Summary Basis for Regulatory Action

Date: January 23, 2015

From: Margaret C. Bash, M.D., M.P.H., Chair of the Review Committee

BLA/ STN#: 125546/0

Applicant Name: Novartis Vaccines and Diagnostics, Inc.

Date of Submission: July 24, 2014

PDUFA Goal Date: March 24, 2015

Proprietary Name: BEXSERO®

Established Name: Meningococcal Group B Vaccine

Indication: BEXSERO is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Marion F. Gruber, Ph.D.,
Director
Office of Vaccines Research and Review

√ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	**Reviewer name – Document(s) date**
Clinical Review	Anuja Rastogi, M.D., M.H.S. - January 23, 2015
Statistical Review	Barbara Krasnicka, Ph.D. (Clinical efficacy) - December 17, 2014 Zhong Gao, Ph.D. (Serology assays) - December 17, 2014 Tammy Massie, Ph.D. (Clinical safety) - December 22, 2014 Tsai-Lien Lin, Ph.D. (CMC, Potency assays) - December 20, 2014
Clinical Serology Assay Review	Freyja Lynn, B.S. - December 8, 2014
CMC Review	John Cipollo, Ph.D. - January 23, 2015 James Kenney, Ph.D. - January 13, 2015 Anil Choudhary, Ph.D. - December 3, 2014 Hyesuk Kong, Ph.D. - November 12, 2014 Hsiaoling Wang, Ph.D. - November 17 and December 29, 2014 Tao Pan, Ph.D. - January 6, 2015 Freyja Lynn, B.S. - December 8, 2014
Facilities and CMC Review	Donald Ertel, MT (ASCP), - November 6, 2014 and January 15, 2015
Lot Release Protocol Template	Karen Campbell, M.S - January 6, 2015
Pharmacology/Toxicology Review	Ching-Long (Joe) Sun, Ph.D. - November 5, 2014
Bioresearch Monitoring Review	Carla Jordan, BS, MT (ASCP), SBB - November 18, 2014
Epidemiology/Pharmacovigilance Review	Jane Baumblatt, M.D. - January 23, 2015
Advertising and Promotional Labeling	Michael Brony, Pharm. D. - October 7, 2014
Establishment Inspection Report	September 16, 2014
Inspection Waiver Memos	Donald Ertel, MT (ASCP), - September 8, 2014 - Facility for drug substance manufacturing and drug product final formulation, filling, labeling and packaging, January 21, 2015 - Testing Facility for Drug Substance and Product
Advisory Committee Transcript	April 7, 2011
Approved Draft Labeling	N/A

1. Introduction

Novartis Vaccines and Diagnostics, Inc., submitted Biologics License Application (BLA) 125546/0 for licensure of Meningococcal Group B Vaccine. The proprietary name is BEXSERO®. BEXSERO is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is intended for intramuscular injection administered as a two-dose series at least one month apart in individuals 10 through 25 years of age.

BEXSERO is a sterile suspension of three recombinant proteins and meningococcal outer membrane vesicles (OMV). The recombinant proteins Neisserial adhesin A (NadA), Neisserial Heparin Binding Antigen (NHBA), and factor H binding protein (fHbp), are individually produced in *Escherichia coli* and purified. The OMV component is produced from *N. meningitidis* strain NZ98/254 (expressing outer membrane protein PorA serosubtype P1.4). The antigens are adsorbed onto aluminum hydroxide. Each 0.5 mL dose of BEXSERO is formulated to contain 50 micrograms each of recombinant proteins NadA, NHBA, and fHbp, 25 micrograms of OMV, 1.5 mg aluminium hydroxide, 3.125 mg sodium chloride, 0.776 mg histidine, and 10 mg sucrose at pH 6.4 – 6.7.

Each pre-filled syringe of BEXSERO delivers a 0.5 ml dose of vaccine. BEXSERO contains no preservative. BEXSERO should be stored in the refrigerator at 36-46ºF (2-8ºC). The shelf-life is 24 months and the date of manufacture is the date of initiation of filling into final containers.

