly higher rates at Month 1. The rates at Month 6 included combined data for a 2nd dose or 3rd dose of rMenB+OMV. These rates appear to be similar to the rates seen at Month 2. In general it appears that the rates of reactogenicity are slightly less with a greater time interval between doses. Reports of fever were generally low for this study population. Approximately one-quarter to one-third of subjects reported use of a pain medication following vaccination.*

Revised Solicited Adverse Event Rates:

As discussed in Section 5.1, the rates of solicited adverse events which exclude data that appeared to be obtained by subject recall several weeks or months after the 7-day post vaccination monitoring period when the source document appeared to be missing were assessed and provided in response to CBER request. The applicant notes that, for this study, the collection of solicited AEs data that were obtained by retrospective recall was explicitly permitted. The applicant estimates that the proportion of solicited AEs data not obtained from a source document was 4.6%. By dose, 10.48% of solicited AEs data after the 1st dose of rMenB+OMV was considered to be obtained by retrospective recall compared to 8.24% after the 1st dose of placebo; 6.67% of solicited AE data after the 2nd dose of rMenB+OMV compared to 9.08% after the 2nd dose of placebo; 9.72% after the 3rd dose of rMenB+OMV compared to 10.51% after the 3rd dose of placebo. The following table provides a revised set of reactogenicity rates for each group by dose.

Table 25: Study V72P10- Revised Reactogenicity Rates: % of Subjects with Any *& Severe* Solicited Local & Systemic Adverse Events for 7 Days Post-vaccination after 1st dose & 2nd dose, combined rates* across groups

		Dose 1		Dose 2	
		Bexsero[a]	**Aluminum hydroxide-placebo**	**Bexsero[a]**	**Aluminum hydroxide-placebo**
		N=1318-1492 *N=1311-1479*	N=1195-1365 *N=1192-1361*	N=961-1075 *N=957-1069*	N=689-794 *N=686-790*
Local Adverse Events					
Pain	Any *Severe*	96 *19*	62 *4*	90 *17*	65 *4*
Erythema	Any *>100 mm*	56 *<1*	31 *0*	53 *<1*	27 *<1*
Induration	Any *>100 mm*	44 *<1*	23 *0*	43 *<1*	21 *0*
Swelling	Any *>100 mm*	44 *<1*	20 *<1*	41 *<1*	19 *0*
Systemic Adverse Events					
Malaise	Any *Severe*	58 *7*	31 *2*	52 *8*	33 *2*
Nausea	Any *Severe*	19 *1*	13 *1*	17 *2*	11 *1*
Myalgia	Any *Severe*	49 *7*	26 *2*	43 *7*	26 *2*
Arthralgia	Any *Severe*	25 *2*	14 *1*	23 *3*	13 *<1*
Headache	Any *Severe*	47 *5*	29 *3*	42 *6*	28 *2*
Fever	≥38°C 38.0-38.9°C 39.0-39.9°C *≥40°C*	4 3 1 *<1*	2 2 <1 *0*	5 4 1 *0*	2 2 <1 *0*

Source: Adapted from BLA 125546/0.21 (Information Amendment-Safety Data submitted 10/23/2014) Table 6-1. Placebo contained aluminum hydroxide-saline. *

[a] Dose 1 for rMenB+OMV group comprised: injection 1 at month 0 from the rMenB0, rMenB01, rMenB02, rMenB012, rMenB06, rMenB016, rMenB026 groups, and injection 4 at month 6 for rMenB6 group; Dose 1 for placebo group comprised: injection 1 at study month 0 from the rMenB6 group, injection 2 for rMenB06, rMenB02, rMenB026,and rMenB0 groups, injection 3 at study for rMenB016 and rMenB01 groups and injection 4 for the rMenB012 group. Dose 2 for rMenB+OMV group comprised: injection 2 for rMenB01, rMenB016 and rMenB012 groups, injection 3 for rMenB02 and rMenB026 groups, and injection 4 for the rMenB06 group; Dose 2 for placebo group comprised: injection 2 for the rMenB6 group, injection 3 for rMenB06 and rMenB0 groups and injection 4 for rMenB01 and rMenB02 groups.

Reviewer Comment: *As noted by the applicant ~5% of solicited AE data were potentially obtained by subject recall a time point several weeks or months after the 7-day post vaccination monitoring period. The revised reactogenicity rates excluding potential recalled data are presented in the table above. Though the revised rates differ slightly from the original rates in the CSR, the overall trends in the reactogenicity data for rMenB+OMV recipients appear to be similar. However, the revised rates appear to have lower rates of solicited AEs after the 1st dose of placebo. The applicant estimates that 8.24% of solicited AE data after the 1st dose of placebo was recalled compared to 10.48% recalled data after the 1st*

dose of rMenB+OMV. After the 1st dose of placebo, the revised rates of 'any' pain dropped from 86% to 62%; 'any' erythema dropped from 40% to 31%; 'any' malaise dropped from 48% to 31%; and 'any' myalgia dropped from 41% to 26%. This was not seen as dramatically after the 2nd dose of placebo, or after the 1st or 2nd dose of rMenB+OMV. Therefore while the revised rates of reactogenicity following rMenB+OMV vaccination were similar to the original rates, there appears to be a difference noted in the revised rates of reactogenicity following a placebo dose.

Unsolicited Adverse Events during Entire Study:[28]
For the entire study period (Day 1 through Month 12), the rates of any unsolicited adverse events across all 8 study groups were similar ranging from 51-63%. Frequently observed AEs by preferred terms across all groups were nasopharyngitis (7-14%), bronchitis (2-9%), headache (2-9%), injection site pain (3-8%), pharyngitis (3-6%), and gastroenteritis (2-6%). The majority of these were graded as mild to moderate in intensity, with 0-1% graded as severe in intensity.

The most AEs were classified under the SOC of Infections & Infestations (26-35%); General Disorders & Administration Site Conditions (10-19%); Gastrointestinal Disorders (7-16%); Injury & Poisoning (5-10%); and Musculoskeletal, Connective Tissue & Bone Disorders (5-9%).

***Reviewer Comment**: There was no dose effect noted in the cumulative rates of unsolicited adverse events over the entire 12 month study period.*

Unsolicited AEs during 7-Day Post-Vaccination Time Period by Visit:
The following table includes the rates of any unsolicited adverse event by group within the 7 days post-vaccination time period for the doses administered at Day 0, Month 1, or Month 2 Visits:

Table 26: Study V72P10 Rates-% of Unsolicited AEs by Dose during 7-Day Post-Vaccination Time Period after Day 0, Month 1, and Month 2 Visit-Safety Population

Group (schedule)	Day 0 Visit % (n/N)	Month 1 Visit % (n/N)	Month 2 Visit % (n/N)
Group 1 (Day 0)	18% (68/375)	*11% (38/351)	*6% (20/343)
Group 2 (0, 1)	18% (68/375)	14% (49/356)	*7% (23/350)
Group 3 (0,2)	21% (79/380)	*10% (36/347)	11% (38/341)
Group 4 (0,1,2)	18% (69/373)	11% (37/342)	12% (41/332)
Group 5 (placebo)	*14% (18/128)	*9% (11/124)	*8% (10/121)

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 12.2.3-7 p. 139; Table 12.2.3-8 p141; Table 12.2.3-9 p.142.
n=number of unsolicited AEs observed, N=safety population,
*placebo (aluminum hydroxide-saline) administered at listed visit

[28] Source: from BLA 125546/0, V72P10 Clinical Study Report: Tables 14.3.1.1.11, 14.3.1.1.10.1.1,

The following table includes the rates of unsolicited AE within the 7-day post-vaccination time period for the additional dose administered to a subset of subjects at the Month 6 Visit.

Table 27: Study V72P10 Rates-% of Unsolicited AEs during 7-Day Post-Vaccination Time Period after Month 6 Visit-Safety Population

Group (schedule)	Month 6 Visit % (n/N)
Group 1a (0,6)	10% (11/114)
Group 1b (0)	*4% (9/212)
Group 2a (0,1,6)	11% (12/112)
Group 2b (0,1)	*5% (11/225)
Group 3a (0,2,6)	10% (11/111)
Group 3b (0,2)	*6% (13/222)
Group 4 (0,1,2)	*8% (26/316)
Group 5a (6)	13% (16/119)

Source: Adapted from BLA 125546/0, V72P10 Clinical Study Report, Table 12.2.3-10 p. 144; n=number of unsolicited AEs observed. N=safety population, *placebo (aluminum hydroxide-saline) administered at listed visit

Reviewer Comment:

1. *As described in the two tables above, there are higher rates of AE during the 7 day post-vaccination period at each visit for rMenB+OMV recipients compared to those who received a placebo at that visit.*
2. *After the Day 0 visit, almost half of all rMenB+OMV recipients considered an AE occurrence to be at least possibly related to vaccination compared to 5 of the 18 placebo recipients who reported an adverse event after this visit. This discrepancy was not as apparent after the Month 2 Visit. At the Month 6 Visit, a greater proportion of rMenB+OMV recipients attributed an AE as at least possibly related to vaccination compared to those who received a placebo dose at this visit.*

Unsolicited AEs from Day 8 to Day 30 (MAAEs):
After the Day 0, Month 1, and Month 2 visits the rates of unsolicited AEs (MAAEs) from Days 8-30 were similar across rMenB+OMV groups (4-9%) compared to 8-11% in the placebo group, and very few were considered related to vaccination by the investigator

6.3.12.3 Deaths

There were 2 deaths during the study in subjects who had received study vaccine; and 1 death in an infant born to a subject.

- Subject #15/5009: 17 yo female enrolled in the Group 1a (0,6) suffered craniocerebral trauma after being struck by a car ~ 4 months after her 2nd dose of rMenB+OMV. She died in the ambulance. The death was not considered related to vaccination.
- Subject #41/5044: 17 yo female enrolled in Group 3a (0,2,6) had ingested 60-70 pills of paracetamol ~31 days after her 3rd dose of rMenB+OMV. The subject developed liver failure, and died prior to receiving a liver transplant. The death was not considered related to vaccination.
- Subject #51/5032: 15 year old female enrolled in Group 2a (0,1,6) received 3rd dose ~98 days prior to the subject testing positive for pregnancy. A male baby was born at 34 weeks gestational age ---(b)(6)--- without signs of fetal distress, though was found to

have an absent 2nd toe on the right foot which was 'suspected' to be related to vaccination by the investigator due to the multi-factorial etiology of this malformation. The infant developed transient respiratory distress syndrome, requiring oxygen and transfer to the intensive care unit for apnea. He required supportive care positive pressure ventilation, and medications including aminophylline and caffeine. His hospital course was complicated by pulmonary infiltrates requiring antibiotics and jaundice requiring phototherapy. At 6 days, the subject developed grade 1 intra-ventricular hemorrhage, which began to show cavitation. At 10 days, a heart murmur diagnosed by a cardiologist as left pulmonary artery branch stenosis, which upon re-evaluation on 6/4/2010 was asymptomatic. The infant was discharged home, and was found dead by his mother without any obvious findings on --(b)(6)--. The investigator reported the event as sudden death at not related to the mother's vaccination with rMenB+OMV.

Reviewer Comment*: Neither of the two deaths in the teenage subjects is considered by this reviewer to be related to vaccination. Regarding the death of an infant born to a subject enrolled in the study, it is the reviewer's impression that rMenB+OMV vaccination of the mother ~98 days prior to testing positive for pregnancy was unlikely related to the post-natal death of her infant. There were several post-natal respiratory complications which could have contributed to the infant's demise at 1 ½ months of age.*

6.3.12.4 Nonfatal Serious Adverse Events

There were 35 SAEs during the study and included the following by preferred term by study group and the days since last vaccination:

- Group 1a (0,6):
  - premature labor (99 days); syncope/convulsion (day of vaccination); appendicitis (150 days), road traffic accident –resulting in death (118 days); viral pneumonia (116 days)
- Group 1b (0):
  - dysentery (193 days); convulsion/epilepsy (213 days; 327 days); suicide attempt (487 days); appendicitis (246 days)
- Group 2a (0,1,6):
  - premature labor (286 days); appendicitis (67 days)
- Group 2b (0,1):
  - glomerulonephritis-minimal lesion (197 days); appendicitis (306 days); testicular torsion (312 days); adenoidectomy (288 days); tonsillectomy (288 days)
- Group 3a (0,2,6):
  - Appendicitis (8 days); panic attack (108 days); major depression (116 days); suicide attempt (33 days)
- Group 3b (0,2):
  - drug toxicity (23 days); appendicitis (8 days); drug toxicity (191 days); shigella infection (47 days)
- Group 4 (0,1,2):
  - bacterial meningitis (28 days); asthmatic crisis (23 days); benign ovarian tumor (59 days); syncope (after administration); joint injury (31 days); appendicitis (136 days); appendicitis (18 days); urticaria (33 days); ligament rupture (122 days); juvenile arthritis (198 days); juvenile arthritis (170 days)
- Group 5a (6):
  - fibroadenoma of breast (157 days); suicide attempt (158 days); appendicitis (95 days)

SAEs of Interest:

1. Syncope with Seizure Manifestations: Subjects#12/0073, Group 1a: (0,6). 12 you female without significant past medical history was diagnosed with vaso-vagal syncope with seizure manifestations related to venipuncture procedure carried out prior to receiving a 1st dose of rMenB+OMV. The subject had a strong family history for epilepsy (father and paternal aunt). The subject was evaluated in the hospital and had a full neurologic work-up and consultation by a neurologist. Her symptoms fully resolved, and she was withdrawn from the study. The investigator considered the SAE as not related to study vaccine, but rather associated with conduct of the trial.
2. Bacterial Meningitis: Subject#11/0025, Group 4: (0,1,2). 11 year old male with no significant past medical history he was admitted for meningitis to the intensive care unit 26 days after his 3rd vaccination. Cerebrospinal fluid analysis via polymerase chain reaction (PCR) was positive for *Streptococcus pneumoniae*, and subsequent radiologic studies revealed right otomastoiditis. The investigator did not consider this SAE as related to vaccination.

   Reviewer Comment: *In the opinion of this reviewer, neither SAE (syncope with seizure manifestations & bacterial meningitis) are related to rMenB+OMV vaccination*.

3. Appendicitis: Nine rMenB+OMV recipients were diagnosed with appendicitis over the 12 month study period. These subjects were as follows, listed by group (age/gender at enrollment, and # days since last rMenB+OMV vaccination):
   - Group 1a (0,6): Subject #14/5024 (14 y.o female, 150 days)
   - Group 1b (0): Subject#43/5136 (15 y.o male, 246 days)
   - Group 2a (0,1,6): Subject #61/5067 (17 y.o female, 67 days)
   - Group 2b (0,1): Subject #13/0060 (13 y.o male, 306 days)
   - Group 3a (0,2,6): Subject #11/5057 (17 y.o male, 8 days)
   - Group 3b (0,2): Subject #41/0019 (13 y.o male, 8 days)
   - Group 4 (0,1,2): Subject # 41/0063 (13 y.o male, 136 days); and 41/5001 (15 y.o male, 18 days)
   - Group 5a (6): Subject # 42/0057 (12 y.o male, 95 days)

   Reviewer Comment: *In Study V72P10 in which 1622 subjects received at least one dose of rMenB+OMV, there were 9 cases of appendicitis reported in rMenB+OMV recipients over the 12 month study duration. The interpretation of these reported cases of appendicitis outside the context of national rates of appendicitis in Chile is difficult without a comparator group. Based on CDC analysis of National Hospital Discharge Survey data from 1979-1984[29], the highest incidence of appendicitis in the US was found in persons 10-19 years of age (23.3 cases/10,000 population per year). More recent patient discharge data[30] (1995-2009) from California, a state with a high proportion of Hispanic residents, demonstrate that the highest rates of appendicitis (169.6 cases/100,000) were in children 10-14 years of age. In this latter data, appendicitis was reported more frequently in Whites and Hispanics, and less frequently in African Americans and Asians. The reported rates of appendicitis in Study V72P10 when compared to background rates do not appear to indicate that there is an overall increased risk following rMenB+OMV vaccination. In addition in Study V72_29 the rates of appendicitis in the rMenB+OMV group were not higher than what was observed in the two comparator groups.*

29 Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiology. 1990; 132 (5):910.
30 Anderson JE, Bickler SW, Chang DC, Talamini MA. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. World J Surg. 2012;36(12):2787.

4. Juvenile Arthritis: There were two SAEs assessed by the investigator as possibly/probably related to vaccination.
   - Subject #61/0004: Juvenile Arthritis. 11 year old female [Group 4: (0,1,2)] with a past medical history significant for pain in ankles, tendinitis, and psoriasis treatment developed pain in the left foot between the 1st and 2nd study vaccinations. Further workup demonstrated positive antinuclear antibodies, and positive findings on a bone scan and MRI. The subject was diagnosed with juvenile idiopathic arthritis, psoriatic type ~170 days after the 3rd vaccination of rMenB+OMV. The SAE was ongoing at time of study completion, and the investigator assessed the AE was possibly related to vaccination.
   - Subject #51/0006: Juvenile Arthritis. 13 year old female [Group 4: (0,1,2)] with a past medical history significant for abnormal weight gain, acute appendicitis, bronchial asthma, and varicella developed pain in both her wrists ~198 days after receiving the last dose of rMenB+OMV at Month 2 visit. The subject was referred to a rheumatologist for ongoing symptoms and diagnosed with juvenile idiopathic arthritis, and treated with a NSAID. The condition was ongoing at study completion, and the investigator assessed this as probably related to vaccination.

