



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

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Subject: Pharmacovigilance Plan Review

Applicant: Novartis Vaccines and Diagnostics Inc.

Product: Bexsero™, Meningococcal Group B vaccine
Proposed Indication: For the active immunization against invasive disease caused by *Neisseria meningitidis* serogroup B strains in individuals aged 10 through 25 years of age.

Current Indication: Not applicable in the United States

Submission type: Original BLA

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Contents

1	INTRODUCTION	2
1.1	Product Description.....	2
1.2	Rationale for Development, Indications and Usage.....	3
1.3	Contraindications, Warnings, and Precautions.....	3
1.4	Pertinent Regulatory History.....	4
1.4.1	Regulatory History in Foreign Countries	4
1.4.2	Regulatory History in the United States.....	5
1.5	Worldwide Distribution Data and Post-Marketing (non-study) Exposure.....	5
1.6	Objectives/Scope of the Review	5
2	MATERIALS REVIEWED	5
3	PHARMACOVIGILANCE PLAN REVIEW	7
3.1	Non-Clinical Safety Findings	7
3.2	Clinical Safety Database	7
3.2.1	Sponsor Analysis.....	7
3.3	Safety Concerns Within the Pharmacovigilance Plan	15
3.3.1	Important Identified Safety Issues	15
3.3.2	Important Potential Safety Issues	15
3.3.3	Important Missing Information.....	15
3.4	Action Plan for Safety Concerns.....	17
3.5	Additional Comments on Other Potential Safety Concerns.....	15
3.5.1	Routine Pharmacovigilance Practices	16
3.6	Action Plan for Safety Concerns	16
3.6.1	Ongoing and Planned Post-licensure Studies outside the US.....	20
4	REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS.....	23
4.1	Clinical Overview Summary.....	23
5	POST LICENSURE SAFETY REVIEW	24
5.1	NVD Pharmacovigilance	24
5.2	Canadian Vaccination Campaign.....	24
6	INTEGRATED RISK ASSESSMENT	25
7	RECOMMENDATIONS.....	28
8	REFERENCES	28

1 INTRODUCTION

1.1 Product Description

Bexsero is a multicomponent Meningococcal B vaccine (rMenB+OMVNZ) that contains three purified recombinant *Neisseria meningitidis* serogroup B protein antigens. NadA (Neisserial adhesin A) as a single

protein, NHBA (Neisseria Heparin Binding Antigen) and fHbp (factor H binding protein) as fusion proteins, and PorA subtype P1.4 as the main antigen of Outer Membrane Vesicles (OMV) derived from *N.meningitidis* serogroup B, strain NZ 98/254. The vaccine formulation contains aluminum hydroxide as adsorbent. Bexsero contains 50µg of each of the three purified recombinant protein antigens, 25µg of OMV (amount of total protein containing PorA P1.4) and 1.5 mg of aluminum hydroxide per 0.5 mL dose. The pharmaceutical form is a suspension for injection. The vaccine is supplied in 1 mL hydrolytic glass pre-filled syringes.

1.2 Rationale for Development, Indications and Usage

Meningitis B disease is a serious condition with a case-fatality rate of approximately 9% among patients in the United States during 1994–2002 (1). Among survivors, it is a severely debilitating disease, with approximately 10–30% of patients suffering permanent sequelae. These include hearing loss, significant neurological damage, limb amputation, skin scarring, renal failure, and cognitive deficits (2). *N. meningitidis* colonizes nasopharyngeal mucosal surfaces. It is transmitted through direct contact with large droplet respiratory tract secretions from patients or asymptomatic carriers. Carriage rates are highest in adolescents and young adults who may serve as reservoirs for transmission (2). Meningitis B also has significant societal impact through case clusters and outbreaks, which is unique among bacterial agents causing meningitis. The World Health Organization estimates that there are 1.2 million cases of invasive meningococcal disease (IMD) and 135,000 related deaths annually (3). In the United States, most cases of meningococcal disease are sporadic, with an incidence of 0.35 cases per 100,000 population and 1.01 cases per 100,000 in Europe (1). However, US outbreaks of meningococcal disease continue to occur and, with the widespread implementation of serogroup ACWY glycoconjugate vaccination in adolescents, outbreaks are more likely to be caused by serogroup B.

From March through November 2013, an outbreak of serogroup B meningococcal disease at Princeton University resulted in eight cases epidemiologically linked to the university, caused by genetically similar strains. In November 2013, the Centers for Disease Control and Prevention (CDC) submitted an expanded access investigational new drug (IND) application to use Bexsero to reduce the risk of disease among Princeton students and staff and to control the outbreak by preventing additional cases.

Between November 11 and 21, 2013, the California Department of Public Health reported 4 confirmed cases of serogroup B meningococcal disease caused by genetically similar strains among University of California Santa Barbara (UCSB) undergraduate students. The strains were distinct from those causing the Princeton cases. On review of previous meningococcal disease cases associated with the university, an additional case from March 2013 was identified with matching genetic typing by pulsed-field gel electrophoresis. Because of the relatively short period of time during which these cases occurred, concern for ongoing transmission, and lack of effective methods to control outbreaks, CDC submitted a second protocol to allow use of Bexsero at UCSB to control the outbreak. FDA supported an Expanded Access IND to initiate Bexsero vaccination campaigns at Princeton and UCSB in December 2013 and February 2014, respectively.

Bexsero is licensed/authorized for use in Europe, Canada and Australia. This memo describes the pharmacovigilance review of a biologics licensing application (BLA) submitted by Novartis Vaccines and Diagnostics (NVD) for Bexsero for Priority Review designation as provided by the Prescription Drug User Fee Act of 1992. NVD provides summaries of clinical and safety data available to date in the adolescent and adult age groups for review of the evidence that Bexsero represents an improvement in the prevention of invasive meningococcal disease (IMD), with an acceptable safety profile.

1.2.1 Proposed Indication

The proposed indication in the US is for the use of Bexsero for prevention of serogroup B meningococcal disease in subjects 10 through 25 years of age.

1.3 Contraindications, Warnings, and Precautions

Foreign labeling for Bexsero states the following contraindications, special warnings, and precautions for use:

Contraindications

- Hypersensitivity to the active substances

Special warnings and precautions for use

- In case of severe febrile illness, administration should be postponed. The presence of a minor infection should not defer vaccination.
- In case of disorders contraindicating intramuscular injection, administration may be considered only if the potential benefit clearly outweighs the risks.
- In pregnant females or in females of childbearing potential not using acceptable birth control measures, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection. The potential risk for pregnant women is unknown.

1.4 Pertinent Regulatory History

1.4.1 Regulatory History in Foreign Countries

Bexsero is approved in Europe, Australia, and Canada. By the end of November 2013, it was launched in five European countries, with (b)(4)- doses distributed in UK, Ireland, Germany, France, and Italy.

On January 14, 2013 it was approved in the European Union for “for active immunization of individuals 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B” with age specific schedules. For infants, 2–5 months, 3 doses each of 0.5ml with an interval of at least 1 month between doses, and a booster dose between 12–15 months. For infants 6–11 months of age, 2 doses each of 0.5ml at least 2 months apart and 1 booster dose in the second year of life with an interval of at least 2 months between the primary series and the booster dose. For children 12–23 months of age, 2 doses each of 0.5ml at least 2 months apart and 1 booster dose with an interval of 12–23 months between the primary series and booster dose. For children 2–10 years of age, 2 doses of 0.5 mL with an interval of at least 2 months between doses. For adolescents ≥11 years and adults, 2 doses, each of 0.5 mL, with an interval of at least 1 month between doses.

On August 14, 2013, it was approved in Australia “for active immunization against invasive disease caused by *N. meningitidis* group B strains.” It is indicated for vaccination of individuals ≥2 months of age. The approved schedules for individuals are as follows: Infants aged 2–5 months, 3 doses, each of 0.5 ml, with an interval of at least 1 month between doses. A booster dose is recommended between 12–23 months. For unvaccinated infants aged 6–11 months, 2 doses of 0.5 mL each, with an interval of at least 2 months between doses. A booster dose is recommended in the second year of life with an interval of at least 2 months between the primary series and booster dose. Unvaccinated toddlers and children aged 12 months to 10 years, 2 doses of 0.5 mL with an interval of at least 2 months between doses. For individuals 11–50 years of age, 2 doses, each of 0.5 mL, with an interval of at least 1 month between doses.

On December 6, 2013, it was approved in Canada “for active immunization of individuals from 2 months through 17 years old against invasive disease caused by *Neisseria meningitidis* serogroup B strains.” The approved schedules are as follows: For infants aged 2–5 months, 3 doses each of 0.5ml with an interval of at least 1 month between doses. A booster dose is required between 12–23 months of age. For unvaccinated infants aged 6–11 months, 2 doses each of 0.5ml, at least 2 months apart. A booster dose is required in the second year of life, with an interval of at least 2 months from the last dose. For unvaccinated children aged 12–23 months, two doses of 0.5ml each, given at least 2 months apart. For children aged 2–10 years, 2 doses each of 0.5 mL, given at least 2 months apart. For individuals 11–17 years, 2 doses, each of 0.5 mL, with an interval of at least 1 month between doses.