2. Background

Invasive disease caused by *N. meningitidis*, typically meningitis and sepsis, is a serious condition with high morbidity and mortality, even with optimal medical treatment. Among survivors, permanent sequelae may include hearing loss, significant neurological damage, limb amputation, skin scarring, renal failure, and cognitive deficits. While most cases of invasive meningococcal disease are sporadic, clusters, outbreaks, and prolonged epidemics can occur, 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 caused by all pathogenic serogroups of *N. meningitidis* (1). In the United States, most cases of meningococcal disease are sporadic, with an incidence of 0.15 to 0.35 cases per 100,000 population. Serogroup B *N. meningitidis* is now the most frequently reported cause of IMD in the US. The Centers for Disease Control and Prevention (CDC) estimates that an average of 402 cases of serogroup B meningococcal disease occurred annually between 2002 and 2011 (2); in 2012, the estimated serogroup B incidence rate was 0.06/100,000 (3).

N. meningitidis strains are classified based on their capsular polysaccharide into serogroups. Vaccines composed of serogroup-specific capsular polysaccharides are available to prevent invasive disease caused by serogroups A, C, Y, and W. Serogroup B polysaccharides, even when conjugated to immunogenic carrier proteins, are poorly immunogenic. Thus, meningococcal serogroup B vaccines have been developed that are based on immunogenic

outer membrane proteins. Serogroup B OMV vaccines have been used outside the US to control prolonged outbreaks caused by a single predominant serogroup B *N. meningitidis* strain. The immune responses to OMV vaccines are directed primarily to the PorA major outer membrane protein and are strain-specific. To expand the breadth of the immune response to encompass antigenically diverse serogroup B strains, BEXSERO includes three recombinant proteins, in addition to the OMV component that was developed for and used during an epidemic in New Zealand. The three recombinant proteins are immunogenic bacterial surface proteins fHbp, NadA and NHBP. fHbp is a virulence factor that contributes to the ability of *N. meningitidis* to avoid complement-mediated killing in the host. NadA and NHBP are adhesins. PorA is a major outer membrane protein that is important for the survival of the bacterium. All four proteins contribute to the ability of meningococci to survive in the human host and cause disease. fHbp is less diverse than the PorA protein, but immunologically distinct variants exist. NadA is expressed by some but not all strains. NHBA is highly conserved. The recombinant proteins in BEXSERO are based on the most common sequence types of these antigens identified among endemic disease isolates (4).

While the incidence of meningococcal serogroup B disease in the US is relatively low, recent outbreaks on college campuses in the US have heightened concerns. 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 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. Given the public health concerns about meningococcal serogroup B disease in the US, CBER agreed 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. On July 24, 2014, Novartis Vaccines and Diagnostics Inc., submitted a BLA for BEXSERO. The established name for this vaccine is Meningococcal Group B Vaccine.

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

BEXSERO contains four meningococcal serogroup B antigenic components consisting of Outer Membrane Vesicles (OMV) and three recombinant outer membrane proteins: rp287-953 (NHBA chimera), rp936-741 (fHbp chimera), and rp961c (NadA). The composition of the BEXSERO final drug product and the function of the ingredients are provided in Table 1.

Table 1: Composition of BEXSERO Final Drug Product

Ingredient	Function	Amount/Dose
rp287-953 (NHBA chimera)	Active ingredient	0.05 mg
rp936-741 (fHbp chimera)	Active ingredient	0.05 mg
rp961c (NadA)	Active ingredient	0.05 mg
OMV (PorA)	Active ingredient	0.025 mg
Aluminum hydroxide	--(b)(4)-------	1.5 mg
Histidine	--(b)(4)----------	0.776 mg
Sodium chloride	--(b)(4)--	3.125 mg
Sucrose	--(b)(4)--	10 mg
Water for injection	Solvent	--(b)(4)-------

rp: recombinant protein; OMV: Outer Membrane Vesicles

Presentation and Packaging System

BEXSERO is supplied in 1 ml pre-filled hydrolytic glass --(b)(4)- Luer Lok™ syringes without needle, with a --(b)(4)- rubber tip cap. A single dose of vaccine is 0.5 ml with no preservative. The plunger stopper (--(b)(4)- rubber) and syringes (--(b)(4)- glass) are ----(b)(4)------ with a ----------(b)(4)----------. The Tip-cap is a ----------(b)(4)---------- rubber closure that contains natural rubber latex.

Manufacturing Overview

BEXSERO consists of four separate Drug Substances:

- Outer Membrane Vesicles (OMV) from *N. meningitidis* serogroup B strain NZ98/254
- Neisserial adhesin A (NadA) as single protein: rp961c
- Neisserial Heparin Binding Antigen (NHBA) as fusion protein: rp287-953
- Factor H binding protein (fHbp) as a fusion protein: rp936-741

The three recombinant protein drug substances (rp287-953, rp936-741, and rp961c) are manufactured at ----------(b)(4)----------. The OMV drug substance is manufactured at Novartis Vaccines and Diagnostics, Bellaria-Rosia, Italy.