Reviewer Comment:

1. *Subject #61/0004 was diagnosed with juvenile arthritis ~5 ½ months after rMenB+OMV vaccination. Based on the case narrative provided, it is possible that the subject had rheumatologic findings associated with juvenile arthritis prior to vaccination. The subject's clinical presentation continued to evolve during the study period which was possibly due to natural disease progression or exacerbation due to rMenB+OMV vaccination. While the reviewer agrees with the investigator's assessment that the AE was possibly related to vaccination, it is unlikely the onset of juvenile arthritis symptoms were caused by vaccination.*
2. *The onset of juvenile arthritis symptoms for subject #51/0006 was diagnosed over 6 months following the last dose of rMenB+OMV. Based on the information provided, the subject did not appear to have symptoms associated with a diagnosis of juvenile arthritis prior to vaccination. It is clinically feasible that a relationship with a preceding vaccination exists because juvenile arthritis is an immune mediated medical condition. Yet, there were no other reported cases of juvenile arthritis or other rheumatologic conditions in the 4 main studies submitted as part of this application in individuals 10 years through 25 years of age, which included 3058 subjects who received at least one dose of rMenB+OMV. Additionally there were no reported cases of juvenile arthritis or rheumatologic conditions following rMenB+OMV vaccination in the pre-licensure vaccination campaigns conducted at two US universities in 15,351 individuals. In the opinion of this reviewer the reported case of juvenile arthritis in Subject #51/0006 is possibly associated with rMenB+OMV vaccination. Based on review of all the safety data in this BLA, there does not appear to be a safety concern for juvenile arthritis following rMenB+OMV vaccination.*

6.3.12.5 Adverse Events of Special Interest (AESI)

Pregnancies

There were 19 pregnancies reported during the study, with no reports of spontaneous abortions. Two pregnancies resulted in congenital malformation as follows:

- Subject #51/5032: Pregnancy/Congenital Malformation. 15 year old female enrolled in Group 2a (0,1,6) had received the 3rd dose~98 days prior to the subject testing positive for pregnancy. A male baby was born at 34 weeks gestational age without signs of fetal

distress, though was found to have an absent 2nd toe on the right foot which was 'suspected' to be related to vaccination by the investigator due to the multi-factorial etiology of this malformation. As described above in Section 6.3.12.3, the infant died 1 ½ months after birth, which was not considered related to vaccination.

- Subject #11/0007: Pregnancy/Congenital Genetic Condition. 13 yo female enrolled in Group 1a (0, 6) who received her last dose of rMenB+OMV on 1/16/2009, and then confirmed pregnancy on 4/28/2009. The infant was born at 35 weeks gestation on without malformations, though hypotonia was subsequently noted. Genetic testing confirmed a diagnosis of Prader Willi Syndrome. The investigator did not consider this chromosomal anomaly to be related to vaccination.

Reviewer Comment: *It is unlikely that these congenital anomalies were related to vaccination. Further rMenB+OMV pregnancy outcome data collection is recommended.*

For additional review of AESI across all studies, please see Section 8 for an overview of AESI across all studies.

6.3.12.6 Clinical Test Results

N/A

6.3.12.7 Dropouts and/or Discontinuations

Based on the data presented in the final CSR, there were 3 withdrawals from the study due to an adverse event. These included the following cases:

- Subject #51/5009. Road traffic accident (death). Discussed above in Section 6.3.12.3.
- Subject #41/5044. Paracetomol overdose/suicide attempt (death). Discussed above in Section 6.3.12.3.
- Subject #61/0004. Juvenile arthritis (SAE). Discussed above in Section 6.3.12.4

Reviewer Comment*: As noted in Section 3.2 of this review, FDA clinical site inspections conducted by BIMO (DIS), revealed that some subjects withdrew due to an adverse event, which was documented in the source documents, but was not captured in the case report forms because there was nowhere to capture this information. At the two sites inspected (site #14 and #41), there were 49 study withdrawals, of which 16 were related to injection site reactions.*

6.3.13 Study Summary and Conclusions

The study evaluated multiple rMenB+OMV schedules in 11-17 year old Chilean adolescents, with a placebo control group only through the Month 3 visit and without a control group from the Month 6 visit through Month 12 visit. For the purpose of accelerated approval, data pertaining to 2 dose regimens were primarily presented.

Based on the modified immunogenicity hSBA analyses, the percentage of rMenB+OMV recipients (1 month after the 2nd dose) with at least a 4-fold response in hSBA titers against H44/76 and 5/99 strains was 93-98%, and against NZ98/254 strain was 83-85%. The percentage of subjects with baseline hSBA titers $\geq$ LLOQ was 18-23% against all strains, which may be the result of natural exposure in the study population. Common solicited reactions include injection site pain, injection site erythema, myalgia, and headache. Although the rates of severe pain were relatively high (17-19 %), the rates for other severe reactions were lower. When evaluating the relevant two-dose regimens, the rates of unsolicited adverse events in the 1st week after any

vaccination were higher in the rMenB+OMV group when compared to a placebo control group. This difference appeared to be less when comparing rates over the entire study time period. There were 2 subjects with reports of juvenile arthritis during this study, one of whom was possibly symptomatic prior to vaccination. There were no other reported cases of juvenile arthritis in the data presented in the other clinical trials or in the vaccination campaigns. Therefore this single case of juvenile arthritis does not appear to represent a safety concern following rMenB+OMV vaccination. Although there were 19 cases of appendicitis reported in this study, review of all safety data submitted as part of this BLA in the context of background appendicitis rates does not suggest a causal association with rMenB+OMV vaccination. There were 3 deaths associated with this trial, none of which were related to vaccination; therefore the reviewer does not recommend inclusion of this information in the package insert.

6.4 Trial #4: Study V102_03

A Phase 2, Observer Blinded, Controlled, Randomized Multicenter Study in Adolescents and Young Adults (10-25 years old) to Evaluate Safety and Immunogenicity of Two Different rMenB+OMV with MenACWY Combination Vaccination Formulations

> ***Reviewer Comment:*** *The review of this study will focus on the analysis of safety data collected from rMenB+OMV vaccine recipients, and not the pentavalent product which is not under review in this application.*

6.4.1 Objectives

Safety

- To evaluate the safety of 2 doses of the pentavalent product.

Reviewer Comment:

1. *Study objectives relevant to the evaluation of rMenB+OMV vaccine are listed and do not include all pre-specified study objectives.*
2. *Only safety of two doses of rMenB+OMV will be evaluated in this review.*
3. *----(b)(4)------- hSBA ((b)(4)-hSBA) assay was used in this study to assess serum bactericidal activity. (b)(4)-hSBA performed at Novartis Vaccines, ----------(b)(4)----------, has not been fully validated. CBER considers the assay as ---(b)(4)----------. Therefore, the immunogenicity data collected in this study were not considered in the evaluation of vaccine effectiveness.*

6.4.2 Design Overview

Study V102_03 is a Phase 2, observer-blinded, controlled, randomized, multicenter study in healthy adolescents and young adults from 10 years to 25 years of age which evaluated three different meningococcal vaccines. Two different formulations of the ---(b)(4)--- product containing full dose -----(b)(4)----------), or quarter dose OMV (----(b)(4)----------) were evaluated. All subjects received two doses of each vaccine, 2 months apart, except for Menveo, in which subjects received one dose of placebo, followed by vaccine two months later. Subjects were randomized 1:1:1:1 across the four treatment groups, with a planned enrollment of 480 subjects. Each subject was enrolled for 8 months.

Study Groups-each group received two doses as follows (N=#enrolled):

- ----(b)(4)---------- (full dose OMV): Day 0, and Month 2 (N=120)
- ----------(b)(4)---------- (quarter dose OMV): Day 0, and Month 2 (N=121)
- rMenB+OMV (full dose OMV): Day 0, and Month 2 (N=122)

- Placebo on Day 0, and Menveo on Month 2 (N=*121)*

Reviewer Comment*: This study provides additional safety data for rMenB+OMV. The trial was conducted in the US and Poland and was conducted under IND and received regulatory input from CBER.*

6.4.3 Population

Subjects were eligible for participation in the study if they were healthy 10-25 years old; gave informed consent or assent (if applicable); if under 18 years old, whose parents gave written informed consent and were able to attend all scheduled visits. Subjects were excluded for participation if they had a history of any meningococcal vaccination, suspected or confirmed *N. meningitidis* disease, chronic or progressive disease, impairment of immunity (due to treatment or underlying condition), severe allergic reactions after prior vaccinations or hypersensitivity to any vaccine component, and/or any condition which was considered by the investigator to interfere with the evaluation of the study objectives. In addition, subjects were excluded if they had contact with individual with laboratory confirmed case of *N. meningitidis* within 60 days (of enrollment), significant illness and/or fever (temperature measured by axillary route of ≥38.0C) within 7 days, antibiotics within 7 days prior to vaccination or blood draw, pregnancy/nursing mothers, females not using acceptable method of birth control for the 2 months prior to study entry through the duration of the study, receipt of blood or blood products within prior 90 days, receipt of any other vaccine within 14 days prior (28 days for live viral vaccines, 14 days for influenza vaccines), participation in another clinical trial within prior 30 days or during study, and/or family/household members of staff.

6.4.4 Study Treatments or Agents Mandated by the Protocol

There were four vaccine treatment groups: rMenB +OMV; ----------(b)(4)----------; and Placebo/Menveo. Each subject received 2 doses (0.5mL of each study vaccine: 1st on Day 1 of the study, and 2nd on Day 61; each dose was administered intramuscularly in the deltoid region of non-dominant arm.

Reviewer Comment*: Only the relevant vaccines for the reviewer's analysis are listed below. MenACWY-CRM (*Menveo®), *which is a licensed product in the US, serves as a comparator group for safety in the reviewer's analyses of the investigational vaccine under review in this application.*

1. rMenB+OMV: please see Section 6.1.4 of this review for vaccine description;
    - Lot number: 090101B4/090101B5
2. MenACWY+CRM, Menveo®: please see Section 6.2.4 of this review for vaccine description;
    - For US: Lot number: A10154/X10154
    - For Poland: Lot number: A10153/Z10153
3. Placebo:
    - Lot number: X38D23N1C
    - Each dose contained the following: 4.5 mg sodium chloride with water (quantity sufficient to 0.5mL) for injection.

6.4.5 Directions for Use

See above

6.4.6 Sites and Centers

The study was conducted in 8 sites in the United States and 5 sites in Poland. The sites include the following: (N=total subjects enrolled)

United States:
- Site 21: Dr. Wendy Daly, Louisville, Kentucky (N=70)
- Site 22: Dr. Charles Jordan, Lebanaon Tennessee (N= 7)
- Site 23: Dr. William Johnston, Birmingham, Alabama (N=15)
- Site 24: Dr. Aftab Naz, Madera California (N=120)
- Site 25: Dr. Mildred Rey, Paramount California (N=47)
- Site 26: Dr. Julie Shepard, Dayton Ohio (N=32)
- Site 27: Dr. Julie Shepard, Kettering Ohio (N=12)
- Site 28: Dr. Stanley Block, Bardstown, Kentucky (N=49)

Poland:
- Site 11: Dr. Leszek Szenborn, Wroclaw, Poland (N=48)
- Site 14: Dr. Teresa Jackowska, Warszawa, Poland (N=40)
- Site 15: Dr. Witold Galczak, Izabelin, Poland (N=22)
- Site 17: Dr. Ryszard Konior, Krakow, Poland (N=13)
- Site 18: Dr. Hanna Czajka, Krakow, Poland (N=9)

Reviewer Comment: *The majority of participants were enrolled at a US site (~72%).*

6.4.7 Surveillance/Monitoring

Schedule of Events: All subjects received 2 vaccinations (one month apart) and were followed for 6 months after the last dose. The following list includes the scheduled visits and telephone contacts with the subjects, including trial activity associated with each visit/contact:

- *Day 1-Visit 1:* Informed Consent; medical history/concomitant medications; review of eligibility criteria; physical examination with oral temperature, blood pressure, pulse, and heart/lung examination; urine pregnancy test; randomization; baseline blood sample given (20mL maximum); vaccination; 30 minutes safety observation; Diary Card provided to all subjects; instruction provided on how to complete for 7 days post-vaccination, including recording of oral temperatures.

- *Day 3-Telephone Call (window Day 3-5):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian to record adverse events/concomitant medications on diary card.

- *Month 2 (Day 61)-Visit 2 (window Day 57 to 75):* Diary card collected/reviewed by blinded study personnel; history, brief physical assessment, determine ongoing eligibility; urine pregnancy test; study vaccination by unblinded vaccine administrator, 30 minute safety observation, Diary Card provided and instructions given as above

- *Day 63-Telephone Call 2 (window Day 63-65):* Subjects contacted to query for SAEs and/or any other concerns, and to remind subject or parent/guardian to record adverse events/concomitant medications on diary card.

- *Month 3 (Day 91)-Visit 3 (window Day 87 to 105):* Diary card collected/reviewed by blinded study personnel; history, brief physical assessment, determine ongoing eligibility; collect blood sample (20mL); distribute 'Memory Aide' and instructions for completion

- *Month 8 (Day 241)-Telephone Call 3 (window Day 221 to 266):* Subjects contacted to query for any changes in health (new diagnoses, worsening of pre-existing illnesses, symptoms-leading to a medical visit) and to collect information on the 'Memory Aide.' Completion of Study Termination eCRF was also done on this call.

Immunogenicity Assessments:

Sera were collected for analysis using ------(b)(4)------ assays for serum bactericidal activity using human complement ((b)(4)-hSBA) on all subjects at baseline (Day 1) and again 30 days after the 2nd vaccination. This (b)(4)-hSBA assay was performed at Novartis Vaccines, ----------(b)(4)---------- has not been fully validated.

Reviewer Comment: *As discussed in Pre-BLA communications, CBER considers the ------(b)(4)---------- hSBA assay ((b)(4)-hSBA) using ----------(b)(4)----------. Therefore the immunogenicity data collected in this study using this assay were not considered in the evaluation of vaccine effectiveness.*

Safety Assessments:

- *Immediate post-vaccination*: subjects were observed for the 30 minute post-vaccination, including oral temperature measurement, examination of injection site for any local reactions, and assessment of systemic reactions or other AEs. Any AEs or reactions were recorded on the subject's source document and the appropriate eCRF.

- *Solicited Local, Systemic Reactions*: collected for 7 days post-vaccination, frequencies and percentages of subjects experiencing each reaction was presented based on symptom severity.
    - *Local injection site reactions*: pain, erythema, and induration. Severity grading scale:
        - *Pain:* mild, moderate and severe
        - *Erythema and induration*: by two categorization methods as follows:
            - 1st category: none (0mm) or any (1-24mm; 25-50mm; 51-100mm, >100mm)
            - 2nd category: none (<25mm); any (25-50mm, 51-100mm, >100mm)
            -

Reviewer Comment*: Based on the pre-specified severity grading scale in V102_03 Revised Protocol v4.0 (17 Dec 2013) erythema and induration were graded as follows: 0mm (none); >0-24mm, 25-50 mm (mild); 51-100mm (moderate), and >100mm (severe). This grading scale will be used by the reviewer to present reactogenicity data.*

    - *Systemic reactions*: chills, nausea, fatigue, myalgia, arthralgia, loss of appetite, headache, rash, and fever. Severity grading scale:
        - *Fever:* present (≥38.0C) or absent
        - *Rash*: none, urticarial, or other
        - *Other systemic AEs*: 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
    - *Other indicators of reactogenicity:* medically attended fever; medication used to prevent or treat fever/other symptoms; staying home due to reaction

- *Temperature*: measured by subject (or guardian) oral route; severity grading scale by 3 categorization methods as follows:
  - 0.5C from 36.0C up to ≥40.C
  - <36.0; ≥36.0 to <37.0; ≥37.0 to <38.0; ≥38.0 to <39.0; ≥39.0 to <40C; ≥40C
  - According to defined cutoffs: 38.0C, 38.5C, 39.0C, 39.5; and 40.0C

- *All Unsolicited Adverse Events (including solicited AEs that persist beyond 7 days); concomitant medications to treat these AEs, prophylactic/therapeutic analgesic/antipyretic medications:* collected after each study injection for 2 months after 1st injection, and 1 month after 2nd injection. Severity of AEs is noted as mild, moderate, or severe. This data were collected on diary card.

- *Serious Adverse Events, Medically Attended AEs, AEs Leading to Withdrawal, and medications to treat these AEs* collected on the Memory Aide from one month after 2nd vaccination through 8 months (Day 241)-end of study.

- *Data Monitoring Committee (DMC) early evaluation:* A pilot group of the 1st 10% of subjects enrolled had their safety data evaluated by an external DMC for the 7 days following vaccinations #1 and #2. If there were no safety concerns, in particular urticarial rash, then the remainder of subjects could continue with their next vaccination. The 7 day data from this pilot group was collected by study personnel (nurse) who used a scripted phone call to contact subjects on Day 8 and Day 68.

  Reviewer Comment: *The applicant states the subject diary cards were the only source for solicited AE data, and that the investigator (or designee) was to review the diary card in the presence of the subject to validate or clarify the recorded data in terms of correctness, completeness, legibility, and accuracy. Of note, this procedure was included in the 2nd amendment to the protocol dated 06 July 2012, and therefore was not implemented until after all subjects were enrolled, and most had completed the protocol. Yet as discussed in Section 6.4.12.2 in the results section of this study's review, despite the late implementation of this procedure, solicited AE data were primarily obtained from source documents.*

6.4.8 Pre-specified Endpoints and Criteria for Study Success

The response variables are listed as follows pertaining to the evaluation of rMenB+OMV only:

*Safety Endpoints: (*as described in Section 6.4.7 above)
All subjects who received at least one vaccination dose, and provided some safety data were considered for the safety analyses. All safety data were evaluated using descriptive statistics.

- Safety variables assessed included
  - Local and systemic solicited reactions during the 7 days following each injection, and by severity, and by group
  - Unsolicited AEs, SAEs, MAAEs, and AEs leading to withdrawal.