1.4.2 Regulatory History in the United States

On May 4, 2006, FDA granted Fast Track Designation for the Recombinant Meningococcal B Vaccine. Following the 2013 and 2014 outbreaks of MenB meningitis at Princeton University, and UCSB respectively, NVD provided the multicomponent meningococcal group B vaccine Bexsero under expanded access IND (BB-IND 15,810) to the at risk population associated with the universities. Over 15,000 students have been vaccinated at the two universities.

In the context of these outbreaks and following two Type C meetings between NVD and CBER on February 10 and 12, 2014 to discuss pathways for licensure, NVD requested a Pre-BLA meeting in preparation to submit the application under an accelerated approval process. FDA granted Breakthrough Therapy Designation for this vaccine. During the Type C meeting (CRMTS # 9292) held on February 12, 2014 FDA agreed that the safety and immunogenicity data accrued to date in the NVD MenB vaccine clinical development program may be adequate to support an application for licensure under FDA's accelerated approval licensure pathway (21 CFR 601.41). Based on the Designation of Breakthrough Therapy received on April 1, 2014, Novartis sought Priority Review of this BLA.

Bexsero is the -(b)(4)- meningococcal B vaccine --(b)(4)-- by the US FDA for licensure. On October 29, 2014, the FDA licensed Trumenba® in the US for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. Trumenba is similar to Bexsero in that it is also a recombinant meningococcal B vaccine based on fHbp but is composed of two lipidated fHbp variants. As of the date of this review, Trumenba has not been licensed in any countries outside the US.

1.5 Worldwide Distribution Data and Post-Marketing (non-study) Exposure

Bexsero received marketing authorization through the centralized procedure in Europe on January 14, 2013. Product launch occurred in 5 European countries in late November 2013. As of the data lock point (DLP) of January 13, 2014 for the risk management plan (RMP) submitted in support of this BLA, the vaccine was on the market in the UK, Ireland, France, Germany, and Italy. The number of doses distributed was -(b)(4)-; the number of doses sold was -(b)(4)- (provided by the Novartis Vaccine Marketing Department); and the number of doses used was estimated to be -(b)(4)-, by the 5 country Novartis affiliate in Europe, based on the re-order of doses in those countries. Due to the short time period and the small amount of doses sold, this estimate of number of doses utilized may not be accurate. It is not feasible to evaluate the exact number of subjects exposed, because depending on the age group, subjects are receiving either 3 doses (infants below 6 months) or 2 doses (children 6 months and older, adolescents and adults), plus a booster dose in children 2–23 months of age.

1.6 Objectives/Scope of the Review

The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be licensed in the US, and to evaluate the pharmacovigilance plan (PVP) submitted by NVD for the Bexsero BLA.

2 MATERIALS REVIEWED

Date	Source	Document Type	Document(s) Reviewed
6/16/2014	NVD	BLA Sequence 0000	125546/0.0; Module 1.2, Cover Letters: Original Submission & Attachment (FDA form 3674)
6/16/2014	NVD (136pg)	BLA Sequence 0000	125495/0.0; Module 1.16, Risk Management Plan
7/23/14	NVD (176pg)	BLA Sequence 0002	125495/0.2; Module 2.7.4, Summary of Clinical Safety (ISS Summary)
6/16/14	NVD (25pg)	BLA Sequence 0000	125495/0.0; Module 2.4, Non-clinical Overview

Date	Source	Document Type	Document(s) Reviewed
7/23/14	NVD (49pg)	BLA Sequence 0002	125495/0.2; Module 2.5, Clinical Overview
6/16/14	NVD (10pg)	BLA Sequence 0000	125495/0.0; Module 2.7.6, Synopses of Individual Studies
7/23/14	NVD	BLA Sequence 0000	125495/0.0; Module 5.3.5, Reports of Safety Studies <ul style="list-style-type: none"> • Subsection 5.3.5.1: Study Reports of Controlled Clinical Studies <ul style="list-style-type: none"> ➤ Study Report V72P10 RCT ➤ Study Report V72_29 RCT ➤ Study Report V72_41 RCT ➤ Study Report V102_03 RCT
6/16/14		BLA Sequence 0000	<ul style="list-style-type: none"> • Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies <ul style="list-style-type: none"> ➤ Study Report V72P4 OLE ➤ Study Report V72P5 OLE
7/23/14		BLA Sequence 0000	<ul style="list-style-type: none"> • Subsection 5.3.5.4: Other Study Reports <ul style="list-style-type: none"> ➤ Study Report V72_68TP ➤ Study Report V72_70TP
9/5/14	NVD	BLA Sequence 0010	125546/0.10 <ul style="list-style-type: none"> • Subsection 5.3.6: PSUR3 • Subsection 1.11.4: Response to Information Request on Pharmacovigilance Plan • Subsection 5.3.5.4: Study Protocols for planned foreign post marketing studies <ul style="list-style-type: none"> ➤ Study Protocol V72_36OB ➤ Study Protocol V72_38OB ➤ Study Protocol V72_39OB ➤ Study Protocol V72_52OB ➤ Study Protocol V72_53OB ➤ Study Protocol V72_62
10/31/14	NVD	BLA Sequence 0022	125546/0.22 <ul style="list-style-type: none"> • Subsection 5.3.6: English translation of the Bexsero vaccination campaign in the Saguenay-Lax-St. Jean region of Quebec, Canada
12/11/14	NVD	BLA Sequence 0036	125546/0.34 <ul style="list-style-type: none"> • Subsection 1.11.4: Multiple Module Information Amendments Pregnancy Registry
12/30/2014	NVD	BLA Sequence 0043	125546/0.39 <ul style="list-style-type: none"> • Subsection 1.14.1.3: Draft Labelling Text • Subsection 5.3.5.4: UCSB FDA Safety Report 11-13-14
1/7/15	NVD	BLA Sequence 0044	125546/0.41 <ul style="list-style-type: none"> • Subsection 1.11.4: Response to IR re: Dose Distribution Data
1/9/15	NVD	BLA Sequence 0045	125546/0.42 <ul style="list-style-type: none"> • Subsection 1.11.3: Efficacy Information Amendment-Pregnancy Registry • Subsection 5.3.5.1: V102_03 Erratum To Clinical Study Report Table Of Contents
1/13/15	NVD	BLA Sequence 0046	125546/0.43 <ul style="list-style-type: none"> • Subsection 1.14.1.3: Draft Labelling Text
9/29/14		References	Medical literature review

RCT – randomized control trial
OLE – open label

3 PHARMACOVIGILANCE PLAN REVIEW

3.1 Non-Clinical Safety Findings

- No adverse local or systemic toxicities were identified based on the findings from single or repeat dose toxicity studies in rabbits.
- No maternal reproductive concerns were identified based on reproductive toxicity studies in rabbits.
- No developmental concerns were identified based on developmental toxicity studies in rabbits.

3.2 Clinical Safety Database

A total of 8 studies were included in this BLA to support the safety of rMenB+OMV NZ (Bexsero). NVD sponsored 6 studies (V72P10, V72_41, V72_29, V102_03, V72P4, and V72P5), and CDC sponsored 2 studies (V72_68TP and V72_70TP). The breakdown of studies is as follows;

- 2 studies (V72P10 and V72_41) in adolescents 11 through 17 years of age
- 1 study (V72_29) in university students 18 through 24 years of age
- 1 study (V102_03,) in subjects 10 through 25 years of age
- 2 studies (V72_68TP and V72_70TP) sponsored by the CDC during the Princeton University and UCSB vaccination campaigns in individuals from 16 through 68 years of age
- 2 supportive studies (V72P4 and V72P5) in adults 18 through 50 years of age

A total of 18,490 subjects have been exposed to at least 1 dose of Bexsero in the 8 studies presented in support of vaccine safety. The total number exposed to at least 1 dose in the 6 Novartis-sponsored clinical studies (V72P4, V72P5, V72P10, V72_29, V72_41, and V102_03) was 3,139, and the total number of subjects 10 through 25 years of age exposed to at least 1 dose in the 4 Novartis-sponsored studies (V72P10, V72_29, V72_41 and V102_03) who provided any unsolicited safety data was 3,058.

In all NVD sponsored studies, safety collection measures included solicited and unsolicited adverse events (AEs) 7 days post vaccination. In study V102_03 only, unsolicited AEs were collected for a further 84 days post vaccination. All serious adverse events (SAEs), and AEs leading to premature withdrawal were collected throughout the study period. AEs leading to a physician’s visit were collected.