The drug product is manufactured (formulated, filled, inspected, labeled, and packaged) at Novartis Vaccines and Diagnostics Bellaria-Rosia, Italy. The final vaccine is a sterile liquid suspension.

Drug Substances

Protein rp287-953 is a fusion protein of meningococcal NHBA, the primary antigenic component, and 953, an accessory protein that enhances the immunogenicity of its fused counterpart. Protein rp936-741 is a fusion protein of meningococcal fHbp, the primary antigenic component, and 936, an accessory protein that enhances the immunogenicity of its fused counterpart. Protein rp961c is a fragment of meningococcal NadA. Each of the recombinant proteins is individually expressed in *Escherichia coli*. The manufacturing process can be divided into ----------(b)(4)----------.

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

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

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

----------(b)(4)----------
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2 pages determined to be not releaseable: (b)(4)

[(b)(4)]

Drug Product

The BEXSERO drug product contains the drug substances rp287-953, rp936-741, rp961c and OMV. During formulation, the drug substances are adsorbed to aluminum hydroxide. Additional ingredients are histidine as a ----(b)(4)---------, sodium chloride and sucrose as --(b)(4)-- agents, and water for injection (WFI). The composition of the drug product is shown in Table 1. The BEXSERO drug product manufacturing process is divided into five stages including formulation, filling, inspection, labeling and packaging.

At formulation, ---.

In-process controls (process parameters and in process tests) are used to ensure control of the process and product quality. Appropriate validation of the process was conducted. The manufacturing process and in-process controls were reviewed and found to be acceptable. Specifications for release and stability testing of drug product were deemed to be appropriate. The release and stability specifications for the drug product are shown in Table 6. Tests performed on stability are footnoted.

Table 6: BEXSERO Drug Product Specifications

Test	Method	Specification
Final Bulk		
-------(b)(4)----------	---(b)(4)----	---(b)(4)---------
---(b)(4)--	---(b)(4)----------	--(b)(4)--
Filled Product (Pre-filled syringe)		
Identity[a]	---(b)(4)---------	---(b)(4)--------- ---(b)(4)---------- ---(b)(4)---------- ---(b)(4)---------
Volume	---(b)(4)---------	---(b)(4)---
Appearance[a]	Visual inspection	Opalescent liquid (white suspension)
---(b)(4)----------	---(b)(4)---	---(b)(4)-------
---(b)(4)----------	---(b)(4)---	---(b)(4)-
---(b)(4)----------	---(b)(4)---	---(b)(4)----
pH[a]	---(b)(4)-------	6.4-6.7
---(b)(4)----	---(b)(4)----------	---(b)(4)----
Endotoxin[a]	---(b)(4)----------	---(b)(4)----
---(b)(4)----------	---(b)(4)---	---(b)(4)----
Sterility[a]	---(b)(4)-------	Sterile
Pyrogen	---(b)(4)----	---(b)(4)----
Immunogenicity[a] rp961c rp936-741 rp287-953 OMV	---(b)(4)---------- ---	 -----(b)(4)---------- ---- -----(b)(4)---------- ---------- -----(b)(4)---------- ---------- -----(b)(4)----- ----------
Visible particles[a]	Visual inspection	Conforms
General safety/Abnormal toxicity	---(b)(4)---	Not toxic
Packaged Product		
Identity	---(b)(4)----------	-----(b)(4)---------- -----(b)(4)---------- -----(b)(4)---------- -----(b)(4)----------

[a] These tests are performed for the stability assessment

Abbreviations: ----------(b)(4)----------OMV: Outer Membrane Vesicles rp: recombinant protein; RP: Relative Potency; ----------(b)(4)----------: upper confidence limit.

An (b)(4) potency test (immunogenicity test) is used to assess the potency of the final drug product. ----(b)(4)---------- are tested using (b)(4), and evaluated relative to a reference vaccine. Performance of the test over time was evaluated. Consistency of lot release data and the absence of trends indicating changes in the assay or product over time, supported consistency of manufacturing.

Stability data up to 18 months for the three validation lots of BEXSERO were provided as well as supporting stability data performed under stressed conditions when stored at (b)(4) and at (b)(4)---. All data remained within the proposed commercial stability specifications. CBER determined that the submitted data support a dating period of 24 months.