6.4.9 Statistical Considerations & Statistical Analysis Plan

All safety data were evaluated using descriptive statistics.

> ***Reviewer Comment****: The study was powered to evaluate immunogenicity objectives which are not applicable to the evaluation of rMenB+OMV in this BLA. Safety testing was only descriptive.*

Missing Data:

- No imputations of missing data were performed.

Significant Changes in the Conduct of the Study:

The final version of the protocol was Version 4.0, dated 11 April 2013. There were 3 protocol amendments to the original protocol which was initially issued in December 2010. The major changes to the protocol relevant to the analyses of rMenB+OMV are listed below by amendment:

Am. 1, May 2011- The following changes were made prior to enrollment of any subject:

- Addition of rMenB+OMV was added as a 4th study group with the addition of the relevant study objective listed above
- Age range changed from 11-18 years to 10-25 years
- DMC formed to conduct safety assessment on first 10% of subjects enrolled, followed by a pause in enrollment to evaluate for safety, particularly urticarial rash

Am. 2, July 2012- The following changes were made after all subjects were enrolled and the majority of subjects had completed the protocol:

- Secondary immunogenicity endpoint was modified to include hSBA titers $\geq$1:8 and 4-fold increase in hSBA titer for serogroup B strains
- Safety data collection instructions included the prohibition of subject recall of solicited AEs at follow-up study visits rather than collection of this data from a protocol specified source document, and clarification of what a primary source for each reported AE was.

Am. 3, April 2013- The following changes were made after all subjects had completed the protocol:

- Specification of serogroup B test strains to be used for assays, including test strain or exploratory analyses

Change in Planned Analyses:

- September 2012: Amendment 2 of the protocol specified that solicited AE data entered onto an eCRF after the 7-day post vaccination monitoring period was no longer permitted. Therefore in September 2012, the applicant retrospectively removed verbally recalled solicited AE data from the eCRF, and transferred the recalled data to the unsolicited AE eCRF page.

6.4.10 Study Population and Disposition

The first subject was enrolled on 08 august 2011 and the last subject completed the study on 08 September 2012. A total of 484 subjects were enrolled in the study, including 122 subjects enrolled in the rMenB+OMV group and 121 subjects in the placebo/Menveo group.

6.4.10.1 Populations Enrolled/Analyzed

Analysis Sets:

- *All Enrolled Population*: all subjects who have signed an informed consent, undergone screening procedures, and were randomized
- *Exposed Population:* all enrolled subjects who actually received a study vaccination
- *Overall Safety Set:* All subjects in the All Exposed Set who provided post-vaccination solicited or unsolicited AE data
- *Solicited Safety Sets:* all subjects in the Exposed Population who provided post vaccination solicited safety data from Day 1 (6 hours) through Day 7. There are separate sets for each vaccination, ie Vaccination #1 and Vaccination #2.
- *Unsolicited Safety Set:* All subjects in the Exposed Population who provided post-vaccination unsolicited AE data
- *Restricted Safety Set:* All subjects in the Unsolicited Safety Set who
    - correctly received the vaccine at Visit 1 and Visit 2
    - did not receive vaccines or take investigational products forbidden in the protocol (major deviations) and
    - for whom the randomization code had not been broken
    - completed the long-term safety follow-up (completed Visit 4)
- In case of randomization errors, subjects were analyzed as treated.

6.4.10.1.1 Demographics

Table 28: Study V102_03 Demographics of All Enrolled Subjects

	rMenB+OMV N= 122	**Placebo/Menveo N=121**
% Female	60 (49%)	64 (53%)
% Male	62 (51%)	57 (47%)
Age –Mean (years)	15.3 ± 4.9	15.0±5.1
Racial origin:	(%)	(%)
-Asian	2 (2%)	0
-Black, Non-Hispanic	4 (3%)	5 (4%)
-White, Non-Hispanic	74 (61%)	72 (60%)
-Hispanic	41 (34%)	41(34%)
-Other	1 (<1%)	3(2%)
Weight	57.7±17.6 kg	61.1±20.6
Height	159.0±13.8	157.2±13.2

Source: Adapted from BLA 125546/0, V102_03 Clinical Study Report, Table 11.2-1 on p.104 of 6361.

Reviewer Comment:

The mean age for all enrolled subjects was 15.0±4.9 years, which is similar to the mean age groups for the rMenB+OMV and Menveo groups. The age range of all study participants was from 10-25 years of age, and the median age for subjects in the rMenB+OMV group was 14.0, and for the placebo/Menveo group was 12.0. Demographic characteristics across these two groups are generally similar.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study was conducted at sites in the US and Poland. Per CBER request the applicant provided study characteristics of the enrolled population by country. There were 352 subjects the enrolled at US sites, including 88 subjects in the rMenB+OMV group and 88 subjects in the

placebo/Menveo group. There were 132 subjects enrolled at Polish sites, including 34 subjects in the rMenB+OMV group and 33 subjects in the placebo/Menveo group. The following table provides the demographic characteristics for US enrolled subjects.

Table 29: Study V102_03 Demographics of All Enrolled US Subjects

	rMenB+OMV N= 88	**Placebo/Menveo N=88**
% Female	46 (52%)	40 (45%)
% Male	42 (48%)	48 (55%)
Age –Mean (years)	13.9 ± 4.6	13.3±4.5
Racial origin:	(%)	(%)
-Asian	2 (2%)	0
-Black, Non-Hispanic	4 (5%)	5 (6%)
-White, Non-Hispanic	40 (45%)	39 (44%)
-Hispanic	41 (47%)	41(47%)
-Other	1 (1%)	3(3%)
Weight	54.61±18.0 kg	60.26±22.3
Height	154.6±12.6	153.1±12.2

Source: Adapted from BLA 125546/0.22, Section 1.11.4, Information Amendment, Table 11.2-1u on p.3 of 22.

Reviewer Comment: *The demographic characteristics of US enrolled subjects differ from that of all enrolled subjects for both countries combined. The median age for US subjects was 12.0 years, and for Polish subjects it was 19.0; and the median weight for US subject was 52.3kg and for Polish subjects it was 64.0kg. As shown in the table above, the racial origin of US subjects was more diverse than that of Polish subjects, which was 100% Caucasian (White). The gender distributions in both countries were similar. The younger age of US subjects in this study reflects current ACIP guidelines which recommend a dose of Menveo (MenACWY conjugate vaccine) at 11-12 years of age.*

6.4.10.1.3 Subject Disposition

There were 484 subjects enrolled and randomized in the study, of which 65 subjects (13% of all subjects) withdrew early, leaving 419 subjects (87% of all subjects) who completed the study. The following table provides the number of subjects enrolled, vaccinated, and included in the analyses populations, in addition to the number of subjects discontinued for various cited reasons.

Table 30: Study V102_03 Disposition of Subjects and Study Populations Evaluated

Population	**rMenB+OMV N= 122**	**Placebo/Menveo N=110***	**Total** N=484**
Enrolled (N)	122	110*	484
Received both Vaccinations	111 (91%)	109 (90%)	438 (90%)
Completed Study	109 (89%)	107 (88%)	419 (87%)
Subjects Discontinued (due to)			
-AE	1 (<1%)	0	1 (<1%)
-Inappropriate enrollment	1 (<1%)	1 (<1%)	2(<1%)
-Lost to follow-up	8 (7%)	10 (8%)	47 (10%)
-Withdrawal of consent	3 (2%)	2 (2%)	13 (3%)
Exposed Population	120 (98%)	110 (100%)	480 (100%)
Overall Safety Population	120 (98%)	109 (99%)	469 (99%)
Solicited Safety Set-Vac #1	114 (93%)	96 (87%)	426 (90%)
Solicited Safety Set-Vac#2	109 (89%)	94 (85%)	409 (86%)
Restricted Safety Set	95 (78%)	80 (73%)	352 (74%)

Source: Adapted from BLA 125546/0, V102_03 Clinical Study Report, Table 10.1-1 on p. 95 of 6361; Table 11.1-1 on p.101 of 6361; Table 14.1.1.8 on p.230 of 6361; N= enrolled; for explanation of analyses populations see text in Section 6.4.10.1.
*There were 121 subjects actually enrolled in the placebo/Menveo group, but 11 subjects in this group received vaccinations 1 & 2 in the incorrect order (Menveo given at 1st vaccination, and placebo at 2nd vaccination), therefore the applicant states that the enrolled population included 110 subjects. Vac#1: vaccination #1; Vac#2: vaccination#2; **The total column includes two additional study groups (----------(b)(4)----------products) not included as part of this review.

Reviewer Comment*: There were 120 subjects who received at least one dose of rMenB+OMV, and there were 112 subjects who received 2 doses of rMenB+OMV, 2 months apart.*

The following table provides a comparison of major protocol deviation for the rMenB+OMV group compared to the placebo/Menveo group.

Table 31: Study V102_03 Summary of Protocol Deviations

Population	**rMenB+OMV N= 122**	**Placebo/Menveo N=121**
Major Protocol Deviation*	30 (25%)	45 (37%)
-No vaccination	2 (2%)	1 (<1%)
-Wrong vaccination course	1 (<1%)	13 (11%)
-Unauthorized Conc. Vaccination	1 (<1%)	4 (3%)
-Visit 1 or 3: No lab result ACWY or B	10 (8%)	15 (12%)
-Visit 1: Entry criteria not met	3(2%)	2(2%)
-Visit1: No blood drawn	1 (<1%)	1 (<1%)
-Visit 2: No vaccination	2 (2%)	1 (<1%)
-Visit 2: Vaccination out of window	11 (9%)	12 (10%)
-Visit 3: Blood draw out of window	8 (7%)	5 (4%)
-Visit 3: No blood drawn	1 (<1%)	1 (<1%)
Minor Protocol Deviation	8 (7%)	12 (10%)
-Visit 1: Entry criteria not met	0	1 (<1%)
-Visit 1: Premature study termination	7 (6%)	10 (8%)
-Visit 2: Premature study termination	1 (<1%)	1 (<1%)

Source: Adapted from BLA 125546/0, V102_03 Clinical Study Report, Table 14.1.1.8 on p. 231 of 6361. * All subjects with a major protocol deviation were excluded from the per protocol immunogenicity populations (not included as part of this review).

Reviewer Comment: *The subject disposition, study populations, and the rates and types of protocol deviations are similar across groups. As described above, more subjects were enrolled at US sites compared to Polish sites. When compared to U.S sites, there were no subjects who were lost to follow-up at Polish sites. All other study characteristics were similar between subjects enrolled at either country.*

6.4.11 Immunogenicity Analyses

Not applicable.

6.4.11.3 Subpopulation Analyses

Please see Section 7.1.2 of this review memo for commentary on subpopulation analyses based on gender and racial origin differences of enrolled subjects.

6.4.11.4 Dropouts and/or Discontinuations

No imputation was performed for missing data, because missing values were regarded as non-informative.

6.4.12 Safety Analyses

6.4.12.1 Methods

As prespecified in the protocol, and defined in Section 6.4.10.1 above, there were several safety populations, included the Exposed Set, Overall Safety Set, Solicited Safety Set, Unsolicited Safety Set, and the Restricted Safety Set. Of the 484 subjects enrolled, 473 subjects comprised the Exposed Set who received at least 1 dose of study vaccination, and 469 subjects were included in the Overall Safety Set and the Unsolicited Safety Set, of which 120 subjects were in the rMenB+OMV and 109 subjects in the Placebo/Menveo group. The Solicited Safety Set #1 included 114 rMenB+OMV subjects (93% of enrolled), and 96 Placebo/Menveo subjects (87%);

and Solicited Safety Set included 109 rMenB+OMV subjects (89%), and 93 Placebo/Menveo subjects (85%).The Restricted Safety Set included 95 rMenB+OMV subjects (78%), and 80 Placebo/Menveo subjects (73%). There were 112 subjects who received 2 doses of rMenB+OMV, 2 months apart.

As outlined in Section 6.4.7, safety data collection for this study included immediate AEs within 30 minutes of vaccination; solicited local/systemic AEs and all unsolicited AEs for 7 days post-vaccination and through one month after the 2nd injection; SAEs, MAAEs, and AEs leading to withdrawal from one month after the 2nd injection through the end of the study. A diary card was provided after each vaccination to collect both solicited and unsolicited AE data, and was collected one month later. A Memory Aide was provided at 'Month 3 Visit' to record SAEs, MAAEs, and AEs leading to withdrawal. During the 'Month 8 Telephone Call' this data were collected by the site with a scripted telephone call.

6.4.12.2 Overview of Adverse Events

Solicited Adverse Events:

The majority of rMenB+OMV recipients reported a solicited adverse event after any dose. After the 1st dose, 92% of rMenB+OMV subjects reported a local reaction, compared to 38% of subjects who had received placebo in the comparator group. After the 2nd dose 83% of rMenB+OMV subjects reported a local reaction, compared to 53% of subjects who had received Menveo. The most common local reaction reported by rMenB+OMV recipients was injection site pain seen in 90% of subjects after the 1st dose, and 83% of subjects after the 2nd dose. Severe pain was seen in 19% of subjects after the 1st dose, and 28% of subjects after the 2nd dose. Injection site erythema was seen in 45-50% of subjects after any dose, with no severe erythema reported. Injection site induration was seen in 28-32% of subjects after any dose, with no severe induration reported.

The most common systemic reaction was myalgia, reported by 49% of rMenB+OMV recipients, compared to 26% of placebo recipients after the 1st vaccination. After the 2nd vaccination, myalgia was reported by 48% of rMenB+OMV recipients compared to 25% of Menveo recipients. Severe myalgia was reported by 12-13% of subjects after either dose of rMenB+OMV, and by 1 subject after placebo administration, and 4 subjects after Menveo administration. Other common systemic reactions included headache and fatigue, seen in 32% and 36% of rMenB+OMV subjects after the 1st injection; and 34% and 35% of subjects after the 2nd injection, respectively. Severe headache or fatigue was seen in 4-6% of subjects after any dose. Fever ($T \geq 38.0C$) was reported by 1 subject after the 1st rMenB+OMV vaccination, and by 5 subjects after the 2nd vaccination. Prophylactic use of antipyretic medication was reported by 11% of subjects prior to the 1st vaccination and 7% of subjects prior to the 2nd vaccination of rMenB+OMV. Therapeutic use of antipyretic medication was reported by 13-15% of subjects after either dose.

> ***Reviewer Comment:*** *The rates of solicited AE by any rMenB+OMV containing formulation were consistently higher than that observed following administration of either placebo or Menveo. The rates reported by any of the rMenB+OMV containing formulations were generally similar for each solicited reaction and followed the same trends by dose. The most common solicited reactions were injection site pain and myalgia. Reports of fever were generally low for this study population. The use of antipyretic medication as a preventive measure was similar prior to the administration of rMenB+OMV or Menveo, though it's therapeutic use was higher after the administration of rMenB+OMV compared to after Menveo.*

Revised Solicited Adverse Event Rates:
After initiating study V102_03, the applicant undertook improvements to safety data collection with CBER's concurrence. The applicant implemented improvements to safety data collection procedures which did not permit retrospective recall of reactogenicity data. This procedural change was incorporated into the study protocol and in the analysis of safety data. During this review cycle, the applicant confirmed that diary card entries by the study subject/parent or guardian were the only source allowed for the collection of solicited AE data and that subject recall of solicited adverse events data beyond the 7 day post-vaccination period were not permitted for this study. As was done with all other main studies, the applicant has provided revised reactogenicity rates for this study which exclude data that appeared to be obtained by subject recall several weeks or months after the 7-day post vaccination monitoring period when the source document appeared to be missing.

Table 32: Study V102_03 Revised Reactogenicity Rates: % of Subjects with Any & *Severe* Solicited Local & Systemic Adverse Events for 7 Days Post-vaccination, by dose

		Dose 1		Dose 2[b]	
		BEXSERO	**Placebo (Saline)**	**BEXSERO**	**Menveo**
Solicited Reaction[a]		N=110-114	N= 94-96	N=107-109	N=90-92
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	> 50-100 mm	1	1	2	4
	> 100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Source: Adapted from BLA 125546 Am 0.21 (Information Amendment-Safety Data submitted 10/23/2014) Table 6-4; and from Am. 0.43 (Information Amendment- Draft Labelling submitted 1/13/2014 under sequence 1.14.1.3 Draft Labeling Text). [a] saline placebo.

***Reviewer Comment**: It does not appear that a substantial amount of subject recall of solicited AE data occurred in this study, as the revised reactogenicity rates remained overall very similar when compared to the rates provided in the CSR.*

Unsolicited Adverse Events during Entire Study:
Based on the Unsolicited Safety Set, 59% of rMenB+OMV subjects reported at least one unsolicited AE, compared to 55% placebo/Menveo subjects over the entire study period (Day 1 to Day 241. By MedDRA preferred term, the most frequently reported AEs across groups included upper respiratory tract infection (rMenB+OMV 9%, placebo/Menveo 7%); headache (7%, 7%); nasopharyngitis (5%, 5%); and pharyngitis (6%, 5%). The majority of rMenB+OMV subjects who reporting an adverse event, graded the severity as mild or moderate, though there were 4 rMenB+OMV recipients who reported severe intensity injection site induration or pain. Subjects that considered an AE at least possibly related to vaccination included 13% of the rMenB+OMV group, and 6% of the Placebo/Menveo group. The most commonly reported AE in the rMenB+OMV group that was considered at least possibly related to vaccination was injection site induration.

Unsolicited Adverse Events during first 30 days:
Within the first 30 days after any vaccination the rates of unsolicited AEs were 38% in the rMenB+OMV group, and 28% in the placebo/Menveo group. The types of AEs (by SOC) reported during the first 30 days after any vaccination were representative of what was reported throughout the study

MAAEs from Day 91 to Day 241:
The rates of MAEES from Day 91 to Day 241 were similar across groups (20-28%), and were not considered related to vaccination.