3.2.1 Sponsor Analysis

Table 1: Summary of Clinical Safety Studies

Study #; Region	Study Objectives (Age Range)	Study Design; Patient Population	# of Subjects	# Subjects/Exposure	Key Safety Findings (SAEs)
Novartis Sponsored					
V72P10; Chile (pivotal)	Safety & immunogenicity of various schedules in healthy adolescents (11-17 y o)	Phase 2b/3 Observer-blind, multicenter RCT	1631 enrolled, 1622 ≥1 dose	0 mos. rMenB+OMV NZ / 247 0, 1 mos. rMenB+OMV NZ/ 247 0, 2 mos. rMenB+OMV NZ/ 253 0, 6 mos. rMenB+OMV NZ/ 128 0, 1, 6 mos. rMenB+OMV NZ/ 128 0, 2, 6 mos. rMenB+OMV NZ/ 127 0, 1, 2 mos. rMenB+OMV NZ/ 373 0, 1, 2 mos. Placebo + rMenB+OMV NZ at 6 mos. / 119	<ul style="list-style-type: none"> • 35 SAEs, including 2 study-unrelated deaths • 1 premature withdrawal due to ¹JIA • 19 pregnancies, 18 live births, 1 unknown. • 1 birth with ²PWS, death @ 2mnths

Study #; Region	Study Objectives (Age Range)	Study Design; Patient Population	# of Subjects	# Subjects/Exposure	Key Safety Findings (SAEs)
V72_29; United Kingdom (pivotal)	Evaluate pharyngeal carriage of <i>N meningitidis</i> in young adults (18-24 y o)	Phase 3 observer-blind multicenter RCT	2968	0,1 mos. rMenB+OMV NZ/ 974 0 mos., placebo 1 mos. MenACWY (Menveo)/ 984 0, 1 mos. Japanese Encephalitis (Ixiaro) / 985	<ul style="list-style-type: none"> • 2-3% SAEs • No deaths • No difference in carriage rates
V72_41; Canada & Australia (pivotal)	Safety and immunogenicity of 2 different vaccine lots in healthy adolescents (11-17 y o)	Phase 3 observer-blind multicenter RCT	344 enrolled	0,2 mos. rMenB+OMV NZ / 170 (Rosia site) 0,2 mos. rMenB+OMV NZ / 174 (-(b)(4)- site) Refused vaccine / 2	<ul style="list-style-type: none"> • No deaths • No SAEs • Lot equivalence demonstrated
V102_03; US & Poland (Pivotal)	Safety & immunogenicity of 2 combined vaccine formulations in adolescents & young adults (10-25 y o)	Phase 2, observer blind multicenter RCT	484 enrolled, 480 randomized	---(b)(4)--- / 120 ----(b)(4)---- / 120 rMenB+OMV / 120 Placebo & MenACWY (Menveo) / 120	<ul style="list-style-type: none"> • No deaths • Local reactogenicity higher in vaccine group
V72P4; Italy & Germany	Safety and immunogenicity in healthy at-risk adults (18-50 y o)	Phase 2, Open label, multicenter	53	0, 2, 6 mos. rMenB+OMV NZ α + (MenACWY β at 7 mos.)	<ul style="list-style-type: none"> • No deaths • No SAEs • 45% unsolicited AEs • 1 pregnancy, live birth no congenital abnormalities
V72P5; Switzerland	Safety and immunogenicity of final vaccine formulation in healthy adults (18-40 y o)	Phase 1, observer blind, single center, randomized	70	0, 1, 2 mos. rMenB+OMV NZ α / 28 0, 1, 2 mos. rMenB--(b)(4)---- / 28 0, 1, 2 mos. rMenB / 14	<ul style="list-style-type: none"> • No deaths • 2 SAE – HIV and appendicitis, both unrelated
CDC Sponsored					
V72_68TP; USA	Ongoing study collecting SAEs from adolescents and adults from Princeton University	Open label	5875 (total eligible population)	0 mos., MenB+OMV NZ / 5520 0,1 MenB+OMV NZ / 5165	<ul style="list-style-type: none"> • SAEs rate 4.2/1,000 vaccinees • 1 SAE possibly related to vaccine
V72_70TP; USA	Ongoing study collecting SAEs from adolescents and adults from UCSB	Open label	9831	0 mos., rMenB+ OMV NZ / 9831	<ul style="list-style-type: none"> • 25 subjects (< 1%) reported an SAE • SAE rate < 1% (1st dose) • < 1% (2nd dose)

¹ JIA: Juvenile Idiopathic Arthritis. ² PWS: Prader Willi Syndrome

mos.: months,

rMenB+OMV NZa: 0.5 ml IM dose of 50 µg of *N. meningitidis* purified antigens 961c, 936-741, and 287-953, plus 25 µg of OMV from *N. meningitidis* strain NZ98/254

MenACWYb: Menveo®, a lyophilized MenA conjugate component reconstituted with 0.5 mL of liquid MenCWY conjugate component

rMenB+OMV (b)(4): 0.5 ml IM dose of 50 µg of *N. meningitidis* purified antigens 961c, 936-741 and 287-953, plus 25 µg of OMV from *N. meningitidis* strain H44/76

rMenB: 0.5 ml IM dose of 50 µg of *N. meningitidis* purified antigens 961c, 936-741, and 287-953

3.2.1.1 Controlled / Randomized Controlled Trial (RCT) Studies in Support of Safety

RCT Study V72P10

Objectives:

To study the safety, tolerability, and immunogenicity of the NVD rMenB+OMV NZ vaccine administered as 1-dose, 2-dose, or 3-dose vaccination schedules in healthy adolescents aged 11 to 17 years.

Study design/population:

A Phase 2b/3, observer-blind, multi-center, randomized, controlled trial in healthy adolescents. A total of 1,631 subjects were randomized in an observer-blind manner into one of 8 groups in a 1:2:1:2:1:2:3:1 and ratio stratified by age group (11 to 13 years and 14 to 17 years). Each individual's participation was approximately 12 months. The safety data for the proposed 2-dose indication in adolescents came from the 0, 1-, 0, 2- and 0, 6-month schedules.

Key Safety Results:

- 1,631 subjects received at least one study vaccination and were included in the safety population.
- 94% of subjects in the vaccine group compared to 92% in the placebo groups reported local or systemic reactions within 7-days after each vaccination
- Overall, the most commonly reported AEs were injection site reactions like pain, induration, and swelling.
- Within 7 days, the most commonly reported AEs within 7 days after each vaccination were in the system organ class (SOC) “general disorders and administration site conditions” and “infections and infestations”, the most common being nasopharyngitis and bronchitis.
- 19 pregnancies were reported;
 - 18 had live born deliveries
 - 1 outcome unknown
 - 2 subjects in vaccine group gave birth to infants with congenital abnormalities
 - Subject 1: last vaccine received 14 weeks prior to pregnancy confirmation. Live born infant with Prader Willi syndrome
 - Subject 2: last vaccine received 12 weeks prior to pregnancy confirmation. Live born infant with absence of the second toe of the right foot and death at 2 months after the birth from sudden infant death syndrome (SIDS)
- 35 SAEs reported (rate 1–2% after primary vaccine dose and 1–4% after booster dose), compared to placebo rate of 1%
 - SAEs in 2 subjects (Juvenile idiopathic arthritis) were assessed to be possibly related to the study vaccination
- 3 subjects were terminated from the study prematurely due to an AE or death;
 - An AE (juvenile arthritis) that was assessed to be possibly related to the study vaccination;
 - 2 Deaths due to study-unrelated events,
 - Road traffic accident
 - Hepatic failure secondary to an acetaminophen overdose

RCT Study V72_41

Objectives:

To demonstrate the equivalence of rMenB+OMV NZ lot 1 and rMenB+OMV NZ lot 2 produced at two different sites, when administered to adolescents. Lot 1 was formulated with OMV manufactured in the Novartis Rosia facility and Lot 2 from the Novartis (b)(4) facility.

Study design/population:

A Phase 3, multicenter observer-blind randomized trial in adolescents 11 through 17 years of age. All subjects received 2 rMenB+OMV NZ vaccinations 1 month apart and were followed for a total of 2 months. Subjects were randomized to 1 of 2 treatment arms to receive either two doses of rMenB+OMV NZ vaccine Lot 1 or two doses of rMenB+OMV NZ Lot 2. Human serum bactericidal activity (hSBA) geometric mean titers (GMTs) against 3 *N. meningitidis* serogroup B reference strains H44/76, 5/99, and NZ98/254 and -----(b)(4)----- geometric mean concentrations (GMCs) against vaccine antigen 287-953 were measured 30 days after a primary vaccination course of two doses one month apart. Of 344 subjects enrolled in the study, 170 were included in Lot1 and 174 were included in Lot2. The per protocol (PP) immunogenicity population was comprised of 299 subjects, 147 from Lot1 and 152 from Lot2 -(b)(4)- The safety population comprised 342 subjects, 169 in Lot1 and 173 in Lot2.

Key Safety Findings:

- The most frequently reported solicited local reaction after any vaccination was pain (96% Lot1; 98% Lot 2). The majority of solicited local reactions were of mild to moderate intensity.
- 80% of subjects in Lot1 and 87% in Lot2 reported ≥ 1 systemic reaction during the 7 days after either vaccination.
- The most frequently reported solicited systemic reaction was myalgia (59% Lot1; 68% Lot2).
- A similar percentage of subjects from Lot1 (40%) and Lot2 (38%) reported ≥ 1 AE, 20% and 22% respectively considered to be possibly related to the vaccine
- 0 SAEs reported
- 0 deaths
- 0 pregnancies
- 1 withdrawal; a subject from Lot2 withdrew on day 34 due to infectious mononucleosis that started on day 14, with moderate severity and was judged as unrelated to the study vaccine.