Among the Chemistry, Manufacturing and Controls (CMC) issues that arose and were resolved during the BLA review were the following: 1) resetting of ----------(b)(4)---------- ---------- specifications during OMV Process Validation studies, 2) setting of specifications outside of manufacturing experience, 3) missing or incomplete filter validation, 4) drug substance manufacturing process ---(b)(4)----- not validated for worst case scenario, 5) incomplete information regarding rp287-953 manufacturing process validation, 6) insufficient information demonstrating control of --(b)(4)-- in rp287-953, 7) missing matrix reuse validation, 8) insufficient information on control of ----------(b)(4)-------- for drug substance ----(b)(4)---, 9) incomplete information regarding final container extractable/leachable (E/L) studies, 10) need for General Safety Test, 11) missing information regarding aluminum hydroxide manufacturing process, validation and stability, 12) assessment of the levels of ----(b)(4)---------- and 13) potency assay optimization. The applicant supplied the necessary data and information, instituted appropriate tests, or, in certain cases, provided timelines for submission of supporting data that CBER deemed to be non-critical.

b. CBER Lot Release

The lot release protocol templates were submitted to CBER for review and found to be acceptable after revisions. Samples from three lots of BEXSERO were submitted in support of the BLA for lot release testing and were found to be acceptable. For post approval lot release, the applicant will submit a lot release protocol, samples of final container drug product from each lot, and samples of each bulk drug substance contained in each lot. Routine Lot Release is performed by reviewing the submitted Lot Release Protocol and by testing submitted samples. Confirmatory testing will be performed by CBER according to a lot testing plan developed by CBER.

c. Facilities Review/Inspection

The facilities involved in the manufacture of BEXSERO are listed in the table below. The activities performed and the inspectional histories of the facilities are included in the table.

Table 7. Manufacturing Facilities for BEXSERO (Meningococcal Group B Vaccine)

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification
Drug Substance ----------(b)(4)----------	--(b)(4)------	--(b)(4)-----	Pre-License Inspection (PLI)	ORA/CDER ---(b)(4)--- Voluntary Action Indicated (VAI)
Drug Substance ----------(b)(4)---------- Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, SI 53018 Italy.	3006738517	445558679	Inspection Waived	Team Biologics June 2013 VAI See notes below
Drug Substance ----------(b)(4)---------- Novartis Vaccines and Diagnostics ----------(b)(4)----------	--(b)(4)------	--(b)(4)-----	Inspection Waived	Waived based on acceptable FDA compliance history
Drug Product Formulation, Fill/Finish, Labeling & Packaging, Testing Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, SI 53018 Italy.	3006738517	445558679	Inspection Waived	Team Biologics June 2013 VAI See notes below
Drug Product Selected Testing for DP Novartis Vaccines and Diagnostics ----------(b)(4)----------	--(b)(4)------	--(b)(4)-----	Inspection Waived	Waived based on acceptable FDA compliance history

ORA, in conjunction with CDER, conducted a PLI of ----------(b)(4)---------- from -----(b)(4)---------- for quality, facilities & equipment, materials, production, packaging & labeling, and laboratory operations. At the end of the inspection, a Form FDA 483 with four observations was issued. Two observations were directly related to Meningococcal Group B Vaccine operations. Deficiencies were related to sample handling and clean hold time validation. The firm responded to the observations on October 8, 2014, and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

Team Biologics performed a surveillance inspection of the Novartis Bellaria-Rosia manufacturing facility from June 10 – 18, 2013. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

Team Biologics last inspected the Novartis (b)(4) Facility from ---(b)(4)-------. The (b)(4) facility discontinued the manufacture of all U.S. approved products, and the facility currently performs only QC testing for U.S. Products, -------(b)(4)----------. The (b)(4) Facility is included in the Team Biologics Inspection Inventory for GMP Surveillance.

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

d. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Reports from three toxicologic studies conducted with BEXSERO (and three supportive toxicologic studies conducted with related formulations) were submitted to provide nonclinical support for this BLA. In the single and multiple dose intramuscular toxicity study, rabbits received intramuscular administration of the vaccine once or five times during eight weeks. The vaccine at the dose equivalent to the absolute human dose or 15 times the human dose on a body weight basis (4 kg in rabbits and 60 kg in humans) was well tolerated with minimal effects. Vaccination of the animals was associated with increases in fibrinogen, leukocyte counts and globulin values that are indicative of inflammation. Increases in creatinine kinase values suggested skeletal muscle involvement which is likely involved at the injection sites. All these changes, although treatment-related, were mild and transient. No significant safety issues were identified.