6.4.12.3 Deaths

There were no deaths in this study.

6.4.12.4 Nonfatal Serious Adverse Events

There were a total of 8 SAEs, including 1 in the rMenB+OMV group and 3 in the Placebo/Menveo group. The one SAE in rMenB+OMV group included the following:

- rMenB+OMV:
    - Subject #24066: Convulsion. 11 yo male with a past medical history significant for seizure disorder, asthma, and syncope received 1 dose of rMenB+OMV. The subject's prior history of seizures was not known at the time of enrollment, which had been increasing in frequency. The subject experienced a grand mal seizure 59 days after his last vaccination. The seizure lasted several minutes, and was followed by a period of unconsciousness (5 minutes), and required hospitalization. EEG was positive (left frontal lobe) and a head CT was normal. The subject was treated with Ativan and Keppra. The subject also had seizures involving the mouth and face 34 days and 57 days after the last vaccination. The SAE was considered ongoing, and the investigator considered the seizure activity as unrelated to vaccination.
- Placebo/Menveo group: the 3 SAEs in the Placebo/Menveo group were in subjects who experienced abdominal pain; spermatocele; sleep apnea syndrome. There was a 4th SAE in a subject in this group who received vaccinations in the incorrect order (Menveo/Placebo), who was diagnosed with multiple sclerosis ~ 3 months, after administration of Menveo. None of the SAEs in any group were considered by the investigator to be related to vaccination.

  Reviewer Comment: *The SAE of convulsion in the rMenB+OMV recipient appears to have been a pre-existing condition that was not captured at the time of enrollment. It is unlikely related to vaccination.*

6.4.12.5 Adverse Events of Special Interest (AESI)

There 2 pregnancies during the 8 month study period, one of which were in the rMenB+OMV group: Subject #28/028 was vaccinated on 10/18/2011 and gave birth on ---(b)(6)--- to full-term infant without congenital anomalies.

For additional review of AESI across all studies, please see Section 8 for an overview of AESI across all studies.

6.4.12.6 Clinical Test Results

N/A

6.4.12.7 Dropouts and/or Discontinuations

There were 2 subjects in the rMenB+OMV group who prematurely withdrew from the study due to an unsolicited AE as follows:

- Subject #24066: Convulsions. See Section 6.4.12.4 above for case narrative.
- Subject #11/040: Lymphadenopathy. 23 year old female had received one dose of rMenB+OMV, and five days later developed moderate generalized lymphadenopathy (non-vaccine site) and withdrew from the study prior to receiving the next dose. The investigator considered the AE to be possibly related to vaccination.

  Reviewer Comment*: The AE of generalized lymphadenopathy is possibly related to vaccination*.

6.4.13 Study Summary and Conclusions

In this study, the applicant evaluated two doses of rMenB+OMV administered two months apart in subjects 10 through 25 years of age, including 72% who were enrolled at a US site with a median age at enrollment of 12 years in the US, compared to 19 years in Poland. The younger US cohort reflects current ACIP guidelines which recommend that the study comparator (Menveo) be given to individuals 11-12 years of age. Therefore the evaluation of rMenB+OMV in US subjects in this study was at a clinically relevant time point for adolescents in the US vaccination schedule.

The safety data collection procedures for this study did not permit subject recall of solicited adverse event data, therefore the revised reactogenicity rates remained overall very similar to the original rates presented in the submitted clinical study report. The most frequently reported solicited reactions were injection site pain, injection site erythema, and myalgia. Severe injection site pain was reported by ~20-29% of subjects, and severe myalgia was reported by 12-13% of rMenB+OMV recipients. The rates of reported unsolicited adverse events were higher in the rMenB+OMV group than in the Menveo group, with a greater difference noted in the first 30 days (38% versus 28%), when compared to the entire study period (59% versus 55%). The most frequently reported types of unsolicited adverse events over the entire study period across groups were similar and included upper respiratory tract infection, headache, nasopharyngitis, and pharyngitis. More rMenB+OMV recipients reported an adverse event as at least possibly related to vaccination than control recipients (13% versus 6%). The most frequently reported unsolicited AE that was considered at least possibly related to vaccination was injection site induration that persisted beyond 7 days. There were no serious adverse events which were considered by this reviewer to be related to vaccination, and there were no deaths in this study.

Based on the overall study findings, the vaccine is safe for its intended use in the prevention of invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10-25 years of age.

6.5 Trial #5: Study V72P13

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

6.5.1 Objectives

Primary Immunogenicity Objective:

- To show the consistency of immune response from 3 lots of rMenB+OMV, by serum bactericidal activity Geometric Mean Titer response (hSBA GMTs) when administered to healthy infants at 2, 4, and 6 months of age at 1 month after the 3rd vaccination.

Safety Objective:

- To assess the safety and tolerability of 3 doses of rMenB+OMV when given concomitantly with routine infants vaccines at 2, 4, and 6 months of age.

Reviewer Comment*: Study V72P13 was a Phase 3 study conducted from March 2008 until January 2010. The following comments are provided to support the inclusion of Study V72P13 in this BLA and to add clarity on study limitations in the context of the indication that the applicant is seeking.*

1. *Study V72P13 was designed to assess the consistency of the immune responses following administration of vaccines from 3 different lots of rMenB+OMV when given to infants as 3 doses. Though this study is not in the age group for which the applicant is seeking licensure, the study provides an adequate characterization of lot-to-lot consistency based on pre-specified immunological criteria.*
2. *The study also evaluated the immunogenicity and safety of the candidate vaccine in an infant population. This infant data will not be reviewed for effectiveness as the population that the applicant is seeking to obtain licensure for is 10 to 25 years of age. Therefore study objectives and data pertaining to the consistency of the 3 different lots evaluated in this trial will only be presented. The reviewer will evaluate the safety data to determine if the safety profile across the 3 different lots was consistent.*

6.5.2 Design Overview

Study V72P13 is a Phase 3, partially blinded, multi-center, randomized controlled study in healthy infants in Europe evaluating the consistency of 3 different lots of rMenB+OMV. The study also evaluated the immunogenicity and safety of 3 doses administered at 2, 4, 6 months of age in infants concomitantly administered with routine infants vaccines (RIV) [31] compared to RIV alone, or a meningococcal group C vaccine concomitantly administered with RIV.

5 Study Groups-each infant group received 3 doses of study vaccine as follows (N=#enrolled):

- Group 1- Lot 1 rMenB+OMV with RIV: 2 mo., 4 mo., and 6 mo. of age (N=833)
- Group 2- Lot 2 rMenB+OMV with RIV: 2 mo., 4 mo., 6 mo. of age (N=828)
- Group 3- Lot 3 rMenB+OMV with RIV: 2 mo., 4 mo., 6 mo. of age (N=820)
- Group 4- RIV only: 2 mo., 4 mo., 6 mo. of age (N=659)
- Group 5- Meningococcal Group C vaccine[32] with RIV: 2mo., 4mo., 6mo. of age (N=490)

31 Infanrix-Hexa® (DTPa-HBV-IPV/Hib)- not licensed in the US; and Prevenar® (Pneumococcal 7-valent Conjugate Vaccine)- licensed in the US as Prevnar®.
32 Menjugate® (meningococcal group C vaccine)- not licensed in the US.

Reviewer Comment:

1. *Only data pertaining to Study Groups 1, 2 and 3 will be evaluated in order to assess lot-to-lot consistency of rMenB+OMV.*
2. *Subjects in Groups 1, 2, and 3 were randomized 1:1:1.*

Healthy infants 2 months of age (55-89 days of age) who were the product of a full term pregnancy with an estimated gestational age ≥37 weeks and a birth weight of ≥2.5kg were included in the trial. The study was conducted in Italy, Germany, Austria, Finland, and Czech Republic.

As described above, study groups 1, 2, and 3 evaluated three different lots of rMenB+OMV and enrolled ~800 subjects per group. There were two different study design approaches for subjects enrolled in these groups, and each study design specified different variables to be assessed. These included the following:

- Observer-blinded approach[33] for ~200 subjects/group
  - subjects had safety only assessed (through 12 months of age)
- Open-label approach[34] for ~600 subjects/group
  - subjects had safety assessed (through 12 months of age), in addition to immunogenicity assessed at baseline (2 months of age) and again at one month post dose-3 (7 months of age).

Reviewer Comment*: The study was designed to be partially open-label, and partially observer-blinded.*

The immunogenicity variables assessed pertinent to the evaluation of lot to lot consistency include the following:

- hSBA GMTs and Geometric Mean Ratio (GMR) against strains H44/76, 5/99, and NZ98/254 prior to the 1st dose and 30 days post-dose 3.

Reviewer Comment*: Immunogenicity was evaluated in only those subjects enrolled in the 'immunogenicity subset' in Groups 1, 2, 3, and 4 at sites in the Czech Republic and Finland. Sera were to be collected from these subjects at baseline and 1 month post-dose 3 for hSBA testing for strains H44/76, 5/99, and NZ98/254 in ~400 subjects in each of the 3 different lot groups.*

The safety variables assessed in this trial include the following

- medical history; all medications (except vitamins, and creams); and all vaccinations from birth through Day 1 of study
- immediate reactions 30 minutes after each vaccination dose
- daily assessment for 7 days post-vaccination: daily body temperature (rectally recommended, but axillary route allowed), medically attended fever, anti-pyretic medications (prophylactic/therapeutic); solicited reactogenicity, including injection site reactions (tenderness, erythema, swelling, induration), and systemic reactions (change in eating habits,

33 Observer-blinded: each subject's parents/caretakers, as well as the investigators evaluating the subject would be blinded as to whether the subject received the investigational vaccine (rMenB+OMV) with RIV in Groups 1, 2 or 3; or the comparator meningococcal C conjugate vaccine with RIV in Study Group 5. The study personnel administered the vaccines were not blinded, but were not involved in the monitoring or conduct of the trial, and these personnel were instructed not to reveal the identity of the vaccines to the subject's family or the study site personnel involved in monitoring or conduct of the trial.

34 Open-label: subject's parents/caretakers and the investigators were unblinded to determine the specific impact of rMenB+OMV on safety and the immunogenicity profile of RIV in Groups 1, 2, and 3, compared to RIV alone in Group 4. This was done to separate any confounding contribution that meningococcal group C conjugate vaccine might have on the immune response to RIV in Group 5.

sleepiness, unusual crying, vomiting, diarrhea, irritability, rash); all adverse events (including Medically Attended Adverse Events (MAAEs); adverse events leading to withdrawal; SAEs; and all medications

- assessments from Day 8 through next vaccination or 30 days after last vaccination: SAEs; MAAEs; AEs leading to withdrawal; solicited reactions persisting beyond 7 days; all medications for treatment of adverse events; and all vaccinations
- assessment from Day 31 after last vaccination to last study visit (end of study): SAEs; MAAEs; adverse events leading to withdrawal; all medications for treatment of adverse events; and all vaccinations

6.5.3 Study Treatments: Lot Numbers of rMenB+OMV Vaccine Evaluated

The vaccine description for rMenB+OMV, including composition is provided above in Section 6.1.4 of this review.

The 3 rMenB+OMV vaccine lots compared in this trial for lot to lot consistency differed by the country of enrollment. The lot numbers by country include the following:

- Italy:
  - X38D27N1A; X38D28N1; X38D29N1
- Austria:
  - X38D27N1B; X38D28N1A; X38D29N1A
- Germany:
  - X38D27N1B; X38D28N1A; X38D29N1A
- Finland:
  - X38D27N1D; X38D28N1C; X38D29N1C, and
  - X38D27N1C; X38D28N1B; X38D29N1B
- Czech Republic:
  - X38D27N1E; X38D28N1D; X38D29N1D

Reviewer Comment*: During the review cycle and per CBER request, the applicant provided clarification on the numbering system used for each lot number listed above.*[35] *The last letter (ie A, B, C, etc) at the end of some of the lot numbers indicates the packaging order of the lot. The same 3 lots were evaluated in each country, and included the following:*

- Lot 1 *was* X38D27N1
- Lot 2 was X38D28N1
- Lot 3 was X38D29N1

6.5.4 Endpoints and Criteria for Study Success

The response variables and criteria for study success pertaining to the evaluation lot to lot consistency of 3 different lots of rMenB+OMV are presented below.

Analysis of Immunogenicity Criteria for Lot-to-Lot Consistency:

- For the primary immunogenicity objective (hSBA GMTs): the 3 lots of rMenB+OMV were considered equivalent if for each of the 3 strains and each pair of vaccine lots, the 2-sided 95% CI on the ratio of GMTs at 1 month post dose-3 was contained within the interval [0.50, 2.00].

35 BLA 125546/0.22; Section 1.11.3 (10/30/2014)

6.5.5 Immunogenicity Analyses

The results presented below for Study V72P13 pertain only to lot to lot consistency of the immune response for the 3 different lots of rMenB+OMV evaluated in study groups 1, 2, and 3.

Primary Immunogenicity Objective
This objective evaluated the GMT hSBA titers 1 month post dose-3 using three different indicator test (reference) strains to evaluate the immune response to its respective vaccine antigen as follows:

- H44/76 which evaluated the immune response to vaccine antigen fHbp
- 5/99 which evaluated the immune response to vaccine antigen NadA
- NZ98/254 which evaluated the immune response to vaccine antigen PorA P1.4

As mentioned above, if the 2-sided 95% CI on the ratio of GMTs for the lot-to-lot comparisons was between 0.50 and 2.00, then the objective was met. The table below provides the baseline hSBA GMTs and 1 month post dose-3 hSBA GMTs. In addition it provides the lot-to-lot ratio of 1 month post dose-3 GMTs as follows:

- Lot 1:Lot 2
- Lot 2:Lot 3
- Lot 2:Lot 3

For all three indicator strains, the lot-to-lot ratios ranged from 0.88 to 1.12, of which the lowest 95% CI was 0.79 and the highest 95% CI was 1.24. Therefore the primary immunogenicity objective was met.

Table 33: Study V72P13 GMT hSBA Titers at Baseline & 1 month Post Dose-3; and Lot-to-Lot Ratio of Titers (95%CI) by MenB Test Strain-Per Protocol Set

Strain	Time	Lot 1 N=384-386	Lot 2 N=379-380	Lot 3 N=390-394	Lot1:Lot2	Lot1:Lot3	Lot2:Lot3
H44/76 (fHbp)	Baseline	8.15 (8.02-8.29) N=383	8.07 (7.93-8.2)	8.22 (8.08-8.36)	1.01 (0.99-1.03)	0.99 (0.97-1.01)	0.98 (0.96-1)
	1 mo. PD #3	88 (82-95)	98 (91-106) N=377	88 (81-94) N=388	**0.89 (0.81-0.99)**	**1 (0.91-1.11)**	**1.12 (1.02-1.24)**
5/99 (NadA)	Baseline	8.26 (8.05-8.48)	8.17 (7.96-8.39) N=379	8.36 (8.15-8.58)	1.01 (0.98-1.05)	0.99 (0.95-1.02)	0.98 (0.94-1.01)
	1 mo. PD #3	599 (553-649) N=384	681 (629-739)	618 (570-670) N=388	**0.88 (0.79-0.98)**	**0.97 (0.87-1.08)**	**1.1 (0.99-1.23)**
NZ98/254 (PorA P1.4)	Baseline	4.03 (3.98-4.09)	4.05 (3.99-4.11)	4.01 (3.95-4.06)	1 (0.98-1.01)	1.01 (0.99-1.03)	1.01 (0.99-1.03)
	1 mo. PD #3	15 (13-17) N=385	15 (13-17) N=378	16 (14-18) N=389	**1 (0.86-1.17)**	**0.94 (0.8-1.09)**	**0.93 (0.8-1.09)**

Source: Adapted from BLA 125546/0, V72P13 Clinical Study Report, Table 11.4.1-1 on p.126 of 20649; and from BLA 125546/ 0.17, Section 1.11.3 Information Amendment, Response to Question 5, Table Q5-1 on p.25 of 31. GMT: Geometric Mean hSBA titers; 1mo. PD3: 1 month post dose-3; GMR: Geometric Mean Ratios of 1 month post dose-3 to baseline.

Reviewer Comment*: During the review of the BLA, CBER had sent the applicant an information request (September 5, 2014) requesting that the applicant reanalyze the data comparing the GMTs across lots after setting all values less than the LLOQ to ½ the LLOQ. This information was provided to the BLA on October 3, 2014 under Amendment 0.17.*

The re-analysis demonstrated that the immunogenicity of all 3 lots of rMenB+OMV were equivalent, with the lowest 95% CI, 0.79 and the highest 95% CI limit, 1.24. Both of the limits are contained within the applicant's pre-specified interval demonstrating lot-to-lot consistency [0.50, 2.00] for the primary immunogenicity objective. This re-analysis confirmed findings observed from the applicant's original analysis[36] of the primary objective.

Therefore the primary immunogenicity objective evaluating the lot to lot consistency of the immune response based on hSBA GMTs one month after the 3rd dose of rMenB+OMV was met.