RCT Study V72_29

Objectives

The objectives were twofold:

1. To investigate carriage prevalence of virulent sequence types of *N. meningitidis* B at 1 month following administration of two doses of rMenB+OMV NZ, compared to the control group receiving Japanese Encephalitis vaccine.
2. To evaluate the safety and tolerability of two doses of rMenB+OMV NZ vaccine, given 1 month apart, and a single dose of MenACWY conjugate vaccine in healthy young adults.

Study Design/Population

A phase-3, multicenter, observer-blind randomized trial that enrolled university students 18 through 24 years of age in the UK. All subjects received two injections 1 month apart and were followed-up for a total of 12 months. Subjects were randomized to 1 of 3 treatment arms (two doses of rMenB+OMV NZ vaccine, one dose of placebo followed by MenACWY-CRM197conjugate vaccine (Menveo), or 2 doses of Japanese encephalitis vaccine (IXIARO™), administered one month apart as a control (Table 1).

Key Safety Findings

- 2,968 subjects received ≥ 1 dose of either test vaccine or control vaccine.
- 99% included in the safety population for assessing unsolicited AEs
- The rMenB+OMV NZ group reported a higher percentage of solicited AEs after the first and second vaccinations compared with the Menveo and Ixiaro groups

- 98% rMenB+OMV NZ vs 77% Menveo and 79% Ixiaro groups after 1st vaccination
- 94% rMenB+OMV NZ vs 74% Menveo and 66% Ixiaro groups after 2nd vaccination
- The most commonly reported solicited local AE across vaccine groups was injection site pain of mild or moderate intensity (48–93% after 1st vaccination; 40–88% after 2nd vaccination).
- The most commonly reported solicited systemic AEs across vaccine groups were;
 - Myalgia - 42–75% after 1st vaccination, 35–69% after 2nd vaccination
 - Headache - 25–30% after 1st vaccination, 11–23% after 2nd vaccination
 - Malaise - 15–20% after 1st vaccination, 11%–22% after 2nd vaccination
- Overall, 2–3% of subjects reported SAEs; a large proportion of these were assessed to be unrelated to the study vaccination. In most cases the events were transient and the subjects recovered within the study period
- 3 subjects reported premature withdrawal from the study due to an AE.
 - A 20 year old male who developed a fine tremor in both hands 18 days post 2nd dose of rMenB+OMV NZ
 - A 21 year old female who developed paresthesia of both feet 2 days post 1st dose of rMenB+OMV NZ
 - A 20 year old female who developed acute thyroiditis 38 days post 1st dose of rMenB+OMV NZ
- 8 pregnancies occurred during the study; 3 in the rMenB+OMV NZ group, 1 in the MenACWY group and 4 in the Ixiaro group.
 - Of 3 pregnancies in the rMenB+OMV NZ group;
 - 1 delivered a live newborn without congenital abnormalities
 - 1 had a therapeutic abortion
 - 1 had an ectopic pregnancy 57 days after the 2nd vaccination)
 - For the 1 pregnancy in the MenACWY group, outcome was a live birth without congenital abnormalities
 - For the 2 pregnancies in the Ixiaro group, outcomes were therapeutic abortions.
- 0 deaths reported

RCT Study V102_03

Objectives

To evaluate the safety and immunogenicity of 2 different combined meningococcal vaccine formulations -----
 -----(b)(4)----- in healthy adolescents and young adults 10 through 25 years of age. This study had an additional study group of participants given 2 doses of rMenB+OMV NZ 2 months apart.

Study Design/Population

This was a phase 2, observer-blinded, controlled, randomized, multicenter study in healthy adolescents. A total of 480 healthy subjects were randomized in a 1:1:1:1 ratio to 1 of 4 groups to receive vaccinations as follows;

- Group I: ----(b)(4)---- vaccine formulation with full dose OMV on a 0,2-month schedule
- Group II: ----(b)(4)----- vaccine formulation with a quarter dose of OMV on a 0,2-month schedule
- Group III: rMenB+OMV NZ vaccine on a 0,2-month schedule
- Group IV: Single dose of placebo and a single dose of MenACWY vaccine respectively, on a 0,2-month schedule

Key Safety Findings:

- 484 subjects enrolled, 480 (99%) were exposed to study vaccines
- 120 subjects in each of groups I-IV, and 109 subjects in the placebo/ACWY group comprised the overall safety set
- 86–93% vs. 63% in the vaccine and placebo/ACWY groups, respectively, reported any solicited AEs.
- 62–70% vs 47% in the vaccine and placebo/ACWY groups, respectively, reported any systemic AEs
- The most common local AE was injection site pain;
 - 84–90% in the -----(b)(4)-----, and rMenB+OMV groups vs 27% in the placebo/ACWY group after first vaccination

- 73–83% in the -----(b)(4)-----, and rMenB+OMV groups vs 42% in the placebo/ACWY group after second vaccination
- The most common systemic AEs were;
 - Myalgia - 49–52% vaccine vs 26% placebo/ACWY
 - Fatigue - 23–36% vaccine vs 22% placebo/ACWY
 - Headache - 23–32% vaccine vs 20% placebo/ACWY
 - Arthralgia 8–19% vaccine vs 4% placebo/ACWY
 - Loss of appetite 9–17% vaccine vs 9% placebo/ACWY
- 1–4% reported fever in each group after the first vaccination and 0–5% after the second vaccination
- 2 subjects in the rMenB+OMV group reported an AE that led to premature withdrawal; 1 was considered possibly related to study vaccine.
 - 1 case of generalized lymphadenopathy on day 6 after the first vaccination; considered possibly related to study vaccine.
 - 1 case of convulsions on day 60 after the first vaccination in a patient with seizure disorder prior to enrollment
- 9 subjects (1–3% in each study group) reported 10 SAEs; none were considered related to study vaccine. All SAEs except seizure disorder and multiple sclerosis resolved.
- 2 pregnancies reported, 1 of which was in the rMenB+OMV group. Subject discovered pregnant ~7 months after last dose. Each pregnancy resulted in a live born infant without congenital abnormalities
- 0 deaths

RCT Study V72P4

Objectives

Objectives of this study were two-fold;

1. To explore immunogenicity, safety and tolerability of Novartis rMenB+OMV in healthy at-risk adults when administered at a 0, 2, 6- month schedule.
2. To explore the safety and tolerability of a single dose of Novartis MenACWY conjugate vaccine in healthy at-risk adults.

Study Design/Population

A Phase 2, open-label, multi-center study in healthy at-risk adults routinely exposed to *N. meningitidis*. Novartis rMenB + OMV (0.5 mL each dose) was administered intramuscularly (IM) according to a 0, 2, 6-month immunization schedule. A single dose (0.5 mL) of Novartis MenACWY conjugate vaccine was to be administered at study month 7. Blood samples were obtained for meningococcal serology from all subjects at baseline and at 1 month after each vaccination. A total of 54 subjects were enrolled in this study after screening for inclusion and exclusion criteria. A total of 53 (98%) subjects received at least one vaccination and were included in the safety analysis. A total of 46 (85%) subjects were included in the per protocol (PP) analysis for immunogenicity. The number of subjects included in the PP immunogenicity analysis at each time point were; 25(46%) after first vaccination, 46(85%) after second vaccination, 39(72%) after third vaccination and 23 (43%) after MenACWY vaccination.

Key Safety Findings

- 54 enrolled subjects, 53 subjects received at least one vaccination and were included in the safety analysis.
- Overall, the most commonly reported AEs after any vaccination were injection site pain (11%) and nasopharyngitis (11%) followed by rhinitis (6%), bronchitis (4%), gastritis (4%) and injection site induration (4%). Five subjects reported fevers, 2 had fever >39°C.
- More subjects experienced local reactions after rMenB+OMV (98–100%) than after MenACWY (44%). Reactions were transient and mild or moderate, with few continuing past the day 7 observation window.
- The most common local reaction after rMenB+OMV vaccination was injection site pain (96–100%). After MenACWY vaccination, the most common local reaction was pain (24%) and no severe local reactions.