In the reproductive and developmental toxicity study, five intramuscular administrations of the vaccine at the equivalent of an absolute human dose or 15 times the human dose on a body weight basis during pre-mating and gestation periods revealed no significant reproductive and developmental effects in rabbits. Based on the data derived from these studies, BEXSERO received a pregnancy category B designation which will be reflected in the Prescribing Information for BEXSERO under Section 8.1: Pregnancy.

5. Clinical Pharmacology

Mechanism of Action

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

NHBA, NadA, fHbp and PorA are proteins on the surface of meningococci and contribute to the ability of the bacterium to colonize human mucosal surfaces and to avoid host defenses. Vaccination with BEXSERO leads to the production of antibodies directed against NHBA, NadA, fHbp, and PorA (present in OMV). The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with BEXSERO is dependent on the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

6. Clinical/Statistical

In 2013 and 2014, 13 cases of serogroup B meningococcal disease were reported among students associated with two US universities, including one fatality. Importantly, the outbreak at one university extended across two academic years, showing a sustained transmission within that community. At that time, no vaccine for prevention of serogroup B meningococcal disease was licensed and available in the US to prevent this serious and life-threatening condition. Through an expanded access IND submitted by the Centers for Disease Control and Prevention (CDC), BEXSERO was used in vaccination campaigns on both campuses. The urgent public health need for a group B meningococcal vaccine 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, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit. As the result of communications between FDA and Novartis Vaccines and Diagnostics, Inc., this original Biologics License Application was filed with data intended to support an accelerated approval.

General Description of Clinical Studies

BEXSERO has been licensed in the EU, Canada and Australia. Data from nine completed clinical trials, including six randomized trials and one extension study conducted among adolescents and young adults, were provided in the application. The three main immunogenicity studies were conducted in Chile, the United Kingdom (UK) and Canada/Australia. One study, conducted in the US, contributed safety data only, as immunogenicity was tested using assays that are still under development. In addition, two small phase I/II studies conducted in Europe contributed safety data (Table 8A). Taken together, these trials provide safety and immunogenicity data that support accelerated approval of BEXSERO for use in individuals 10 through 25 years of age. Safety data from the expanded access IND immunization campaigns, in which serious adverse events were monitored up to 30 days following the second dose, were submitted to the BLA as interim and final reports. These were reviewed and further supported the safety assessment of BEXSERO (Table 8B). Manufacturing consistency was supported by two studies, including a phase III lot consistency study conducted in European infants (Table 8C).

Table 8A. Clinical Studies of Safety and Immunogenicity in Participants 10 through 24 Years of Age

Study	Age	Number of subjects receiving at least 1 dose BEXSERO	Country / Region	Vaccination Schedule and Design
V72_41	11 through 17 years	342	Canada, Australia	2 doses one month apart Randomized comparison of two lots of BEXSERO bridging OMV manufactured at Rosia to previous manufacturing site.
V72_29	18 through 24 years	974	United Kingdom	2 doses one month apart Randomized, observer-blind, active-controlled
V72P10	11 through 17 years	1662	Chile	2 doses, one and two months apart. Randomized, observer-blind, placebo controlled (first and second doses) *Study included one, two and three dose groups on various schedules*
V102_03	10 through 25 years	120	U.S, Poland	2 doses two months apart Randomized, active controlled
V72P5	18 through 40 years	28	Switzerland	3 doses one month apart Phase 1
V72P4	18 through 50 years	53	Germany, Italy	3 dose series (0, Month 2, Month 6) Phase 2

Table 8B. Vaccination Campaigns under Expanded Access IND

Study	Age	Number of subjects receiving at least 1 dose BEXSERO	Country / Region	Vaccination Schedule and Design
V72_68TP	16-65 years	5520	US	Open label. Expanded access IND immunization campaign
V72_70TP	16-68 years	9831	US	Open label. Expanded access IND immunization campaign