6.5.6 Safety Analyses[37]

***Reviewer Comment**: The safety data collected in infants from Study V71P13 was evaluated for any inconsistencies in the safety profile of each of the 3 lots assessed.*

Solicited Adverse Events:
The rates of reactogenicity were similar across all three lots. The rates of any local reaction ranged from 85% to 95% across all 3 lots and across all 3 vaccination doses. The rates of any systemic reaction across all 3 lots were similar, but differed after each dose as follows:

- 1st dose: 96%-97% across all 3 lots
- 2nd dose: 95% across all 3 lots
- 3rd dose 90%-91% across all 3 lots

***Reviewer Comment:** Further analyses of the rates of fever (T≥38.5C), severe fever (T≥40C); and medically attended fever did not reveal any differences in rates across the 3 lots evaluated.*

Unsolicited Adverse Events:
The rates of any unsolicited adverse events across all 3 lots were similar, but also differed after each dose as follows:

- 1st dose: 44-47% across all 3 lots
- 2nd dose: 54% across all 3 lots
- 3rd dose: 75%-77% across all 3 lots

The rates of serious adverse events across all 3 lots were similar for the 1st and 2nd dose (1%-2%), and slightly higher after the 3rd dose (5%-7%), though similar across lots. In addition based on MedDRA System Organ Class (SOC), the rates of SAEs by class were similar, including for the most common SOC, 'Infection and Infestation' with an incidence of ~5-7% across lots for these adverse events. There were no deaths in this study. A review of adverse events of special interest will be presented in Section 8, Integrated Summary of Safety.

***Reviewer Comment:** No important safety concerns were identified and no safety findings indicative of manufacturing inconsistency were observed in this study.*

6.5.7 Study V72P13 Conclusion

Study V72P13 evaluated three different lots of rMenB+OMV for consistency of immune response across manufacturing lots in ~1100 subjects in 5 different countries, including Italy,

36 Original analysis: the lowest 95% CI limit was 0.78 and the highest 95% CI limit was 1.27, both of which are contained within the pre-specified interval of [0.50, 2.00].
37 *Source: Adapted from BLA 125546/0, V72P13 Clinical Study Report, Table 12.2.1-2; Table 12.2.1-4; Table 14.3.1.1.3.6.1;*

Germany, Austria, Finland, and Czech Republic. Although the study was not conducted in the 10-25 year old age group for which the applicant is seeking a licensed indication, it did provide an important comparison of the consistency of immune response across different vaccine lots. The study met its primary immunogenicity objective, which assessed lot-to-lot consistency based on the ratio of hSBA GMTs at 1 month after the 3rd vaccination. The study also met its secondary immunogenicity objective which evaluated the differences across lots in the percentage of subjects with hSBA titer ≥1:5 one month after the 3rd dose. The applicant has satisfactorily demonstrated consistency of lot performance across the 3 different lots. In addition, there were no unexpected increases in the rates or types of adverse events seen, thus indicating similar safety profiles across lots.

6.6 Trial #6: Study V72P16

A Phase 2 Partially Observer-Blind Randomized Controlled Multicenter Dose-Ranging and Formulation-Finding Study of a Meningococcal B Recombinant Vaccine Evaluating the Safety and Immunogenicity When Given Concomitantly with Routine Infant Vaccines in 2-month old Infants.

6.6.1 Objectives

Primary Immunogenicity Objective:

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

Primary Safety Objective:

- If subjects enrolled in Groups 2-6 or Group 8 (different vaccine formulations/doses per group) had a reduced incidence in fever (T≥38.5C rectal) within 3 days following the 1st vaccination when compared to the incidence of fever in subjects enrolled in Group 1, which evaluated rMenB+OMV formulation.

  Reviewer Comment: *Study V72P16 was included in this BLA to provide supportive data for final dose and formulation selection for the applicant's final vaccine formulation, rMenB+ OMV. Only the relevant study objectives pertaining to final formulation and dose selection are presented; and not those objectives pertaining to the safety and immunogenicity of the investigational vaccine in an infant population.*

6.6.2 Design Overview

Study V72P16 is Phase 2, partially observer-blind, multi-center, randomized controlled study in healthy infants conducted in the Czech Republic, Italy, Hungary, Chile, and Argentina which evaluated different formulations of rMenB+OMV based on a reduction of OMV alone (½ or ¼ dose) or a reduction of both the recombinant proteins and OMV (½ dose both). Other formulations evaluated included rMenB alone, in addition to rMenB+OMV formulation manufactured by a different process ('Phase 2' versus 'Phase 3'). All groups received concomitant routine infant vaccines (RIV) [38], and the control group received a meningococcal C vaccine.[39]

38 Infanrix-Hexa® (DTPa-HBV-IPV/Hib)- not licensed in the US; and Prevenar® (Pneumococcal 7-valent Conjugate Vaccine)- licensed in the US as Prevnar®.
39 The control group received meningococcal C vaccine Menjugate® manufactured by Novartis Vaccines & Diagnostics, which is not licensed in the US.

8 Study Groups-each infant group received 3 doses of study vaccine as follows (N=#enrolled):

- Group 1- rMenB+OMV with RIV: 2mo., 3mo., 4 mo. of age (N=188)
- Group 2- rMenB+ ½ OMV with RIV: 2mo., 3mo, 4mo. of age (N=190)
- Group 3- rMenB+ ¼ OMV with RIV: 2mo., 3mo., 4 mo. of age (N=192)
- Group 4- rMenB alone with RIV: 2mo., 3mo., 4 mo. of age (N=188)
- Group 5- ½ (rMenB+OMV) with RIV: 2mo., 3mo., 4 mo. of age (N=191)
- Group 6- Phase 2 manufactured rMenB+OMV with RIV: 2mo., 3mo., 4 mo. of age (N=188)
- Group 7- Meningococcal C vaccine with RIV: 2mo., 3mo., 4 mo. of age (N=186)
- Group 8- Paracetamol prior to rMenB+OMV with RIV: 2mo., 3mo., 4 mo. of age (N=184)

Reviewer Comment:

1. *Study V72P16 was designed to evaluate whether a different formulation of rMenB+OMV or a change in the formulation manufacturing process would result in a reduced frequency of febrile reactions in an infant population when compared to the presumptive final formulation, rMenB+OMV as a 3 dose primary immunization regimen. The reviewer will present the overall safety profile and the associated immune response for the relevant formulations evaluated in this study, and not the fever profiles of each vaccine in an infant population.*
2. *Data from the relevant formulations evaluated in Study Groups 1-6 will be included in this review.*
3. *Based on the study design of each group, subjects and investigators were either blinded or unblinded to treatment group assignment.*
4. *In Amendment 2 (21 January 2010) to the protocol, the study was expanded to allow all subjects to receive a booster dose of the same vaccine at 12 months of age. The study objectives associated with the additional booster dose immunogenicity will not be reviewed.*
5. *Group 1 subjects received the applicant's selected final formulation, rMenB+OMV.*
6. *Group 6 subjects received rMenB+OMV formulation manufactured by a "Phase 2 process" versus a Phase 3 process. The quantity of rMenB proteins (150ug) and OMV (25ug) will remain the same as the formulation being evaluated in Group 1.*
7. *Group 7 subjects received meningococcal group C vaccine at 2, 3, and 4 months, followed by 2 doses of rMenB+OMV (one dose at 12 months, one dose at 13 months). A booster dose of meningococcal group C vaccine was offered as a non-test vaccine at 13 months as well. In addition all subjects in other groups were offered a 1st dose of the same meningococcal group C vaccine at 13 months of age as a non-test vaccine.*
8. *Group 8 subjects received oral anti-pyretic medication paracetamol before and after vaccination as follows: before or at the time of vaccination at the study site, and then after vaccination by parents for 2 more doses at 4-6 hour intervals after vaccination. The dose was 10-15 mg/kg.*

Healthy infants 2 months of age (55-89 days of age) who were the product of a full term pregnancy with an estimated gestational age ≥37 weeks and a birth weight of ≥2.5kg were included in the trial. Subjects were excluded if they had received any other antipyretic medication in the prior 6 hours before enrollment. The study was conducted in Czech Republic, Italy, Hungary, Chile, and Argentina.

The immunogenicity variables assessed pertinent to the evaluation of dose and formulation selection include the following:

- percentage of subjects with hSBA titers ≥1:5 against strains 44/76-SL, 5/99, and NZ98/254 prior to the 1st dose and 30 days post-dose 3

- hSBA GMTs and Geometric Mean Ratio (GMR) against strains 44/76-SL, 5/99, and NZ98/254 prior to the 1st dose and 30 days post-dose 3.

  Reviewer Comment: *The reviewer notes that the immunogenicity endpoints specified in the protocol are exploratory and are used by the applicant for dose selection, and are not used to demonstrate effectiveness.*

The safety variables assessed in this trial include the following

- medical history; all medications (except vitamins, and creams); and all vaccinations from birth through Day 1 of study
- immediate reactions 30 minutes after each vaccination dose
- daily assessment for 7 days post-vaccination: daily body temperature (rectal), medically attended fever[40], anti-pyretic medications (prophylactic/therapeutic); solicited reactogenicity, including injection site reactions (tenderness, erythema, swelling, induration), and systemic reactions (change in eating habits, sleepiness, unusual crying, vomiting, diarrhea, irritability, rash); all adverse events (including Medically Attended Adverse Events (MAAEs); adverse events leading to withdrawal; SAEs; and all medications
- assessments from Day 8 through next vaccination or 30 days after last vaccination: SAEs; MAAEs; AEs leading to withdrawal; solicited reactions persisting beyond 7 days; all medications for treatment of adverse events; and all vaccinations
- assessment from Day 31 after last vaccination to last study visit (end of study): SAEs; MAAEs; adverse events leading to withdrawal; all medications for treatment of adverse events; and all vaccinations

6.6.3 Study Treatments: Lot Numbers used for Each Formulation Evaluated

The vaccine description for rMenB+OMV, including composition is provided above in Section 6.1.4 of this review. The following lots of each formulation were used for the 3 dose primary vaccinations administered at 2, 3, and 4 months of age:

- Group 1- rMenB+OMV: X38D28N1-I, -A3, -A5, -L
- Group 2- rMenB+ ½ OMV: X38D28N1-R, -A1, -A9, -S
- Group 3- rMenB+ ¼ OMV: X38D28N1-T,-Y,-A7,-U
- Group 4- rMenB: Z37P22N1-A,-AG,-AH,-AA
- Group 5- ½ (rMenB+OMV): X38D28N1-P, -A2, -A8,-Q
- Group 6- Phase 2 manufactured rMenB+OMV: Z38D30N1, Z38D30N1-B,-C, -A
- Group 7- Meningococcal C vaccine-Menjugate ®: 266011B, 266011N, 266011Q, 266011C
- Group 8-Paracetamol with rMenB+OMV: X38D28N1-M, -A4,-A6, -N

6.6.4 Endpoints and Criteria for Study Success

The success criterion for this study is a composite based upon meeting the primary immunogenicity and safety objective by at least one vaccine formulation.

Analysis of Immunogenicity Criteria:

- For the primary immunogenicity objective (percentage of subjects with hSBA titers $\geq$1:5): the antibody response for each of the formulations evaluated was considered sufficient if, for each of the *N. meningitidis* serogroup B strains 44/76-SL, NZ98/254, and 5/99, the lower limit of the 2-sided 95% CI (ie, the lower limit of the 1-sided 97.5% CI) for the percentage of subjects with hSBA $\geq$1:5, at 1 month post dose-3 was at least 65%.

40 Medically attended fever was defined as a rectal temperature $\geq$38.5C

Analysis of Safety Criteria:

- For the primary safety objective (reduced incidence of fever in the 3 days post-vaccination in Groups 2-6, and Group 8 compared to Group 1): the percentage of subjects with fever >38.5C (rectal temperature) within 3 days (Days 1, 2, and 3) after the 1st vaccination was tabulated by vaccine group. The pair-wise comparisons of the percentage of subjects with fever between any of the 6 different formulations: rMenB+½ OMV; rMenB+¼ OMV; rMenB; ½(rMenB+OMV); Phase 2 formulated rMenB+OMV; or paracetamol with rMenB+OMV compared to rMenB+OMV (Group 1) was performed using Pearson's chi-square test, or Fischer's Exact test where appropriate due to small expected cell sizes. The null and alternative hypothesis were as follows:

  H_0: $P_{GroupsK} = P_{Group\ 1}$
  H_a: $P_{GroupsK} \neq P_{Group\ 1}$

  Reviewer Comment: *The purpose of this safety objective is to characterize the fever/safety profile of the evaluated formulations in an infant population, and not in an adolescent/young adult population. Therefore the results of this analysis will not be presented.*

6.6.5 Immunogenicity Analyses

The immunogenicity results for Study V72P16 which evaluated 3 doses of different doses and formulations of the study vaccine in an infant population are presented below.

Primary Immunogenicity Objective
This objective evaluated the percentage of subjects with hSBA titer ≥1:5 one month after the 3rd dose against three serogroup B indicator strains (44/76-SL, NZ98/254, and 5/99). The immune response was considered sufficient if for each strain the lower limit of the 2-sided 95% CI for the percentage of subjects with hSBA ≥1:5 was at least 65%. The table below provides the baseline and one month post 3rd dose values for the percentage of subjects with hSBA titer ≥1:5 by indicator strains for Study Groups 1-6.

For all 3 indicator strains and all formulations assessed, the percentage of subjects with hSBA titers ≥1:5 at baseline was low. For indicator strains 44/76-SL (fHbp antigen) and 5/99 (NadA antigen), the percentage of subjects with hSBA titers ≥1:5 one month post dose-3 was 99%-100%, and the lower limit of the 95%CI was 96%-98%. For these two indicator strains, the primary objective was met for all formulations evaluated in Groups 1-6. Yet for indicator strain NZ98/254 (PorA P1.4 antigen), only the formulations evaluated in Group 1 (rMenB+OMV) and Group 6 (rMenB+OMV manufactured by 'Phase 2' process) met this objective. For either group, 78%-81% of subjects had hSBA titers ≥1:5, and the lower limit of the 2-sided 95% CI was 71%-74%. In contrast, only 1% of subjects in Group 4 (rMenB alone); and 56%-67% of subjects in Group 2 (rMenB+ ½ OMV), Group 3 (rMenB+ ¼ OMV), or Group 5 (½ (rMenB+OMV)) had a sufficient immune response one month post-dose 3. Therefore only rMenB+OMV formulation generated a sufficient immune response in the evaluated infant population as defined by the criteria for success for the primary objective.

Table 34: Study V72P16 Percentage of Subjects with hSBA ≥1:5 at Baseline & 1 month Post Dose-3 by MenB Test Strain-StudyV72P16 Per Protocol Set

Strain (Ag)	Time	Group 1: rMenB+OMV N=165-171	Group 2: rMenB+ ½ OMV N=167-174	Group 3: rMenB+ ¼ OMV N=161-171	Group 4: rMenB N=166-174	Group 5: ½(rMenB+OMV) N=166-172	Group 6: Phase 2 process rMenB+OMV N=166-173
44/76-SL (fHbp)	Baseline	5% (2-9) N=166	2% (0-5)	4% (1-8)	4% (2-8)	4% (2-8)	4% (2-8)
	1 mo. PD #3	100% (**98**-100)	99% (**97**-100) N=170	99% (**97**-100) N=166	100% (**98**-100) N=166	99% (**97**-100)	99% (**96**-100) N=167
5/99 (NadA)	Baseline	5% (2-9) N=162	3% (1-7) N=162	6% (3-10)	4% (2-9) N=161	8% (5-14)	4% (2-8)
	1 mo. PD #3	99% (**97**-100)	100 (**98**-100)	99% (**97**-100)	100% (**98**-100)	100% (**98**-100) N=165	99% (**97**-100) N=161
NZ98/ 254 (PorA P1.4)	Baseline	1% (0.015-3) N=170	0 (0-2)	1% (0.015-3)	1% (0.015-3)	1% (0-4) N=171	1% (0-4)
	1 mo. PD #3	78% (**71**-84)	67% (59-74) N=172	56% (**48**-64) N=169	1% (**0.015**-3) N=168	62% (**54**-69)	81% (**74**-87) N=169

Source: Adapted from BLA 125546/0, V72P16 Clinical Study Report, Table 11.4.1-1 on p.127-8 of 13538; Ag: antigen; 1mo. PD3: 1 month post dose-3.

Reviewer Comment:

1. *All study formulations evaluated in this study generated a bactericidal antibody response against indicator strains 44/76-SL and 5/99 which met protocol-defined success criteria, yet only rMenB+OMV formulation generated an adequate hSBA response against strain NZ98/254. Based on these findings, inclusion of full dose OMV (25ug) in the final formulation will provide increased vaccination coverage against strain NZ98/254 which is an epidemiologically significant strain in the US and Europe.*
2. *rMenB+OMV, regardless of manufacturing process, was the only formulation which generated a sufficient hSBA immune response one month post dose-3 in infants against all three indicator strains as defined by the success criteria for the primary objective.*
3. *Though this dose/formulation selection study evaluated the hSBA immune response in infants, the applicant considers these results generalizable to older age cohorts. The applicant conducted this study from 2009 to 2011, and subsequently continued its clinical development program in all age cohorts with rMenB+OMV.*

6.6.6 Safety Analyses

Reviewer Comment*: The reviewer presents the safety profiles of the various different formulations in the context of the chosen dose/formulation, rMenB+OMV.*

Solicited Adverse Events:
Overall, up to 99% of subjects experienced a local or systemic reaction. When comparing any of the OMV formulations to the rMenB alone formulation, the rates of reactogenicity were higher in the group receiving OMV. The table below provides a comparison of the most frequently reported local and systemic reactions for rMenB+OMV formulations, low dose OMV formulations, and rMenB alone formulation.