- For rMenB+OMV recipients, the most common systemic reaction after the first vaccination was malaise (30%), after the second vaccination was myalgia (37%), and after the third vaccination was malaise (52%). The most common systemic reaction reported after MenACWY vaccination was malaise (27%).
- 2 subjects withdrew from the study
 - 1 due to syncope on day 1 post 1st vaccination
 - 1 due to nasopharyngitis on day 212 post 1st vaccination
- 1 subject was confirmed pregnant on day 86, after having received 2 doses of rMenB+OMV, and withdrew consent. She delivered a live born infant without congenital abnormalities.
- 0 SAEs reported
- 0 deaths reported

RCT Study V72P5

Objectives:

To explore immunogenicity, safety and tolerability of Novartis meningococcal B recombinant Vaccine (rMenB +/- OMV) in healthy adults

Study Design/Population

A Phase I, observer-blind, single-center, randomized study in healthy adults. rMenB +/- OMV was administered intramuscularly (IM) according to a 0-, 1-, and 2-month immunization schedule. A cohort of 70 healthy adults 18–40 years of age was randomized in a 2:2:1 ratio to 1 of the following 3 groups;

- Group I - Novartis Meningococcal B Recombinant Vaccine + OMV New Zealand (NZ) at 0, 1, and 2 months: 26 subjects (rMenB+OMV NZ)
- Group II - Novartis Meningococcal B Recombinant Vaccine + OMV ---(b)(4)----- at 0, 1, and 2 months: 26 subjects (rMenB+OMV (b)(4))
- Group III - Novartis Meningococcal B Recombinant Vaccine without OMV at 0, 1, and 2 months: 13 subjects (rMenB)

Meningococcal serology (bactericidal activity and immunoglobulin G [IgG] antibody levels) and selected clinical laboratory tests from all subjects were performed at baseline and during the study. All local and systemic reactions and all AEs 7 days post vaccination were collected.

Key Safety Findings:

- Pain at the injection site was the most commonly reported local reaction (100% in both rMenB+OMV NZ and rMenB+OMV (b)(4) groups and 86% in the rMenB group).
- Severe pain was more common in the rMenB+OMV NZ group (32%) and in the rMenB+OMV (b)(4) group (36%) than in the rMenB group (7%).
- The most common systemic reactions were;
 - Myalgia - 82% rMenB+OMV NZ, 86% rMenB+OMV (b)(4), 71% rMenB
 - Headache - 57% rMenB+OMV NZ, 61% rMenB+OMV (b)(4), 43% rMenB
- The frequency of local and systemic reactions and other indicators of reactogenicity were similar after the first, second, and third vaccine dose.
- Frequency of unsolicited AEs was similar in the three vaccine groups (21% rMenB+OMV NZ, 18% rMenB+OMV (b)(4), 21% rMenB).
- The SOC associated with the most unsolicited AEs (2–3%) was gastrointestinal disorders namely diarrhea, toothache, vomiting, and pruritus
- 2 SAEs reported, both assessed as unrelated to study vaccine
 - 1 (rMenB+OMV (b)(4) group) case of acute appendicitis
 - 1 (rMenB+OMV NZ group) HIV infection
- 1 AE of submandibular lymphadenopathy in the rMenB+OMV (b)(4) group led to premature withdrawal from the study
- 1 pregnancy in the rMenB+OMV-(b)(4) group; subject withdrew from the study

- 0 deaths occurred

3.2.1.2 Open label studies in support of safety

OLE Study V72_68TP

Objectives

An ongoing study during a vaccination campaign with Bexsero during a serogroup B meningococcal disease outbreak at Princeton University, New Jersey.

Study Design/Population

The investigational rMenB+OMV NZ vaccine was recommended for undergraduate or graduate students living in dormitories, and for other students or staff on the Princeton University campus with medical conditions putting them at risk for meningococcal disease. The vaccine was administered by Princeton University in consultation with CDC. The clinical Site Investigators monitor SAEs from the time of receipt of the first dose of rMenB+OMV NZ up to 30 days following receipt of the second dose. SAEs are collected using active and passive surveillance.

Key Safety Findings

- Study is ongoing. DLP of 1/13/14 used for these data
- Of 5,875 recipients of the rMenB+OMV NZ vaccine, 1 SAE was reported to be possibly vaccine related
 - 20-year-old male vaccinee diagnosed with rhabdomyolysis 10 days after receipt of second dose. Temporal relationship with vaccine exists, but confounders such as heavy exercise and binge drinking made causality difficult to establish.
- No concerning patterns among other types of AEs reported have been identified.
- No deaths up until the DLP
- 1 pregnancy occurred during the study for which the study participant obtained a therapeutic abortion.

OLE Study V72_70TP

Objectives

An ongoing vaccination campaign in which students and staff at UCSB, California, received Bexsero during an outbreak of serogroup B meningococcal disease during January 2014.

Study Design/Population:

Most individuals taking part in this study were university students 18–25 years of age. The investigational rMenB+OMV NZ vaccine was recommended for the following groups; UCSB undergraduate students, faculty, and staff residing in UCSB owned dormitory style residence halls, and graduate students, faculty and staff who had a medical condition putting them at increased risk for meningococcal disease. The vaccine was administered by UCSB in consultation with CDC. The study monitors for SAEs from the time of administration of the first dose of rMenB+OMV NZ up to 30 days following administration of the second dose. Additionally, the study monitors AEs using active and passive surveillance. Adverse events not meeting the requirements for expedited reporting will be reported to FDA in the IND Annual Report.

Key Safety Findings:

- Of 9,831 recipients of the rMenB+OMV NZ vaccine, 25 (0.2%) reported a SAE as of June 27, 2014.
- The SAE frequency within 30 days after the first dose was 12/9,831 (0.1%) and 9/7,713 (0.1%) after the second dose

- 1 SAE, anaphylaxis, occurred on the same day as the first dose. Subject recovered completely.
- 1 death was reported during the study
 - 19-year-old male died of sudden cardiac death while swimming, 27 days after the first dose. The investigator assessed the relationship with vaccination as “unknown” pending autopsy results
- 4 pregnancies occurred during the study for which the 4 participants each had a therapeutic abortion planned.

3.3 Safety Concerns within the Pharmacovigilance Plan

The sponsor outlined the adverse events listed below as safety concerns that were either identified, potential, or had missing information.

3.3.1 Important Identified Safety Issues

Fever – in infants and children <2years of age

3.3.2 Important Potential Safety Issues

- Guillain-Barre syndrome
- Acute Disseminated Encephalomyelitis
- Anaphylaxis and Anaphylactic shock
- Chronic Fatigue Syndrome
- Kawasaki Disease – in infants
- Seizure and febrile seizure – in infants and toddlers
- Decrease of Immunogenicity secondary to prophylactic use of paracetamol (acetaminophen)

3.3.3 Important Missing Information

- Vaccine Effectiveness
- Vaccine Failure (lack of efficacy)
- Strain/Serotype replacement Data
- Elderly Subjects
- Immuno-compromised subjects
- Chronic Medical condition patients
- Safety during pregnancy or lactation
- Compliance in adolescent population

3.4 Other Potential Safety Concerns

3.4.1 OMV Potential Risk

The OMV antigen suspension consists of small, membranous spherical vesicles or fragments containing the most abundant proteins of the outer membrane (PorA/B), some minor proteins, and lipopolysaccharides (LPS). Several OMV-containing meningococcal B vaccines have been used worldwide, including MenBvac and MenNZB (Vesicles derived from *Neisseria Meningitidis* serogroup B strain NZ98/254). Systematic reactogenicity and safety studies have mostly been published for MenBvac and MeNZB. As with rMenB+OMV NZ, the most pronounced adverse reaction in adults is pain/tenderness, and fever is highest among younger children and infants.

3.4.2 Aluminum Potential Risk

Aluminum adjuvants, such as aluminum hydroxide, have been used historically for hypo sensitization of allergic patients without adverse results, but also may increase the levels of antigen-specific and total IgE antibodies, theoretically leading to IgE-mediated allergic reactions. There have also been reports of systemic accumulation of aluminum, in patients with impaired renal function, leading to bone disease and nervous system disorders. However, this is also a theoretical risk, as the aluminum intake from the vaccine is less than the standard dietary intake or from medications.

3.5 Sponsor's Proposed Actions and Timelines

3.5.1 Routine Pharmacovigilance Practices

NVD's proposed routine pharmacovigilance includes the following;

- Case processing by trained physicians to identify safety issues
- Use of a key events list to ensure a standardized approach to case management. The events list is based on terms from the Council for International Organizations of Medical Sciences (CIOMS V), the FDA Code of Federal Regulations, scientific and regulatory literature, medical judgment, and experience with other vaccines on the market
- Active follow up of key event reports where warranted
 - Questionnaires will be used for GBS, ADEM, Kawasaki disease, and seizure/febrile seizure reports
- Weekly regular medical case review meetings will involve:
 - Physicians from both the pharmacovigilance and clinical research and development groups
 - Timely review of key events and targeted case follow-up
- Signal Detection and evaluation
 - Regular cross-functional signaling meetings for signal detection and evaluation, including incidence analysis and disproportionality analysis versus other vaccine in Novartis vaccine database when necessary.
 - Review of potential signals internally by the Safety Management Team (SMT) and the Product Stewardship Board (PSB). External consultants and safety data sources will be used as warranted in adjudicating signals.