Table 8C. Clinical Studies of Manufacturing Consistency

Study	Age	Number of subjects receiving at least 1 dose BEXSERO	Country / Region	Vaccination Schedule and Design
V72P13	Infants	2480	Europe	Phase 3 lot-to-lot consistency study Randomized, active control 3 doses (2 mo, 4mo, 6 mo) Routine immunizations
V72P16	Infants	367	Europe Argentina Chile	Phase 2 dose ranging study 3 doses (2mo, 3mo, 4mo) Routine immunizations

Vaccine Effectiveness

Evaluating the effectiveness of vaccines for prevention of serogroup B meningococcal disease is challenging. Clinical end-point efficacy studies are not feasible due to low rates of meningococcal disease. At the VRBPAC meeting held April 7, 2011, the committee supported the use of hSBA to evaluate effectiveness of protein-based meningococcal B vaccines. However, antigenic diversity and variable expression of meningococcal surface proteins, and limitations in methods developed to bridge immunogenicity data generated using specific strains to a broad range of disease isolates, complicate the approach to extrapolating effectiveness from immunogenicity.

Through several meetings and multiple communications between the applicant and CBER, different approaches for evaluating effectiveness were examined. The approach agreed upon addresses the conditions for accelerated approval by providing data to demonstrate the likely benefit of the vaccine: a) the vaccine stimulates the production of antigen-specific bactericidal antibodies; and b) individuals develop an immune response that is active against multiple strains. Further clinical development post-licensure would provide confirmation that the vaccine will induce an immune response that is protective against a broad range of diverse strains responsible for endemic and epidemic meningococcal disease in the US. CBER determined that the available immunogenicity data from completed clinical trials could be analyzed using modified immunogenicity end-points that address more definitively the criteria described above to support accelerated approval. Subsequently, effectiveness will be evaluated in confirmatory studies that will assess the bactericidal activity of NHBA, fHbp, NadA, and PorA P1.4 specific antibodies and the effectiveness of BEXSERO against a broad panel of *N. meningitidis* serogroup B strains (approximately 100) that have been isolated from people with invasive disease.

Clinical Immunogenicity Data

In pre-clinical and clinical studies, specific antibody responses were demonstrated to each of the antigens in BEXSERO: NHBA, fHbp, NadA, and PorA P1.4. To assess effectiveness for this accelerated approval, bactericidal responses to three of these antigens were evaluated in individuals 11 through 24 years of age following 2 doses of BEXSERO. Serum bactericidal antibodies were measured with hSBA assays using three strains selected to measure responses to one of three vaccine antigens, either fHbp, NadA or PorA P1.4, prevalent among strains in the US. A suitable strain for quantifying bactericidal activity of NHBA-specific antibodies was not available. Studies assessed the proportion of subjects who achieved a 4-fold or greater increase in hSBA titer for each of the three strains (measuring the immunogenicity of the vaccine components), 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 (composite response used to show the proportion of vaccinees with quantifiable serum bactericidal antibodies to all three indicator strains). The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified.

In a clinical trial conducted in Canada and Australia, adolescents 11 through 17 years of age received two doses of BEXSERO one month apart. The hSBA responses one month after the second dose are shown in Table 9.

Table 9: Bactericidal Antibody Response Rates Following 2 Doses of BEXSERO Administered 1 Month Apart to Canadian and Australian Adolescents [a, b]

≥ 4-Fold hSBA Response 1 Month Post Dose 2[b, c]			
Strain (Antigen)	**N**	**%**	**95% CI**
H44/76 (fHbp)	298	98	95, 99
5/99 (NadA)	299	99	98,100
NZ98/254 (PorA P1.4)	298	39	33,44
Composite hSBA Response[c, d]			
Time point	**N**	**%**	**95% CI**
Baseline (pre-vaccination)	299	0	
1 Month Post Dose 2	298	63	57, 68

NCT 01423084
Abbreviations: CI = Confidence interval; hSBA = Serum bactericidal activity measured using human complement; LLOQ = Lower limit of quantitation
[a] Evaluable Immunogenicity Population (11 through 17 years of age)
[b] ≥ 4-fold hSBA response is defined as: a post-vaccination hSBA ≥ 1:16 for participants with pre-vaccination hSBA <1:4, a post-vaccination titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA ≥1:4 but < LLOQ, and a post-vaccination 4-fold rise for participants with pre-vaccination hSBA ≥ LLOQ.
[c] LLOQ = 1:16 for H44/76; 1:16 for 5/99; 1:8 for NZ98/254.
[d] Composite hSBA Response means hSBA ≥ LLOQ for all 3 indicator Meningococcal B strains.