Table 35: Study V72P16-Frequently Reported Solicited Local/Systemic Reactions by Dose: Comparison of rMenB+OMV, Low Dose OMV formulations, & rMenB Alone - Safety Set

Local/Systemic Reaction -by dose #	Group 1: rMenB+OMV N=182 (Group 6: Phase 2 rMenB+OMV N=180)	Groups 2,3,5: Low Dose OMV formulations N=180-186	Group 4: rMenB alone formulation N=184
Tenderness			
-1st	63% (67%)	53-64%	29%
-2nd	66% (64%)	48-64%	26%
-3rd	56% (62%)	42-55%	26%
Erythema			
-1st	59% (59%)	42-55%	29%
-2nd	57% (58%)	49-63%	39%
-3rd	61% (56%)	52-61%	39%
Induration			
-1st	55% (47%)	46-54%	29%
-2nd	57% (52%)	46-58%	34%
-3rd	54% (49%)	44-51%	34%
Irritability			
-1st	70% (73%)	69-72%	54%
-2nd	71% (70%)	64-67%	51%
-3rd	64% (64%)	50-57%	40%
Sleepiness			
-1st	66% (66%)	64-73%	52%
-2nd	58% (61%)	51-56%	46%
-3rd	41% (44%)	37-44%	35%
Unusual Crying			
-1st	52% (60%)	53-56%	33%
-2nd	49% (55%)	45-50%	38%
-3rd	42% (56%)	34-46%	26%
Fever ≥38.5C			
-1st	52% (42%)	33-51%	13%
-2nd	49% (50%)	41-46%	20%
-3rd	30% (30%)	21-30%	9%

Source: Adapted from BLA 125546/0, V72P16 Clinical Study Report, Table 12.2.3-1a on p. 187-188 of 13538; Table 12.2.3-2a on page 198-199 of 13538.

Across all doses, the most frequently reported local reactions were tenderness, erythema, and induration for all study groups. In general, the rates do not increase with sequential doses, but are higher in the OMV formulations compared to the rMenB alone formulation. This is most evident

in the percentage of rMenB+OMV subjects reporting tenderness, which is almost double the rate as that reported by the subjects receiving rMenB+OMV. The rates of severe local reactions are generally low across groups. For example, when comparing the rates of severe erythema and induration between the rMenB+OMV group and the rMenB alone group, the rates are similarly low (0-1%). Yet rates of severe tenderness are slightly higher in the rMenB+OMV group, seen in 15%, 9%, and 9% of subjects after each dose, compared to rMenB alone group that had low rates after each dose (0-3%).

The mostly frequently reported systemic reactions were irritability, sleepiness, unusual crying, and change in eating for all formulations, which are reported at higher rates after the 1st and 2nd doses compared to the 3rd dose. The rates of systemic reactions were slightly higher in those subjects receiving the OMV formulations compared to rMenB alone formulation, most evident of which is in the rates of unusual crying and irritability. The rates of severe systemic reactions are generally low across groups, seen in 0-6% of subjects based on solicited systemic reaction.

The rates of fever (T≥38.5C) were also reported at higher rates in the rMenB+OMV group, with 49-52% of subjects reporting a fever after the 1st and 2nd doses, which decreased by the 3rd dose to 30%. In the rMenB alone group, the rates of fevers were 13% after the 1st dose, 20% after the 2nd dose and 9% after the 3rd dose. Yet no reports of severe fever (T≥40.5C) were reported across groups.

The local and systemic reactogenicity rates observed for rMenB+OMV manufactured by a "Phase 2 process" (Group 6) were similar to that observed for rMenB+OMV (Group 1).

Reviewer Comment:

1. *The analysis of fever was based on a definition of fever T≥38.5C. The applicant also provided a summary of body temperature based on the Brighton Collaboration guidelines[41]. The percentage of subjects in the rMenB+OMV group with a maximum temperature≥38.0C was 70%, 77%, and 57% for dose 1, 2 and 3, respectively. In contrast for the rMenB alone group, the maximum temperature T≥38.0C was 39%, 39%, and 31% after each subsequent dose. Yet when comparing the rates of severe fever (T≥40.0C), both group reported similarly low rates. For rMenB+OMV group, only one subject (N=184) reported a maximum T≥40.0C after the 1st dose, though after the 2nd and 3rd dose there were no reports. Similarly, rMenB alone group had no reported T≥40.C after any dose. While the rates of mild/moderately graded fever are higher in the OMV formulations, the rates of severe fever (T≥40.0C) are low.*
2. *In general the OMV formulations are more reactogenic than the rMenB alone formulation in terms of mild/moderately graded reactions. This is more evident for local injection site reactions, than systemic reactions. Other than a slightly higher rate of severe tenderness, the reports of severe reactogenicity across all groups are similarly low.*
3. *Based on these findings, the inclusion of OMV at full dose in the final formulation results in higher rates of mild/moderate reactogenicity compared to rMenB alone formulation, though rates of severe reactions are similarly low.*
4. *The reactogenicity profiles of rMenB+OMV formulation manufactured by a "Phase 2 process" (Group 6) was similar to that of the standard method of manufacturing for rMenB+OMV (Group 1). The formulation evaluated in Group 5 included ½ dose of both*

41 Marcy SM, et al and Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:551-556.

rMenB + OMV. The reactogenicity profile of this group was slightly better than the Group 2 (rMenB+ ½ OMV), but not as low as that seen with in the rMenB alone group.

Unsolicited Adverse Events:
The rates of any unsolicited adverse events were similar across groups, with ~79-85% of subjects reporting at least one adverse event. The most frequently reported AE by preferred term (MedDRA) was injection site induration, which was seen in slightly more subjects in the rMenB+OMV group than the rMenB alone group, though all other reported AEs had similar rates across groups. Other common AEs were bronchitis, viral infection, and rhinitis.

There were a total of 123 SAEs reported, with ~6-11% of subjects reporting at least one serious adverse event across all groups. The most prevalent MedDRA System Organ Class (SOC) across groups was Infections and Infestations, seen in 5-9% across groups. There were two subjects who received rMenB+ ¼OMV formulation and subsequently experienced SAEs (vomiting and injection site erythema) that were considered possibly related to vaccination; both subjects recovered. Another subject experienced a SAE associated with somnolence, which was considered probably related to vaccination, and fully recovered. There were no deaths in this study. A review of adverse events of special interest will be presented in Section 8, Integrated Summary of Safety.

6.6.7 Study Summary and Conclusions

Study V72P16 evaluated different formulations of rMenB+OMV based on a reduction of OMV alone (½ OMV, ¼ OMV dose, or no OMV) or a reduction of both the recombinant proteins and OMV (½ dose both). It also evaluated rMenB+OMV manufactured by a different method, which did not have an impact on either immunogenicity or safety of the vaccine. Though the data generated from this study was collected in healthy infants, for the purpose of dose selection it provides valuable data that is generalizable to older age cohorts.

Only the rMenB+OMV formulation (Groups 1 and 6) met the primary immunogenicity objective which evaluated the percentage of subjects with hSBA titer $\geq$1:5 one month after the 3rd dose against three serogroup B indicator strains (44/76-SL, NZ98/254, and 5/99). The rMenB+OMV formulation was more reactogenic than the formulation without OMV (rMenB alone). While this difference was more pronounced for local reactions, fever rates were also higher based on the Brighton Collaboration definition of fever (T$\geq$38.0C). Yet the rates of severe local/systemic reactions and severe fever (T$\geq$40.0C) were low across all groups with and without OMV. In conclusion, while rMenB+OMV formulation is the most immunogenic against all 3 indicator strains, it has higher rates of mild/moderate solicited reactions, though similar rates of severe solicited reactions, unsolicited AEs, and SAEs, thus an acceptable formulation for dose selection.

6.7 Trial #7: Supportive Study V72P5

Phase 1, Observer Blind, Single Center, Randomized Study of the Safety, Tolerability, and Immunogenicity of Meningococcal B Recombinant Vaccine with and without OMV at 0, 1, 2-Month Schedule in Healthy Adults (18 - 40 years old).

Reviewer Comment: *Study V72P5 was a Phase 1 study conducted from February 2006 to October 2006 that was the first clinical trial to evaluate the safety and immunogenicity of rMenB+OMV. The study evaluated 3 doses one month apart in adults 18-40 years of age, and included two control groups: rMenB alone, and rMenB +OMV ---(b)(4)------, which includes OMV component from strain -(b)(4). The safety data generated from this early*

phase development study will be evaluated to support findings from main trials mentioned earlier in this review.

6.7.1 Study Overview

Primary Safety Objective:

- To explore the safety and tolerability of rMenB+OMV (final formulation).

Study Design:

Study V72P5 is a Phase 1, partially blinded (observer), randomized study in adults (18-40 years of age) conducted at one study site in Switzerland.

Study Groups: subjects received 3 doses of study vaccines as follows (N=#enrolled):

- Group 1: rMenB+OMV-final formulation: Day 0, Month 1, Month 2 (N=28)
- Group 2: rMenB+OMV-(b)(4): Day 0, Month 1, Month 2 (N=28)
- Group 3: rMenB alone: Day 0, Month 1, Month 2 (N=14)

There were 70 healthy adults (18-40 yo) enrolled in this study. Subjects were eligible for participation based on similar criteria as described for the previously mentioned main trials. Safety variables assessed included adverse events (including medically attended visits and SAEs) from enrollment until study completion (Month 7), in addition to local (pain, erythema, and induration), systemic (chills, nausea, malaise, fatigue, myalgia, arthralgia, and headache); and other indicators of reactogenicity (temperature, use of analgesics/antipyretics) for 7 days after each vaccination. In addition selected clinical laboratory evaluations were assessed at baseline, 1 week post vaccination, and at study termination. Laboratory values assessed included complete blood count with differential count; complete metabolic panel with liver function studies; and coagulation studies, in addition to erythrocyte sedimentation rate (ESR).

6.7.2 Study Results

All enrolled subjects were included in the safety analyses based on receipt of at least one vaccination dose, and 27 (out of 28) subjects received all 3 doses of rMenB+OMV-final formulation. Safety data collection was descriptive without hypothesis testing.

Safety Findings:

All subjects in the rMenB+OMV-final formulation and rMenB+OMV(b)(4) groups experienced at least one local reaction within 7 days of vaccination, compared to 13/14 subjects in the rMenB alone. The most frequently reported local reaction in all 3 study groups was pain at the injection site: 96% in OMV formulation groups compared to 71% in rMenB alone group. Most subjects who received an OMV formulation reported mild to moderate pain, compared to those in the rMenB alone group with mostly mild pain. The most frequently reported systemic reaction was myalgia: 82% in rMenB+OMV-final formulation group; 86% in rMenB+OMV-(b)(4) group; 71% in the rMenB alone group, the majority of which was mild to moderate in severity. Headache, arthralgia, and chills were also seen in the rMenB+OMV-final formulation group, though less frequently, at rates of 57%, 50%, and 50% respectively. Fever ($T \geq 38.0C$) was reported in 3 subjects in the rMenB+OMV-final formulation group compared to none in the rMenB alone group. None of the reported fevers were $T \geq 40.0C$. The reported usage of antipyretic/analgesic medications in the OMV formulations were 36-39% compared to none in the rMenB alone group.

The most common SOC (MedDRA system organ class) for unsolicited adverse events for rMenB+OMV-final formulation recipients was gastrointestinal disorders (14%), and the most common unsolicited AE by preferred term (MedDRA) were diarrhea and vomiting, both of which

were reported by two subjects. Though all subjects had an abnormal laboratory finding, the vast majority were transient changes in laboratory values that were not associated with clinical signs or symptoms. None of the abnormal lab findings were considered related to vaccination. There were 2 subjects who experienced SAEs, including one with appendicitis (rMenB+OMV-NW recipient) and another with HIV infection (rMenB+OMV-final formulation recipient). Both SAEs were not related to vaccination. One rMenB+OMV-final formulation subject prematurely withdrew from the study due to a non-serious AE (submandibular lymphadenopathy). There were no deaths in the study. There was one pregnancy in the study in the rMenB+OMV-(b)(4) group (this subject had her last menstrual period 5 months after last vaccine dose).

6.7.3 Conclusion

Study V72P5 evaluated the safety of the final formulation of rMenB+OMV in 28 adult subjects (18-40 years of age), who received at least one dose. For these subjects, the most frequent solicited reactions were injection site pain and myalgia, both of which were seen primarily within the first two days of vaccination. The frequency of local and systemic reactions was similar after all doses. The most frequent unsolicited adverse events were diarrhea and vomiting. Two subjects experienced SAEs (appendicitis in rMenB+OMV-b(4) group, and HIV infection in rMenB+OMV final group), none of which were considered related to vaccination; and there were no deaths in this study. The overall safety findings from Study V72P5 for rMenB+OMV final formulation are consistent with findings from the main studies reviewed as part of this BLA.

6.8 Trial #8: Supportive Study V72P4

A Phase 2, Multi-Center, Open-Label Study of the Safety, Tolerability and Immunogenicity of Meningococcal B Recombinant Vaccine when Administered at 0, 2, 6-Month Schedule and of a Single Dose of Meningococcal ACWY Conjugate Vaccine in Healthy At-Risk Adults (18 to 50 Years of Age).

> ***Reviewer Comment****: Study V72P4 is a Phase 2 study conducted from July 2007 to November 2009 in adults (18-50 years of age) who are at increased risk for meningococcal disease due to occupational exposure to cultured organisms originating from invasive meningococcal disease isolates. This open label, single arm study evaluated the safety and immunogenicity of 3 doses of rMenB+ OMV (final formulation) administered at Day 0, Month 2, and Month 6 followed by a single dose of the applicant's meningococcal serogroup A, C, W, and Y conjugate vaccine (MenACWY-CRM, Menveo®) administered at Month 7. The study was conducted at two sites, one in Germany and the other in Italy. The safety data pertaining to the rMenB+OMV generated from this Phase 2 study will be evaluated to support findings from main trials mentioned earlier in this review. MenACWY-CRM is currently licensed for use in the US for individuals 2 months to 55 years of age.*

6.8.1 Study Overview

Primary Safety Objective:

- To explore the safety and tolerability of rMenB+OMV in healthy at-risk adults when administered at a 0, 2, 6- month schedule throughout the clinical study.

Study Design:
Study V72P4 is a Phase 2, open-label, single arm study in healthy adults (18-50 years of age) at risk for exposure to *N.meningitidis* as laboratory workers in Germany and Italy at two study sites.

Study Groups: subjects received the following vaccines (N=#enrolled):

- *rMenB+OMV at Day 0, Month 2, Month 6; then MenACWY-CRM at Month 7 (N=54)*

Subjects were eligible for participation based on similar criteria for the previously described studies. Safety variables assessed included adverse events (including medically attended visits and SAEs) from enrollment until study completion (Month 7), in addition to local (pain, erythema, and induration), systemic (fever ≥38.0C, nausea, malaise, myalgia, arthralgia, and headache); and other indicators of reactogenicity (use of analgesics/antipyretics) for 7 days after each vaccination.

6.8.2 Study Results

Safety Findings:
The majority of subjects (98%-100%) of subjects experienced a solicited adverse reaction within 7 days of any dose of rMenB+OMV. The most frequently reported local reaction was pain (96%-100% of subjects), most of which was mild to moderate pain, though 13-18% was considered severe. The most frequently reported systemic reaction was malaise (30-52%) and myalgia (28-48%) after any dose, the majority of which were mild to moderate in severity. Other common systemic reactions were headache and arthralgia, 28%-42% and 19-40%, respectively. Fever (T≥38.0C) was in frequent, seen only in 2 subjects after the 1st dose and 1 subject after the 2nd dose, and no subject reported severe fever (T≥40.0C). The reported usage of antipyretic/analgesic medications were 19% after the 1st dose, 13% after the 2nd dose, and 10% after the 3rd dose.

At least one unsolicited AE was experienced by 45% (24/53) of subjects, and 7 AEs were considered possibly related to vaccination. The most common SOC (MedDRA system organ class) was 'general disorders and administration site conditions', seen in 15% of subjects.
The most common unsolicited AEs by preferred term (MedDRA) were injection site pain, and naso-pharyngitis (11% each), in addition to rhinitis, bronchitis, gastritis, and injection site induration, all of which were seen in <10% of subjects. Of those with injection site pain, 5 out of 6 subjects considered it possibly or probably related to vaccination. There were no reported SAEs or deaths in the study. Two subjects were withdrawn from the study, one due to syncope and another due to naso-pharyngitis, none of which were considered related to vaccination. There was one pregnancy during the trial involving a 32 yo female who had received two doses of rMenB+OMV (2/20/2008, --(b)(6)--). She did not receive her 3rd vaccination, and had a confirmed pregnancy diagnosed on 5/16/2008 (last menstrual period was 4/09/2008), after which she withdrew consent on 5/19/2009. She delivered a singleton baby without congenital anomalies 254 days after the last rMenB+OMV vaccination.

6.8.3 Conclusion

Study V72P4 evaluated the safety of rMenB+OMV in 53 adult subjects (18-50 years of age) who received at least one dose of the vaccine. For these subjects, the most frequent solicited reactions were injection site pain, malaise and myalgia, the majority of which was mild to moderate in severity. The frequency of the solicited reactions was similar after each dose, and for some of the systemic reactions they were slightly higher after the 3rd dose. The most frequent unsolicited AEs were injection site pain and naso-pharyngitis. There were no SAEs or deaths. The overall safety findings from Study V72P5 for rMenB+OMV final formulation are consistent with findings from the main studies reviewed as part of this BLA.

7. INTEGRATED OVERVIEW OF EFFECTIVENESS

7.1 Indication

The applicant is seeking the following indication for rMenB+OMV as part of its original application under accelerated approval: the prevention of invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age.

7.1.1 Methods of Integration

As discussed in Section 5.1 of this review, modified immunogenicity endpoints were used to evaluate the effectiveness of rMenB+OMV in the 3 main studies included for review in this application. The hSBA measurements used in each study had different LLOQs based on the specific laboratory that performed the assay and/or the indicator strain used in the assay. Therefore, immunogenicity data were not integrated for this application.