NVD also proposes to use enhanced pharmacovigilance to provide a more thorough assessment of the specific AEs of concern (e.g., GBS, ADEM, KD, and FS). This will include the following enhancements:

- NVD SMT will track the cases of specific AEs and compare the incidences with those published in the literature in addition to weekly medical case review
- For GBS, ADEM, KD, and FS, observed-to-expected analyses will be conducted using the cumulative total number of cases.
- Cluster detection with regards to the onset interval

These analyses will be performed monthly. External experts will review the information to ensure an independent and additional level of review. Reporting to the authorities will be done using periodic surveillance reports unless a signal is detected that may affect the benefit/risk ratio of the vaccine. Such a signal will be communicated on an expedited basis. The Sponsor will provide FDA with 15-day expedited reports of all SAEs that are related to the identified or potential risks, regardless of event expectedness (i.e., both unexpected and expected).

3.6 Action Plan for Safety Concerns (see Table 3 for proposed post-licensure observational studies)

Table 2

Safety Issue/Area	Proposed Activity/Plan	Comments
Important Identified Risks		
Fever	<ul style="list-style-type: none"> Listed in SmPC as AEs that are “very common” ($\geq 38^{\circ}\text{C}$) and “uncommon” ($\geq 40^{\circ}\text{C}$) 	<ul style="list-style-type: none"> Temperature elevation may occur following Bexsero vaccination in infants and children (<2 y o) Fever ($\geq 38.0^{\circ}\text{C}$) reported in; 69–79% of subjects receiving Bexsero & routine vaccines concomitantly; 44–59% after routine vaccinations only; 42–63% after MenC & routine vaccines concomitantly Prophylactic administration of antipyretics can reduce frequency and intensity post vaccination fever
Important Potential Risks		
Guillain-Barre syndrome (GBS)	<ul style="list-style-type: none"> Routine and enhanced pharmacovigilance Post licensure observational study (V72_36OB) 	<ul style="list-style-type: none"> GBS has been described as possibly associated with meningitis conjugate and pandemic flu vaccines Risk with Bexsero unknown No case of GBS reported after Bexsero; 1 case reported after Menactra in clinical trials Ongoing surveillance for GBS in association with Bexsero
Acute Disseminated Encephalomyelitis (ADEM)	<ul style="list-style-type: none"> Routine pharmacovigilance Post licensure observational study (V72_36OB) to confirm incidence, identify potential risk factors to further characterize the risk 	<ul style="list-style-type: none"> No cases of ADEM reported in clinical trials
Anaphylactic reactions	<ul style="list-style-type: none"> Routine pharmacovigilance Post licensure observational study (V72_36OB) to confirm incidence, identify potential risk factors to further characterize the risk 	<ul style="list-style-type: none"> *No cases of anaphylaxis considered related to Bexsero reported in clinical trials (*1 case of anaphylaxis reported during CDC expanded access use of Bexsero in UCSB campaign – Study V72_70TP)

Safety Issue/Area	Proposed Activity/Plan	Comments
Chronic Fatigue Syndrome (CFS)	<ul style="list-style-type: none"> Routine pharmacovigilance 	<ul style="list-style-type: none"> No case of CFS considered related to Bexsero in clinical trials
Decrease in immunogenicity secondary to prophylactic use of paracetamol (acetaminophen)	<ul style="list-style-type: none"> Routine pharmacovigilance 	<ul style="list-style-type: none"> Study V72_16 (not applicable to this BLA) did not show any interaction with the antipyretic
Important Missing Information		
Vaccine Effectiveness	<ul style="list-style-type: none"> Vaccine effectiveness study (V72_38OB) to further characterize effectiveness 	<ul style="list-style-type: none"> Efficacy is unknown when vaccine is used by a large number of individuals
Vaccine Failure (lack of efficacy)	<ul style="list-style-type: none"> Routine pharmacovigilance with use of questionnaire, SMT adjudication and possible correlation with vaccine effectiveness studies 	<ul style="list-style-type: none"> Some patients who are vaccinated may not be protected and could still develop the disease if exposed
Strain/Serotype replacement Data	<ul style="list-style-type: none"> Nasopharyngeal carriage study (V72_29) and vaccine effectiveness 	<ul style="list-style-type: none"> Herd effect, possible strain & serotype replacement unknown Study as a first step of evaluation to identify changes in serotype distribution as a consequence of immunization with Bexsero
Older Adults and Immuno-compromised subjects	<ul style="list-style-type: none"> To be included in the SmPC section 4.4 Special warnings and precautions for use: <u>Older Adults</u> "There are no data on the use of Bexsero in subjects above 50 years of age." <u>Immune-compromised</u> "There are no data on the use of Bexsero in subjects with impaired immune responsiveness. In immunocompromised individuals, vaccination may not result in a protective antibody response." 	
Chronic Medical condition patients	<ul style="list-style-type: none"> To be included in the SmPC section 4.4 Special warnings and precautions for use: "There are no data on the use of Bexsero in patients with chronic medical conditions." 	

- Foreign Activities
 - As part of a regulatory commitment with EMA in 2011, NVD committed to monitor the use of Bexsero in pregnancy in the UK. This 1-year study (V72_39OB*) is a collaboration with Public Health England (PHE) to start with launch in a national immunization program including women of childbearing age. It uses the Vaccine in Pregnancy (VIP) surveillance system to monitor the frequency of reported exposure to Bexsero during pregnancy and to monitor for an early signal of a substantial increase in the risk of adverse pregnancy outcomes following vaccine exposure. The VIP currently monitors exposure to rubella, varicella, and human papilloma virus (HPV) vaccines during pregnancy. Healthcare providers or pregnant women will voluntarily report exposure to Bexsero during pregnancy. Reported pregnancies will be subsequently followed, primarily through the woman's general practitioner, to determine the pregnancy outcome. *See section 3.6.2, Table 3 for more details of study V72_39OB.
 - In Canada, the Health Authority of the State of Quebec conducted an active safety surveillance observational study in which a total of 43,740 individuals between the ages of 2 months and 20 years residing in Saguenay – Lac Saint Jean received a first dose of Bexsero. NVD has discussed options to monitor pregnancies in the Saguenay – Lac Saint Jean campaign with MoH experts, but have not stated an outcome to this discussion in their correspondence with FDA. See section 5.2 for more details of Canadian Vaccination Campaign.
 - As part of their routine Pharmacovigilance activities, NVD currently monitors pregnancies in all countries where Bexsero is marketed.

3.6.1 Ongoing and Planned Post-licensure Studies outside the US

As part of NVD's commitment with EMA, one Phase III clinical study and three post-marketing observational studies have been planned in the United Kingdom for Bexsero (Table 3).

- Study V72_62A proposes to study safety and immunogenicity of 2 doses in 2–17 year old immunocompromised patients.
- Study V72_36OB is a self-controlled case series study to assess potential associations between specific safety AEs, i.e. febrile seizures and Kawasaki's disease in children among others, using a general practice database in the United Kingdom.
- Study V72_38OB proposes to use a screening method in collaboration with Public Health England (PHE UK) where uptake and routine surveillance data for meningococcal disease would allow assessment of vaccine effectiveness.
- Study V72_39OB was developed to monitor use of vaccine during pregnancy using the Vaccines in Pregnancy (VIP) surveillance system in the United Kingdom.

As part of the commitment with EMA, the sponsor agreed to provide alternative proposals in case the UK did not launch Bexsero in their national program. As of the submission date of the BLA, the UK is planning to launch Bexsero in its national immunization program.

Table 3: Ongoing and Planned additional Pharmacovigilance studies and activities

Study #; Region	Study Objectives	Study Design; Patient Population	Study Outcome	Status as of 9/5/14
V72_62 A	<p>Safety, tolerability & Immunogenicity of 2 doses of Bexsero in immunocompromised Pts at increased risk of IMD due to complement deficiency or asplenia compared to matched healthy controls.</p> <p>Study proposed in response to request by European Pediatric Committee for a study in pediatric populations at special risk of IMD.</p>	<p>Phase III b Open Label, controlled, multi-center study in 2-17 year olds.</p> <p>Descriptive study with ~ 240 subjects; - Up to 160 with complement deficiency or asplenia - 80 healthy age-matched subjects - All participants receive 2 doses of Bexsero 2 months apart</p>	<p>Immunogenicity & safety endpoints.</p> <p>No AE of special interest proposed as a safety outcome</p>	<p>Study protocol submitted to EMA June 26, 2013.</p> <p>Final study report planned 2016</p>

Study #; Region	Study Objectives	Study Design; Patient Population	Study Outcome	Status as of 9/5/14
V72_36OB; UK (V72_47OB Canadian alternative) (V72_52OB Australian alternative)	To assess safety of Bexsero vaccination in routine clinical care	Post licensure observational study using ------(b)(4)----- -----, an observational database of UK electronic patient records - <u>Stage 1:</u> Descriptive analysis reporting event incidence of each event among all individuals in the age range eligible for vaccination (2-24 months and 15-21 years old) - <u>Stage 2:</u> SCCS Analysis Study population selected from patients aged 6 wks to 26 mnths, and 15 to 21 years with a study event and who had received at least 1 dose of vaccine. Person time for cases assigned to risk & control periods based on date of exposure to Bexsero. Relative incidences & 95% CIs calculated adjusting for age	Febrile seizures, seizures, Kawasaki's disease, GBS, anaphylaxis, ADEM	-EMA endorsed protocol Jan 2013. -Study duration 3 yrs. from launch in UK infant national immunization program (NIP) expected mid- 2015. Final report expected 11 months after end of the study
V72_38OB; UK (V72_53OB Australian alternative) (V72_48OB Canadian alternative)	To assess the effectiveness of Bexsero vaccine against MenB and the impact on IMD (all serogroups) attributable to potential cross protection	Post licensure observational study - Descriptive analyses - Screening method (or alternatively a case- control method) using the (b)(4) data *Alternative study site Canada or Australia	Meningococcal disease (serogroup B), meningococcal disease (other serogroups)	-EMA endorsed protocol Jan 2013 -Study duration min 1 year from launch in infant NIP expected mid 2015 -Final study report Dec 2017.

Study #; Region	Study Objectives	Study Design; Patient Population	Study Outcome	Status as of 9/5/14
V72_390B; UK	Monitor frequency of reported exposure to Bexsero vaccine during pregnancy and adverse pregnancy outcomes following vaccine exposure as captured through the UK Vaccination in Pregnancy (VIP) surveillance system	-Post licensure descriptive observational enrolment-and-follow up study -Monitoring use of Bexsero in pregnancy using data from VIP surveillance system - Enrollment for 1 year - Enrolled women followed up to 1 year after expected delivery date -The study falls within routine surveillance activities coordinated by UK HPA.	Frequency of reported exposure to Bexsero during pregnancy; pregnancy outcomes following Bexsero exposure at birth and at the infant's first birthday	-EMA endorsed protocol Jan 2013. -Study duration 1 year from the start of Bexsero vaccination program -Follow-up until infant's first birthday -Final study report Dec 2017.

4 REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

4.1 Clinical Overview Summary

Safety Analyses:

“Safety data was reviewed on 3139 subjects enrolled in a randomized clinical trials conducted in Canada, Australia, U.K., Chile, U.S., 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 was collected on 15,351 rMenB+OMV recipients as part of vaccination campaigns sponsored by the C.D.C at 2 U.S. universities. As mentioned...[in the clinical reviewer’s executive summary], revised reactogenicity rates were submitted to the BLA which excluded missing data including that which was obtained through verbal recall. The results of this post-hoc safety analyses demonstrated that the overall reactogenicity findings across studies were similar. Common adverse reactions likely to occur include injection site pain, myalgia, malaise, and headache. The rates of unsolicited adverse events following rMenB+OMV administration which were not related to injection site reactions were similar to the rates observed in the control groups. Serious adverse events were rare following rMenB+OMV vaccination, though 2 cases of juvenile arthritis and one case of acute thyroiditis were reported. Though appendicitis is commonly reported condition in adolescent populations, the reviewer notes that the appendicitis was a frequently reported SAE with a total of 19 cases reported in the submitted clinical trials and the C.D.C. vaccination campaigns. Based on detailed review of the safety data submitted, the overall safety profile for rMenB+OMV when administered to individuals in 10 through 25 years of age subjects is acceptable. Both the nature and frequency of events reported were consistent with events commonly observed following other vaccinations administered to adolescents and young adults.”

4.2 Statistical Reviewer Summary

“Based on the data submitted and reviewed, Novartis Bexsero appears to be relatively safe as a vaccine for the prevention of MenB. Based on the solicited and unsolicited adverse events collected and noted during the various Phase II/III studies as well as the open label study of students from UC Santa Barbara and Princeton this product has an acceptable safety profile including generally self-limiting adverse

events and typically mild or moderate adverse events. Although up to 10% of subjects did experience a variety of severe adverse events, this rate of severe adverse events is common in live vaccines and is comparable to approved meningitis vaccines including Menveo® and Menactra®. Therefore, the product appears to be safe for adults 10-25 years of age, based on the statistical analyses performed and data examined by the reviewing statistician.”

5 POST LICENSURE SAFETY REVIEW

5.1 NVD Pharmacovigilance: PSUR

The International Birth Date (IBD) of Bexsero was 1/14/2013 with a marketing authorization valid throughout the European Union. The first launch in five European countries started at the end of November 2013. The data on the only identified risk (fever) and other potential risks has remained unchanged since licensure, and there have been no new data from studies suggesting that efficacy or effectiveness is lower than that described in the clinical studies. There have been no significant actions related to safety observed in clinical trial or from the market, and no batch recall due to safety reasons since licensure outside the United States. Given the relatively short period between licensure and the January 2014 data lock point (DLP), limited spontaneous adverse event data were available. The following is a review of the post marketing safety data currently available. As part of routine pharmacovigilance, NVD reviewed safety data to identify any new or changing safety signals. Per NVD, four potential signals were identified and evaluated during the review period of the most recent periodic surveillance report (PSUR interval 1/14/14 – 6/13/14).

- 2 subjects reported dark urine; both were involved in an eculizumab study at the time of vaccination.
- Allergy and the syncope / vasovagal response to injection are possibly related to Bexsero vaccine injections.
- 2 subjects reported rhabdomyolysis; both with alternative causality and 1 case with a timeline compatible with vaccination.
- No other potential signal was considered confirmed by the NVD pharmacovigilance group. Per PSUR, signal evaluation for rhabdomyolysis, allergic reaction, and vasovagal response to injection are ongoing and further signal management will be conducted during the next reporting interval. These potential signals did not change the vaccine’s risk-benefit ratio.

5.2 Canadian Vaccination Campaign

Introduction:

A targeted vaccination campaign against the spread of serogroup B meningococcal disease was conducted in the Saguenay–Lac-Saint-Jean health region of Quebec, Canada between May 5 and June 17, 2014. A total of 43,740 persons between ages 2 months and 20 years residing in that area received the first dose of 4CMenB vaccine. Passive and active surveillance was implemented to monitor adverse events following immunization. Passive surveillance was conducted based on spontaneous reporting to the ESPRI surveillance program. Active surveillance was performed among vaccinees who provided an email address on the vaccination consent form and subsequently agreed to complete an electronic questionnaire in response to an email invitation 7 days post-vaccination.

Results/Key Findings

Active surveillance:

- 43,740 residents received the first dose, 12,332 (28%) completed an electronic questionnaire by July 2, 2014.
- Of 12,332 respondents, 9% reported fever within 48 hours post-vaccination and 1.9% within 3 to 7 days.
- Of 12,332 respondents, the most frequently reported AEs were general malaise (56%), local reactions (49%), gastrointestinal (34%) or respiratory problems (24%).

- 764 (6.2%) experienced AEs within 7 days after vaccination resulting in absenteeism (person vaccinated or the vaccinee's parent) and 1.2% consulted a physician.
- Of the 764 respondents, 290 presented with more serious health problems requiring a nurse telephone interview for validation. Of the 290 persons contacted, 114 (40%) had systemic reactions lasting ≥ 4 days, 79 (30%) had local reactions lasting ≥ 4 days, 13 (4%) had respiratory problems, 8 (3%) had allergic-like reactions.

Passive surveillance:

- 56 cases of AEs were reported in passive surveillance. Of the reported captured cases, 17 (46%) were for an allergic-like reaction, 11 (30%) were for a fever, and 7 (19%) for a significant local reaction. One case each of arthralgia and febrile seizure (child <6 months) were reported.
- 2 cases were considered to be SAEs. Vaccinees both presented with bronchospasm, thought to be allergic-like reactions occurring 4 and 6 hours post-vaccination resulting in hospitalization for 24 and 48 hours respectively.
- 3 other hospitalizations were attributed to respiratory issues; none appeared to be related to vaccination.

Note: Cases reported in the active surveillance and passive surveillance programs were not mutually exclusive.

Conclusions

- Although a high number of vaccinees complained of pain at the injection site and general malaise associated with the vaccine, almost all intended to receive the second vaccine dose.
- The surveillance program did not reveal any serious or unusual health problems associated with the vaccine.
- Surveillance confirmed a significant incidence of painful local reactions, fever and general malaise, but no concerning safety signals were identified.
- In the clinical trials, cases of Kawasaki's disease (KD), febrile seizure (FS), and transient arthralgia were observed with non-significant excess of risk. In these studies, very few cases (or no cases) were reported for each of these three AEs. Although the at-risk person-time under observation might be insufficient to detect a rare event such as KD, there appeared to be no excess risk of any of these AEs based on the currently available data.

6 INTEGRATED RISK ASSESSMENT

Adverse events:

The safety of Bexsero was evaluated in 8 clinical studies including 6 completed Novartis-sponsored clinical studies and 2 ongoing CDC-sponsored open-label studies with a total of 18,490 subjects (age range: 11-68 years) who received at least one dose of Bexsero. Overall, the incidence of general AEs and SAEs were comparable in the Bexsero and control groups. There were no SAEs or deaths considered related to Bexsero. However, because the clinical safety database consists of subjects aged 10-50 years, much wider than the indicated 10-25 year age range, it is unclear if the safety profile would remain the same in the target population. Since the vast majority of subjects were contributed by the two CDC-sponsored uncontrolled studies, the controlled trials may not contain a sufficient sample size to detect an excess risk of less common adverse events. In addition, there are no pooled safety analyses. The post-marketing data provided were limited due to limited exposure, however, no new safety signals have been identified thus far based on the currently available pre- and post-licensure data. Potential safety concerns in the general and high risk populations will be further monitored in the NVD post marketing studies in the UK (or alternatively in Canada or Australia). These studies, however, do not fully cover the age group (10-25 years) indicated in the US and may not have sufficient power to identify an excess risk in this age group.