7.1.2 Subpopulation Analyses based on Demographics and Baseline Characteristics

The results of descriptive subpopulation immunogenicity analyses performed on small data sets which evaluated differences due to gender and racial origin of enrolled subjects were mainly consistent with the overall immunogenicity findings. One exception was noted in the Canadian/Australian study which evaluated 11-17 year old individuals where a greater hSBA immune response was observed in males (69%) than females (56%) against one strain, NZ98/254. A gender difference in hSBA response rate against any of the three strains evaluated in the 3 other main trials was not observed.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Database

8.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data included in this application and reviewed to characterize the safety profile of rMenB+OMV were from the following sources (N=total number of subjects who received at least one dose of rMenB+OMV):

- Main clinical trials: V72_41, V72_29, V72P10, V102_03 (N=3,058)
- Supportive trials: V72P5, V72P4 (N=81)
- Pre-licensure vaccination campaigns at 2 universities in the US (N=15,351)

8.1.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographic characteristics were reviewed individually for each study. The observed rates of adverse events across different demographic groups based on race, gender, and age were fairly comparable and consistent with overall safety findings.

8.1.3 Categorization of Adverse Events

The categories of adverse events assessed across studies were similar, and included solicited adverse events, unsolicited adverse events, adverse events leading to withdrawal, and serious adverse events.

8.2 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Safety data were not pooled across studies.

8.3 Safety Results

8.3.1 Deaths

There were 3 deaths in Study V72P10, including two deaths which were clearly unrelated to vaccination which were due to a car accident and a suicide attempt. The 3rd death was of an infant born to subject who had received her last dose of rMenB+OMV ~9-10 months earlier. The infant had died ~7 weeks after birth following several post-natal respiratory complications. This death was not considered related to the mother's vaccination.

8.3.2 Nonfatal Serious Adverse Events: Adverse Events of Special Interest

Case narratives for Serious Adverse Events (SAEs) reported in each study are included in the appropriate sections of this review by study. The SAEs which were considered by this reviewer as adverse events of special interest (AESI) included two cases of juvenile arthritis, one case thyroiditis, one case of bacterial meningitis, and 10 cases of appendicitis.

Reviewer Comment:

1. *Juvenile Arthritis. There were two cases of juvenile arthritis reported in Study V72P10 ~5-6 months after rMenB+OMV vaccination. The case narratives are included in Section 6.3.12.4. In one of these cases, the subject appears to have had rheumatologic symptoms associated with juvenile arthritis prior to vaccination, and therefore vaccination does not appear to be causally related to the onset of symptoms. For the other case, there are no other predisposing factors associated with the onset of symptoms, and is therefore considered by this reviewer to be temporally related to vaccination as no other etiology was identified. There were no additional reports of juvenile arthritis or other rheumatologic conditions reported following vaccination in the other clinical trials submitted as part of this BLA. Furthermore, there were no reported cases of juvenile arthritis or rheumatologic conditions following vaccination in the pre-licensure vaccination campaigns conducted at two US universities in 15,351 individuals. Based on review of the all the safety data submitted as part of this BLA, it does not appear that juvenile arthritis is a safety concern following rMenB+OMV vaccination.*
2. *Acute thyroiditis. There was one subject diagnosed with acute thyroiditis in Study V72_29. Based on the information provided, it is possible that subject had symptoms of thyroid disease prior to vaccination. Therefore it is unlikely that vaccination is causally associated with this subject's diagnosis of acute thyroiditis. Review of safety data from all other safety data submitted as part of this BLA did not reveal any other reported cases of thyroid disease. Although there were two reported cases of juvenile arthritis as described above, no other autoimmune conditions were reported in the clinical trials or the university vaccination campaigns, which together evaluated ~18,500 subjects who received at least one dose of rMenB+OMV.*
3. *Bacterial Meningitis. There was one subject diagnosed with bacterial meningitis in Study V72P10. The case narrative is included in Section 6.3.12.4. Laboratory results confirmed cerebrospinal infection with Streptococcus pneumonia. There were no other cases of bacterial meningitis reported in the other studies reviewed as part of this application. The reviewer does not consider this SAE related to vaccination.*
4. *Appendicitis: There were 9 rMenB+OMV recipients in Study V72P10, which did not have a comparator group; and 1 rMenB+OMV recipient in Study V72_29. In this latter study there were 4 cases of appendicitis reported in the comparator group recipients. Based on CDC analysis of National Hospital Discharge Survey data from 1979-1984, the highest incidence of appendicitis in the US was found in persons 10-19 years of age (23.3 cases/10,000 population per year). More recent patient discharge data (1995-2009) from*

California, a state with a high proportion of Hispanic residents, demonstrated the highest rates of appendicitis (169.6 cases/100,000) in children 10-14 years of age. In this latter data, cases of appendicitis were reported more frequently in Whites and Hispanics, and less frequently in African Americans and Asians. The reported rates of appendicitis in the clinical trial data when compared to background rates do not appear to indicate there is an overall increased risk following rMenB+OMV vaccination. These findings are similar to be those described by the CBER Epidemiology/ Pharmacovigilance reviewer for this BLA who found no increased relative risk of appendicitis following rMenB+OMV vaccination based on the available data.

8.3.3 Study Dropouts/Discontinuations

Across studies, the following adverse events led to either study discontinuation or delay in vaccination:

1. Myalgia and Arm Pain (Study V72_41): Reported on Study Day 1 and resulted in delay in vaccination and was considered related to vaccination.
2. Injection Site Rash (Study V72_29): Reported on Study Day 1 and resulted in premature withdrawal from study.
3. Urticaria (Study V72_29): Reported 9 days after 1st vaccination and resulted in premature withdrawal from study.
4. Muscular Weakness (Study V72_29): Reported 29 days after 1st vaccination and resulted in premature withdrawal from study.
5. Arm Swelling/Pain (Study V72_29): Reported Study Day 1 and resulted in premature withdrawal from study.
6. Acute Thyroiditis (Study V72_29): Reported 18 days after 1st vaccination (listed above under SAE) and resulted in premature withdrawal from study.
7. Juvenile Arthritis (Study V72P10): Reported symptoms before the 2nd dose (administered one month after 1st), and then diagnosed 170 days after the 3rd vaccination, resulting in withdrawal from the study. (This SAE is listed above)
8. Generalized Lymphadenopathy (Study V102_03): Reported 5 days after vaccination and withdrew from the study.
9. Submandibular Lymphadenopathy (Study V72P5): Resulted in premature withdrawal from study.

Reviewer Comment*: Common reasons for early study withdrawal included adverse events which were associated with injection site reactions or muscular pain/weakness.*

8.3.4 Common Adverse Events

The types and rates of common unsolicited adverse events reported across studies were similar and included injection site induration, injection site pain, myalgia, headache, upper respiratory tract infection, and nasopharyngitis. The types and rates of common unsolicited adverse events reported across studies were similar, and those that were reported among at least 2% of participants and were more frequently reported after rMenB+OMV recipients than in control recipients were injection site pain, headache, injection site induration unresolved within 7 days of vaccination, and nasopharyngitis.

8.3.5 Clinical Test Results

N/A

8.3.6 Systemic Reactogenicity

Across all studies the most frequently reported systemic reactions included myalgia, headache, and malaise. Severe myalgia was reported more frequently when compared to other systemic reactions. Though fever was not reported often, there was frequent use of antipyretic/analgesic medication after vaccination (up to 20% reported use in some studies).

8.3.7 Local Reactogenicity

The most consistently reported solicited reaction across all studies was injection site pain, with rates as high as 90% after a dose; and severe injection site pain was reported by up to 20-29% of subjects after a vaccination dose. Other common local reactions included injection site erythema and less frequently induration.

8.4 Additional Pre-licensure Safety Experience

8.4.1 Vaccination Campaigns at U.S Universities

Due to separate meningococcal serogroup B outbreaks at two US universities in 2013, vaccination campaigns with rMenB+OMV were conducted prior to licensure under an Expanded Access IND sponsored by the Center of Disease Control and Prevention (CDC). Participants which included undergraduate/graduate students, faculty, and staff were administered two doses of rMenB+OMV at least one month apart. The principal investigator, site sub-investigator, and vaccine safety officer discussed the information available for each SAE report, and assessed causality as either related, possibly related, unlikely related, and not-related. Applicant did not indicate whether the CDC collected data on SAE reporting compliance.

In these vaccination campaigns, SAE safety data were collected up to 30 days after the 2nd dose by intake screening prior to the 2nd dose and by electronic survey 30 days after the 2nd dose. SAE safety data were also collected passively through each university's 24-hour rMenB+OMV safety hotline, CDC's rMenB+OMV specific email box, the university's health services clinic/infirmary visits, and local hospital or ER reports

8.4.2 Serious Adverse Events Reported During CDC Vaccination Campaigns

Vaccination Campaign Participants:
During these vaccination campaigns, 15,351 students and staff were vaccinated with rMenB+OMV at Princeton University and University of California Santa Barbara (UCSB).

Princeton University Vaccination Campaign:
The vaccination campaign and surveillance period was from December 9, 2013 to May 16, 2014. By May 16th, 5520 participants at Princeton University had received the 1st dose and 5165 participants had received the 2nd dose. The demographic characteristics of participants who received the 1st dose included median age 20 years; males 52%; and the most represented races were White (50%), Asian (23%); Black (7.5%); and 19% of subjects the race was not reported.

There were a total of 23 participants who reported a SAE during the surveillance period. The following SAEs are considered to be clinically relevant SAEs by this clinical reviewer:

- Appendicitis was diagnosed in 6 individuals between the ages of 19 to 21 years of age, and included 4 males and 2 females; symptom onset ranged from one day prior to vaccination to 7 weeks after vaccination; all cases required hospitalization and for 5 cases appendectomy procedure was documented to have occurred or was planned; 5 cases resolved and 1 case was ongoing; duration of illness was 2-3 days for the majority of

these cases. None of these cases were considered related to vaccination by the investigator.

- Rhabdomyolysis was diagnosed in two individuals:
  - 20 year old male was diagnosed with rhabdomyolysis one day after the 2nd vaccination. Pertinent history included binge drinking and initiation of a new activity, weight lifting. The subject required hospitalization for 3 days and the duration of illness was 13 days, after which his symptoms resolved. The investigator considered this adverse event possibly related to vaccination.
  - 23 year old male was diagnosed with rhabdomyolysis one month after his 2nd dose. Pertinent history included heavy weight lifting after a period of inactivity. The subject required hospitalization for 3 days and the duration of illness was 16 days after which symptoms resolved. The investigator considered this adverse event as not related to vaccination.

UCSB Vaccination Campaign:

The vaccination campaign and surveillance period was from February 24, 2014 to July 25, 2014. The target population for this campaign included all undergraduate students, graduate students, faculty and staff that resided in UCSB owned residence halls, and those who had a medical condition that predisposed them to have an increased risk for meningococcal disease.
By July 25th, there were 9831 participants who received a 1st dose and 7707 participants who received a 2nd dose. The demographic characteristics of those who received at least one dose included median age 20 years; males 43%; and the most represented races reported were White (41%), Latino/other Spanish American (5%), Asian (40%), Black (4%), and unknown (5%).

There were a total of 27 participants who reported a SAE during the surveillance period. The following SAEs are considered clinically relevant by this clinical reviewer:

- Anaphylaxis was diagnosed in a 22 years female who had received the 1st dose of rMenB+OMV on 4/8/2014. In the 15 days prior to vaccination she had been diagnosed with pruritic rash, scabies, and hives after starting Permethrin, which was being treated with Zyrtec. She developed symptoms within 30 minutes of vaccination including hives, swelling of her lips, face, and the back of her throat. She presented to the student health clinic and was noted to have signs and symptoms consistent with anaphylaxis and was treated with epinephrine and Benadryl, and was transferred to the emergency department of the local hospital. Based on CDC's evaluation of the adverse event, it was assessed as related to vaccination.
- Drowning/Death: a 19 year old male water polo player had received a 1st vaccination dose on 2/25/2014. He was found dead at the bottom of the pool on --(b)(6)--- after doing high intensity workout in the pool while holding his breath for an entire lap. An autopsy report determined the death to be accidental drowning as a result of shallow water blackout. The autopsy report was determined to be not related to vaccination.
- Septic Shock/Unspecified gastrointestinal illness was diagnosed in a 19 year old female who had onset of symptoms 3 days prior to vaccination, and subsequently was hospitalized 2 days after vaccination; subject was hospitalized for 5 days, during which all laboratory cultures were negative. The duration of illness was 11 days after which the subject's symptoms resolved. The investigator did not consider this adverse event related to vaccination.
- Appendicitis was diagnosed in 3 individuals between the ages of 18 to 20 years of age, and included 2 males and 1 female; symptom onset ranged from 11 days to 5 weeks after vaccination; all cases required hospitalization though it was not specified how many

required appendectomy; duration of illness was 2-3 days None of these cases were considered related to vaccination by the investigator.

- Pneumonia was diagnosed in a 20 year old male 14 days after vaccination. The participant was hospitalized for 4 days and duration of illness was 5 days. No pathogen was isolated, and the participant recovered. The investigator did not consider this adverse event related to vaccination.
- Generalized Tonic-Clonic Seizure was diagnosed (new onset) in an 18 year old female 22 days after receiving the 1st dose of rMenB+OMV. The individual was in a lake at the time and also had a near drowning. She was hospitalized for 1 day and had negative CT and MRI brain findings and a normal EEG. Duration of symptoms were 2 days and the symptoms resolved. The investigator did not consider this adverse event related to vaccination.

Reviewer Comment:

1. *The death of the 19 year old water polo player is not considered related to vaccination by this reviewer.*
2. *The SAE of anaphylaxis is considered related to vaccination by this reviewer. The applicant for these vaccination campaigns was CDC, and their assessment of this single case of anaphylaxis across both vaccination campaigns was that the rate of anaphylaxis following rMenB+OMV vaccination was not greater than the rate of anaphylaxis that occurs following other types of vaccine currently licensed in the US*
3. *There were 9 cases of appendicitis reported among 15,351participants who received at least one dose of rMenB+OMV. As mentioned in Section 6.3.12.4, the highest incidence of appendicitis in the US is in persons 10-19 years of age (23.3 cases/10,000 population per year). There does not appear to be an overall increased incidence of appendicitis over background incidence rates during these campaigns.*
4. *The two cases of rhabdomyolysis are not considered related to vaccination by this reviewer. There were several other precipitating factors which are more commonly associated with a diagnosis of rhabdomyolysis.*
5. *The other SAEs listed above (tonic-clonic seizure, pneumonia, septic shock) are not considered related to vaccination by this reviewer.*

8.5 Safety Conclusions

Safety data were reviewed on 3139 subjects enrolled in a randomized clinical trials conducted in Canada, Australia, UK, Chile, US, Poland, Switzerland, Germany, and Italy. These subjects received at least one dose of rMenB+OMV and provided post-vaccination safety data. Additional serious adverse event safety data were collected on 15,351 rMenB+OMV recipients as part of vaccination campaigns sponsored by the CDC at 2 US universities. Based on detailed review of the safety data, the overall safety profile of rMenB+OMV when administered to individuals in 10 through 25 years of age subjects does not demonstrate any safety concerns following vaccination. Common adverse reactions likely to occur include injection site pain, myalgia, malaise, and headache. The rates of unsolicited adverse events not related to vaccination reactions are similar when compared to control groups. Serious adverse events were rare following rMenB+OMV vaccination. Based on the clinical reviewer's analyses of the 2 reported cases of juvenile arthritis and 1 case of acute thyroiditis, the data does not suggest an association between rMenB+OMV vaccination and the onset of autoimmune conditions. Appendicitis is a commonly reported condition in adolescent and young adult populations. CBER analysis of the 19 reported appendicitis cases in the clinical trials and the two vaccination campaigns does not demonstrate an increased overall risk of appendicitis following rMenB+OMV vaccination in individuals 10 years through 25 years of age. Overall, the safety data reviewed demonstrate that the both the

nature and frequency of events reported in subjects 10 through 25 years of age were consistent with events commonly observed following vaccinations administered to adolescents and young adults in the US.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy Category B:
Reproduction studies have been performed in female rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility or harm to the fetus due to rMenB+OMV. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, rMenB+OMV should be used during pregnancy only if clearly needed.

Pregnancy Registry
The applicant maintains a pregnancy registry to monitor the fetal outcomes of pregnant women exposed to rMenB+OMV. The package insert includes language that encourages health care providers to register women who receive rMenB+OMV during pregnancy in NVD's pregnancy registry.

9.1.2 Use During Lactation

It is not known whether rMenB+OMV is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rMenB+OMV is administered to a nursing woman.

9.1.3 Pediatric Use and PREA Considerations

As specified by the Pediatric Research Equity Act (PREA), the submission of this original BLA required a Pediatric Study Plan. The safety and effectiveness of rMenB+OMV has not been established in US children younger than 10 years of age. The applicant's plan for an assessment of rMenB+OMV in pediatric individuals 6 weeks to <10 years of age is as follows:

- Partial waiver in the pediatric age group: 0 to <6 weeks. The statutory reason to support this waiver is the following:
    - Section 505B(a)(B)(iii): *The product does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used.*
- Partial deferral in the pediatric age group: 6 weeks to < 10 years of age. The statutory reason to support this deferral is the following:
    - *Section 505B(a)(3)(A)(i): The biological product is ready for approval for use in adults before pediatric studies are complete*.
    - The following pediatric studies have been deferred:
        - Planned Study V72_57: A phase 3 study to evaluate the safety and immunogenicity of Bexsero in infants ≥6 weeks of age. Total subjects to be enrolled 1059, with one-third enrolled in North America. *(Europe, Russia, US)*
        - Ongoing Study V72_28: A Phase 3B, Open-label, multi-center study to evaluate the safety, tolerability, and immunogenicity of Bexsero when administered alone to infants ≥2.5 months of age (enrolled 1003 subjects) according to different immunization schedule; to children aged 2-5 years of age (enrolled 104 subjects); and to children 6-10 years of

age (enrolled 300 subjects). *(Brazil, Spain, Hungary, Peru).*

- Completed Study V72P12: A Phase 2b study to evaluate the safety and immunogenicity of Bexsero in healthy infants ≥2 months of age. Total subjects enrolled 1885. *(UK, Belgium, Germany, Czech Republic, Italy, Spain)*
- Completed Study V72P13: A Phase 3 study to evaluate the safety and immunogenicity of Bexsero in healthy infants ≥2 months of age. Total subjects enrolled 3630. *(Italy, Germany, Austria, Czech Republic, Finland)*

The Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PerC) on November 19, 2014. The committee agreed with the Pediatric Study Plan, including the partial waiver, partial deferral, and the review division's plans to extrapolate effectiveness to 10 years of age based on the available data.