Pregnancy safety:

Pregnancy was one of the exclusion criteria in the clinical studies due to a general potential safety concern. The pre-clinical reproductive and developmental toxicity studies in female rabbits did not reveal any evidence of reproductive or developmental toxicity in the maternal animals, or in their fetuses on gestation day 29, or in their kids on lactation day 29. In the 8 clinical studies, a total of 36 pregnancies were reported, resulting in 2 congenital abnormalities (one with Prader Willi syndrome and one with absence of the second toe of the right foot), both in the Bexsero group but neither considered related to vaccination according to the investigators. Thus far, no adverse pregnancy outcomes have been reported in post-marketing passive surveillance.

As described in section 3.6, the proposed post-marketing pregnancy study in the UK is a descriptive enrollment-and-follow up study using data captured by the UK national Vaccine in Pregnancy (VIP) surveillance system, and coordinated through the UK Health Protection Agency (HPA). Since this pregnancy registry-type study is for hypothesis generating with no pre-specified sample size, the sample size captured by the VIP may be limited and is dependent on the UK vaccination program design (routine vaccination, catch up campaign, or in an outbreak situation), the uptake of the vaccine, and the completeness of reporting and follow-up.

Given the proposed indication in the US in an age group that includes women of childbearing age, and the limitations of the UK study using VIP surveillance data, OBE/DE supports NVD's proposal of a US-based pregnancy registry for three years to monitor safety in women exposed to Bexsero during pregnancy. NVD plans to add Bexsero to a previously established pregnancy registry for Menveo and Flucelvax in the US. Because Bexsero uptake may not be robust without an Advisory Committee on Immunization Practices (ACIP) recommendation for routine use, NVD proposes not to predefine a minimum number of enrolled subjects. NVD will submit the concept protocol for our review within 4 months of US approval and the final protocol within 6 months of US approval.

Evaluation of Appendicitis post Bexsero vaccination

Appendicitis post vaccination was noted in the clinical review as a potential safety concern (*see section 4.1*) where the clinical reviewer noted that a total of 19 cases of appendicitis occurred among 18,490 subjects in the 6 trials and 2 CDC studies who had received Bexsero. Epidemiological data analyses were completed to investigate this potential safety concern.

A case was defined as a study participant diagnosed with appendicitis (verified either by imaging or appendectomy) within 1 through 30 days after receiving any vaccine or placebo.

For the clinical trials, crude rates of appendicitis occurring among the Bexsero group were compared to rates within the placebo group and a relative risk of appendicitis was calculated with a 95% confidence interval.

Since there was no placebo group for the CDC studies, person-year rates were calculated and compared to background rates found in the literature.

Results

- A total of 24 cases of appendicitis occurred among all subjects in the 6 NVD clinical trials and 2 CDC studies; of those, 9 (38%) met the case definition.
- Of 24, 15 cases occurred among subjects in the 6 clinical trials (9 Bexsero group, 6 placebo); 6 (40%) met the case definition (4 Bexsero group, 2 placebo group).
- Of 24, 9 cases occurred among subjects receiving Bexsero during the CDC studies (6 at Princeton, 3 at UCSB; 3 (30%) met the case definition.

Table 4: Cases and Rates of Appendicitis Among Participants in 6 NVD Clinical Trials

Clinical Trials	N	Cases	Rate/10,000
Bexsero	3139	4 (0.13%)	12.7
Placebo/control	2078	2 (0.10)	9.6
RR (95% CI)	1.32 (0.24-7.22)		

Appendicitis is a relatively common AE in this age population, and with this relatively large dataset, no increased risk of appendicitis was observed in the Bexsero group compared to Control.

Table 5: Appendicitis Rates per 10,000 Person-Years Among CDC Study Participants

CDC Study	N receiving dose 1	Risk Interval days	N receiving dose 2	Risk Interval days	# cases within 1-30 days	Rate/10,000 PYs
Princeton	5520	30	5165	30	1	11.4
UCSB	9831	30	7809	30	2	13.8
Total	15351	30	12974	30	3	12.9

Table 6: Background Rates of Appendicitis per 10,000 Person-Years from Various Literature Sources

Literature Source	Rates / 10,000 PYs
CDC (1990 HCUP, 9-17 yo) ⁹	23.3
CDC(1998 HCUP, 15-44 yo) ¹⁰	11.6
CDC (NHSR 2007, 15-44 yo) ¹¹	11.9
VSD 10,000 PYs ¹² 9-17 yo	13.3
18-26 yo	12.4
US Armed Forces MSMR 2012 ¹³ (overall)	18.4
15-19 yo	21.4
20-24 yo	20.9
Coast Guard	22.5
Navy	17.5

Given the following points:

1. No increased relative risk of appendicitis observed post Bexsero vaccination compared to control from clinical trial data
2. No overall increased incidence of appendicitis observed over background incidence rates during Bexsero use in two population studies
3. The biologic plausibility of appendicitis following menB vaccination is not substantiated in the medical literature

The available data do not suggest an association between increased risk of appendicitis and Bexsero vaccination. This reviewer concludes that there is insufficient evidence to label appendicitis as a safety concern at this time (or to warrant verificatory action such as a post marketing observational epidemiologic study). Post licensure, we can monitor appendicitis through routine surveillance.

Conclusions:

After review of the pre-licensure safety data, the proposed pharmacovigilance plan, and the post marketing safety reports from outside the US, the OBE/DE reviewer has not identified any safety concerns that warrant a post-marketing requirement study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS) . Should the vaccine be licensed, OBE/DE will use standard surveillance tools and processes including VAERS and the Sentinel program to conduct post marketing safety surveillance on a routine basis and to identify and evaluate new or potential safety concerns. FDA may recommend further modification of the sponsor's pharmacovigilance activities if any further safety concerns are identified.

7 RECOMMENDATIONS

Based on the review of the pre- and post-licensure safety data and NVD's proposed pharmacovigilance plan, OBE/DE agrees with the Risk Management Plan as proposed by the Sponsor. These include:

- Routine pharmacovigilance to monitor adverse events in accordance with 21 CFR 600.80 and NVD's plans for enhanced expedited reporting as explained above in section 3.5.
- Pregnancy Registry as described in section 6 above

8 REFERENCES

1. Harrison LH. Epidemiological profile of meningococcal disease in the United States. *Clin Infect Dis* 2010;50 Suppl 2:S37-S44.
2. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. *Popul Health Metr* 2013; 11(1): 17
3. WHO. 2011. *Meningococcal vaccines: WHO position paper, November 2011* [Online]. Available: <http://www.who.int/wer/2011/wer8647.pdf> [Accessed March 14 2014 2014].
4. Caron F, du Chatelet IP, Leroy JP et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infect Dis* 2011;11(6):455-463.
5. Dyet K, Devoy A, McDowell R, Martin D. New Zealand's epidemic of meningococcal disease described using molecular analysis: implications for vaccine delivery. *Vaccine* 2005;23(17-18):2228-2230.
6. Esposito S, Castellazzi L, Bosco A, Musio A, Stoddard J. Use of a multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) for bacterial meningitis prevention. *Immunotherapy* 2014;6(4):395-408.
7. Holst J, Oster P, Arnold R et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. *Hum Vaccin Immunother* 2013;9(6):1241-1253.
8. Holst J, Oster P, Arnold R et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. *Hum Vaccin Immunother* 2013;9(6):1241-1253.
9. Addiss, D.G., Shaffer, N., Fowler, B., Tauxe, R.V., *The epidemiology of appendicitis and appendectomy in the united states*. *Am J Epidemiol* 1990; 132;5

10. Hall, M.J., Popovic, J.R., *1998 Summary: National Hospital Discharge Survey*. National Center for Health Statistics. Advance Data 2000; #316
11. Hall, M.J., DeFrances, C.J., Williams, S.N., Golosinskiy, A., Schwartzman, A., *National Hospital Discharge Survey: 2007 Summary*. National Center for Health Statistics. National Health Statistics Reports 2010; # 29
12. Gee, J., Naleway, A., Shuic, I., Baggs, J., Yinc, R., Li, R., Kulldorff, M., Lewis, E., Fireman, B., Daleye, M.F., Klein, N.P., Weintraub, E., *Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink*. Vaccine 29 (2011) 8279– 8284
13. Francis L. O'Donnell (Editor) *Appendicitis and Appendectomies, Active and Reserve Components, U.S. Armed Forces, 2002-2011*. Armed Forces Health Surveillance Center Medical Surveillance Monthly Report, 2012; 19 (12) 7-16