9.1.4 Immunocompromised Patients

Individuals with altered immunocompetence may have reduced immune responses to rMenB+OMV.

9.1.5 Geriatric Use

Safety and effectiveness of rMenB+OMV in adults older than 65 years of age have not been established.

10. CONCLUSIONS

In 2012, serogroup B meningococcal disease was the most frequently reported serogroup with an estimated incidence rate of 0.06/100,000 according to the CDC. Recent outbreaks of serogroup B meningococcal disease at two university campuses, including one reported fatality, highlight the importance of having available a safe and effective vaccine. Based on this public health need, the applicant submitted an original BLA for the licensure of their candidate Meningococcal Group B vaccine which was in late stage development at the time of these outbreaks. The candidate vaccine, rMenB+OMV is a multicomponent protein and outer membrane vesicle based vaccine intended for use to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. The application was granted both priority review and breakthrough therapy designations. In addition because preliminary clinical data from adequate and well-controlled clinical trials established that the vaccine has an effect on surrogate endpoints that are reasonably likely to predict clinical benefit, the application was reviewed under an accelerated approval licensure pathway in accordance with statutory regulations [21 CFR 601.41].

The 9 studies included for review in this application (V72_41, V72_29, V72P10, V72P10E1, V102_03, V72P13, V72P16, V72P5, and V72P4) were conducted in accordance with GCP guidelines. Effectiveness of rMenB+OMV was demonstrated by measuring serum bactericidal activity. For 3 of the main trials, additional hSBA analyses of existing immunogenicity data were submitted using modified clinical study endpoints at CBER's request.

Three meningococcal test strains were used in hSBA assays. The proportion of subjects who achieved ≥4-fold increase in serum bactericidal activity one month following the 2nd dose of rMenB+OMV against test strain 5/99 were similar across the 3 main studies used to evaluate effectiveness, ranging from 94%-99%. The response rates observed against strain H44/76 were similar, with 93-98% of subjects achieving this response rate by subjects enrolled in the studies

conducted in Canada/Australia and Chile and 78% by subjects enrolled in the UK study. The proportion of subjects who achieved ≥4-fold increase from baseline against strain NZ98/254 was observed in 39% of Canadian/Australian subjects, 67% of UK subjects, and 83-85% of Chilean subjects. Across these 3 main trials, the composite hSBA immune response generated to 3 out of the 3 test strains by rMenB+OMV one month after the 2nd dose was 63% in the Canadian/ Australian trial; 88% in the UK trial; and 90-94% in the Chilean trial. The composite response 11 months after the 2nd dose, evaluated in the UK trial was 65%. The overall immunogenicity data demonstrates that the vaccine is effective in generating bactericidal activity against 3 representative meningococcal serogroup B strains. The different responses observed across studies conducted in different populations may reflect diversity of the meningococcal serogroup B epidemiology across geographic locations. Responses to additional strains may also vary among populations from different countries.

The applicant has demonstrated that the candidate vaccine generates a functional bactericidal immune response in vaccinated adolescents and young adults against three serogroup B test strains that are reasonably representative of prevalent strains in the United States based on criteria set by CBER for the accelerated approval of this candidate vaccine. Because of the low overall incidence of serogroup B disease, traditional approval based on randomized clinical trials using prevention of clinical disease as an endpoint was not feasible. In order to obtain traditional approval the applicant must demonstrate the effectiveness of rMenB+OMV by measuring hSBA responses against an extended panel of serogroup B meningococcal strains, thus confirming that the vaccine can protect against diverse meningococcal strains prevalent in the United States.

Revised safety reactogenicity rates which excluded missing data were generally similar between groups and to the overall safety findings. Across all studies the most frequently reported systemic reactions included myalgia, headache, and malaise. Severe myalgia was reported more frequently when compared to other systemic reactions. Though fever was not reported often, there was frequent use of antipyretic/analgesic medication after vaccination (up to 20% reported use in some studies). The most consistently reported local reaction across all studies was injection site pain, with rates as high as 90% after a dose. Severe injection site pain was reported by up to 20-29% of subjects after a vaccination dose. Other common local reactions included injection site erythema and less frequently induration.

The types and rates of common unsolicited adverse events reported across studies were similar, and those that were reported among at least 2 % of participants and were more frequently reported after rMenB+OMV recipients than in control recipients were injection site pain, headache, injection site induration unresolved within 7 days of vaccination, and nasopharyngitis. Serious adverse events were rare following rMenB+OMV vaccination. Based on the clinical reviewer's analyses of the 2 reported cases of juvenile arthritis and 1 case of acute thyroiditis, the data does not suggest an association between rMenB+OMV vaccination and the onset of autoimmune conditions. Overall, the safety data reviewed demonstrate that both the nature and frequency of events reported were consistent with events commonly observed following other vaccinations administered to adolescents and young adults.

During the submission of this application, there was an unmet medical need for protection against serogroups B in adolescents and young adults at increased risk for meningococcal disease. The totality of data presented in this application supports approval of rMenB+OMV candidate vaccine for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in adolescents and young adults 10 through 25 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The following table provides a risk-benefit assessment of vaccination with rMenB+OMV in adolescents and young adults 10 years through 25 years of age. This assessment weighs both the evidence and uncertainties of the data submitted in the context of the current public health need for an available meningococcal B vaccine.

Table 36: Risk Benefit Assessment of Vaccination with rMenB+OMV in Adolescents and Young Adults 10 years through 25 years of age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• From 2005 to 2011, an estimated 800-1200 cases of meningococcal disease occurred annually in the U.S, representing an incidence of 0.3cases/100,000. • Meningococcal serogroup B, C, and Y strains are the most prevalent in North America. • In 2012, 40% of reported cases of invasive meningococcal disease were due to serogroup B. • There is great genetic and serologic diversity of serogroup B strains such that an effective vaccine has to elicit bactericidal antibody against diverse and epidemiologically relevant strains. • Other than infants, incidence of meningococcal disease is highest in adolescents and young adults (11-21 years of age). • Invasive meningococcal infection is associated with high morbidity and mortality, even with timely initiation of appropriate antibiotics. • Long term sequelae occur in 11-10% of those who survive and include hearing loss, neurologic disability, loss of limbs, and/or other serious conditions, despite treatment. • Case fatality rate is 10-15 %, despite treatment. • rMenB+OMV vaccination is intended to prevent infection against meningococcal serogroup B, one of the most common circulating serogroups in the United States. • At present there is an ACIP recommendation for MenACWY (Menveo® or Menactra®) vaccination at 11-12 years of age, following by an additional dose at 16 years of age. • MenACWY vaccination does not provide protection against infection with meningococcal serogroup B.	• Invasive meningococcal disease is a rapidly progressive, life-threatening illness. • Invasive meningococcal disease is a serious condition because of its high case fatality rate even despite antibiotic treatment, and the chronic morbidity many survivors experience as consequence from infection.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	• In 2013, two meningococcal serogroup B outbreaks occurred at two separate universities in the US. • In the US, there were 4 meningococcal vaccines (ACWY or CY) currently licensed for use in individuals 9 months through 55 years of age, including of which 3 which are conjugate meningococcal vaccines (MenACWY-D, MenACWY-CRM, Hib-MenCY-TT) • There were no meningococcal B vaccines licensed in the US until October 2014 when Meningococcal Group B vaccine, Trumenba® was licensed for use in 10 through 25 years of age individuals. • Aside from meningococcal vaccines, no other drug or biologic is approved for prevention of invasive meningococcal infection. • Standard care includes targeted antibiotic use in close contacts of individuals with meningococcal disease to prevent infection. However, this approach is dependent upon accurate and timely diagnosis of the index case, timely identification of close contacts, rapid communication of risk to close contacts, and access to medical care or medications for those contacts, as well as compliance with the prescribed regimen. • MenACWY (Menomune, Menveo, Menactra) or Hib-MenCY-TT vaccines does not prevent invasive meningococcal disease caused by serogroup B or other serogroups not included in those vaccines • The duration of protection following revaccination is unknown.	• In adolescents and young adults at increased risk for meningococcal disease, there is an unmet medical need for ongoing protection against serogroups B.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Four main randomized clinical trials evaluating the effectiveness and safety of two doses of rMenB+OMV administered at least one month apart in ~3,058 adolescents and adults (10 through 25 years of age) was submitted. Immunogenicity of rMenB+OMV one month following 2 doses was evaluated in all subjects 11 through 24 years of age. Serum bactericidal antibodies were measured with hSBA assays using 3 meningococcal B strains selected to measure responses to one of three vaccine antigens (fHbp, NadA, or PorA P1.4) which are prevalent among circulating strains in the US. The hSBA measurement used to assess effectiveness include the proportion of participants with a $\geq$4-fold response (post-vaccination 2 compared to pre-vaccination 1) for each of 3 meningococcal B test strains, and the proportion of participants with a hSBA response $\geq$ the lower limit of quantitation (LLOQ) to all of the test strains (composite response). • The applicant has not demonstrated sustained effectiveness and breadth of coverage over time of rMenB+OMV against a diverse group of meningococcal circulating strains in the US.	• Vaccination with rMenB+OMV leads to the production of antibodies directed against vaccine antigens: NHBA, NadA, fHbp, and PorA P1.4. The susceptibility of serogroup B meningococci to complement mediated antibody –dependent killing following vaccination with rMenB+OMV is dependent on the antigenic similarity of the bacterial and vaccine antigens, the amount of antigen expressed on the surface of the invading meningococci, and the immune response generated by vaccinated individuals. The immunogenicity results observed in the submitted trials demonstrate that a substantial proportion of subjects achieved CBER specified immunogenicity endpoints against 3 meningococcal B test strains. • The applicant is planning to confirm effectiveness of rMenB+OMV against a group of invasive meningococcal serogroup B strains detected in the US in the confirmatory studies required to be conducted as part of the accelerated approval pathway. At present, strain qualification procedures have been initiated for 110 randomly selected serogroup B strains derived from the larger 442 serogroup B invasive isolates cohort identified as appropriately representative by the CDC.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• Safety endpoints evaluated in the main trials included the frequencies of solicited injection site reactions and systemic adverse reactions (for 7days post-vaccination); unsolicited adverse events (for 7 days post-vaccination for most studies); and serious adverse events, AEs leading to premature withdrawal, and a medically attended AEs (for entire study duration). • Safety data from two US expanded access vaccination campaigns were collected on 15,351 adolescents and adults with a median age of participation of 20-21 years of age. These campaigns were not randomized clinical trials and had no comparator groups and only collected serious adverse event data through 30 days after the 2nd dose. Effectiveness could not be inferred from these campaigns. • The most substantial risks of vaccination with rMenB+OMV are associated with the pain produced at the injection site, as well as systemic symptoms following vaccination, including myalgia, headache, and malaise. However, most reactions were mild to moderate in severity and tended to resolve relatively quickly and without sequelae. • In the vaccination campaigns, there was one case of anaphylaxis which was considered related to vaccination. • In the clinical trials, the reviewer considers one case of juvenile arthritis as temporally related to vaccination and for which no other etiology was identified; therefore a relationship to vaccination cannot be excluded. There were no other reports of juvenile arthritis or any other any other autoimmune conditions following rMenB+OMV vaccination in the other clinical trials or in the vaccination campaigns. • There were 19 cases of appendicitis reported among 18490 total rMenB+OMV vaccine recipients reviewed as part of this BLA. • No other safety signals were apparent in the studied populations.	• The overall safety data from both the clinical trials and the vaccination campaigns at two US universities did not identify any concerning pattern of adverse events other than that associated with injection site pain and post-vaccination myalgia, headache, and malaise which possibly could persist beyond 1 week. • The safety data demonstrate that the both the nature and frequency of events reported were consistent with events commonly observed following other vaccinations administered to adolescents and young adults. • The rate of anaphylaxis following rMenB+OMV vaccination was not greater than the rate of anaphylaxis that occurs following other types of vaccine currently licensed in the US The reviewer recommends that the SAE of anaphylaxis during the vaccination campaigns be included as part of the package insert. • Based on the safety data reviewed, there does not appear to be a higher incidence of juvenile arthritis or any other autoimmune condition following rMenB+OMV vaccination than what is observed in the general population. • The highest incidence of appendicitis in the US is in persons 10-19 years of age (23.3 cases/10,000 population per year). Appendicitis is commonly reported condition in the age groups evaluated in the clinical trials and the vaccination campaigns. Based on the available data, CBER analyses did not demonstrate an overall increased risk of appendicitis following rMenB+OMV vaccination.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The most common risks of vaccination with rMenB+OMV are listed above and primarily include post injection reactions.	• The reactogenicity profile of the vaccine is adequately characterized by the data presented in the package insert. • The applicant's Pharmacovigilance Plan (PVP) is adequate to monitor for any future safety signals and is therefore acceptable to CBER.

11.2 Risk-Benefit Summary and Assessment

Safety and immunogenicity data submitted to this original BLA under the accelerated approval regulatory pathway establish a substantial likelihood of benefit of rMenB+OMV vaccination in a general population of males and females aged 10 years through 25 years for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup B. Clinical benefit is based on the demonstration of immune response as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The safety profile of the vaccine based on the available data demonstrate that both the nature and frequency of events reported were consistent with events commonly observed following other vaccinations administered to adolescents and young adults. No adverse safety signals following vaccination were observed. Therefore the overall risk-benefit profile is favorable.

11.3 Discussion of Regulatory Options

As part of the accelerated approval pathway [21 CFR 601.41], the applicant is required to conduct confirmatory studies to demonstrate effectiveness of Bexsero against an extended panel of serogroup B meningococcal strains, confirming that the vaccine can protect against a breadth of prevalent strains in the United States The confirmatory studies will evaluate the ability of Bexsero to elicit hSBA responses against 3 test strains and hSBA responses against an additional large panel of (~100) invasive disease isolates. The following studies will be conducted to meet this requirement:

- V102_16 - A Phase 2b, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Effectiveness, Immunogenicity and Safety of Novartis Meningococcal (b)(4)-- Vaccine Administered to Healthy Adolescents in the US. The final report is anticipated to be submitted by 1st quarter 2016. The final data collected from this study will be used to inform the main confirmatory study listed below.
- V72_72 - A Phase 3, Randomized, Controlled, Observer-Blind, Multi-Center Study Assessing the Effectiveness, Immunogenicity and Safety of Novartis Meningococcal Serogroup B Vaccine (Bexsero) Administered to Healthy Adolescents and Young Adults. The final protocol is anticipated to be submitted 4th quarter 2015, and the final report is anticipated to be submitted 4th quarter 2018.

As specified by the Pediatric Research Equity Act (PREA), the submission of this original BLA required a Pediatric Study Plan. The applicant has adequately assessed the safety and effectiveness of Bexsero in pediatric individuals 10 years of age to less than 17 years of age as part of this BLA. The applicant was granted a partial waiver for an assessment in infants 0 to <6 weeks of age, and a partial deferral for an assessment in pediatric individuals 6 weeks to <10 years of age. The required deferred studies include

- Planned Study V72_57: A Phase 3 study to evaluate the safety and immunogenicity of Bexsero in North American infants ≥6 weeks of age.
- Ongoing Study V72_28: A Phase 3b study to evaluate the safety and immunogenicity of Bexsero in infants ≥2.5 months of age and in children 2-10 years of age.
- Two completed studies: Study V72P12 and Study V72P13 will be included to support an assessment of infants ≥2 months of age.

11.4 Recommendations on Regulatory Actions

According to my review of the clinical data, approval of this original BLA for Bexsero is recommended under the accelerated approval regulations. In applying the accelerated approval regulations, CBER considers hSBA against a panel of 3 test strains, each expressing an antigen contained in Bexsero, as a serological marker reasonably likely to predict protection against diverse meningococcal serogroup B strains prevalent in the United States. The applicant is required to conduct confirmatory studies to demonstrate effectiveness of Bexsero against an extended panel of serogroup B meningococcal strains, confirming that the vaccine can protect against a breadth of prevalent strains in the United States.

11.5 Labeling Review and Recommendations

The proprietary name BEXSERO was reviewed by the Advertising and Promotional Labeling Branch, CBER and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Post-Marketing Actions

Post-Marketing Requirements

- In accordance with the accelerated approval regulations, confirmatory studies in the post-marketing period are being conducted to confirm the effectiveness of Bexsero against diverse meningococcal group B strains that are epidemiologically relevant in US adolescents and young adults. The confirmatory studies will evaluate the ability of Bexsero to elicit hSBA responses against three indicator strains and hSBA responses against an additional large panel (~100) of invasive disease isolates.
- Studies in children ≥ 6 weeks to <10 years of age will be conducted to fulfill PREA requirements.

Post-Marketing Commitments

- The applicant will submit the clinical study report from a safety and immunogenicity study to assess concomitant use of Bexsero with a second dose of Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate vaccine in persons 16 years through18 years of age.
- The applicant committed to establish a pregnancy registry for Bexsero in the U.S. to collect prospective data on pregnancy and birth outcomes following exposures to Bexsero occurring prior to or at any time during pregnancy. The applicant will submit annual reports as well as a three-year summary report.