In a randomized, controlled clinical trial conducted in the UK among university students 18 through 24 years of age, hSBA responses in a subset of participants who received BEXSERO were measured 1 month and 11 months after the second dose (Table 10).

Table 10: Bactericidal Antibody Response Rates Following 2 Doses of BEXSERO Administered 1 Month Apart to University Students in the UK[a]

≥4-Fold hSBA Response 1 Month Post Dose 2[b, c]			
Strain (Antigen)	**N**	**%**	**95% CI**
H44/76 (fHbp)	148	78	71, 85
5/99 (NadA)	148	94	89, 97
NZ98/254 (PorA P1.4)	147	67	58, 74
Composite hSBA Response[c, d]			
Time point	**N**	**%**	**95% CI**
Baseline (pre-vaccination)	186	24	18, 30
1 Month Post Dose 2	147	88	82, 93
11 Months Post Dose 2	136	66	58, 72

NCT 01214850
Abbreviations: CI = Confidence interval; hSBA = Serum bactericidal activity measured using human complement; LLOQ =Lower limit of quantitation
[a] Evaluable Immunogenicity Population (18 through 24 years of age)
[b] ≥ 4-fold hSBA response is defined as: a post-vaccination hSBA ≥ 1:16 for participants with pre-vaccination hSBA <1:4, a post-vaccination titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA ≥1:4 but < LLOQ, and a post-vaccination 4-fold rise for participants with pre-vaccination hSBA ≥ LLOQ.
[c] LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.
[d] Composite hSBA Response means hSBA ≥ LLOQ for all 3 indicator Meningococcal B strains.

BEXSERO was immunogenic in both study populations. The immunogenicity data presented above are from different studies and were generated in two different laboratories: the ---(b)(4)---------- (Canada/Australia) and the ----------(b)(4)---------- (UK), however they suggest that the two populations differ in baseline sero-positivity to the serogroup B strains tested. Higher baseline titers were also observed in Chilean adolescents 11 through 17 years of age indicating that population differences besides age affect both baseline titers and hSBA responses. Across three trials, the composite hSBA immune response one month after the second dose was 63% to 94% (studies in Canada/Australia, and Chile respectively) and in the UK, the composite response eleven months after the second dose remained significantly above baseline. These immunogenicity data support that effectiveness providing clinical benefit is likely in individuals 10 to 25 years of age following vaccination with two doses of BEXSERO at least one month apart.

Clinical Serology Assays
The benefit of the vaccine is based on the ability of the vaccine to induce serum bactericidal antibody responses as measured by an hSBA assay. The methodology, performance and quality of the hSBA assays used for the clinical studies in this application were supported with detailed methodologies and validation reports. The assays were found to perform adequately for their intended use.

Bioresearch Monitoring
The CBER Bioresearch Monitoring (BIMO) Branch issued six high-priority foreign inspections for three pivotal trials in support of this BLA. The inspections of one study, V72P10, contributed to the Agency requesting that the Sponsor revise its reactogenicity rates. The inspections for two other pivotal studies, V72_29 and V72_41, did not reveal significant problems that impact the data submitted in this application.

Pediatric Research Equity Act (PREA)
In accordance with PREA, the requirement for studies in children ages 0 to less than 6 weeks was waived because use of BEXSERO in this age group does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and BEXSERO is not likely to be used in a substantial number of pediatric patients in this group.

Studies in children ages 6 weeks to <10 years were deferred because the product was ready for regulatory approval for use in adolescents and young adults before studies in children age 6 weeks to <10 years were completed. The requirement for studies in children 10 to <17 years of age was fulfilled by studies in this application.

7. Safety

Safety of BEXSERO
The safety of BEXSERO was evaluated in 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 from 15,351 BEXSERO recipients who participated in vaccination campaigns sponsored by the CDC at two US universities were reviewed.

Revised analyses of local and systemic reactogenicity rates for the four main trials were requested to address FDA (BIMO) inspection findings and patterns of solicited reaction data in the BLA suggesting that data was not obtained solely from source documents. The revised reactogenicity rates were similar to the original analyses and demonstrated that the overall reactogenicity findings were similar across studies.

Common adverse reactions across trials included injection site pain, injection site erythema, myalgia, malaise, and headache. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in BEXSERO recipients than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

In the clinical trials, serious adverse events were rare following BEXSERO vaccination and had etiologies unrelated to vaccination. Juvenile arthritis was reported ~5-6 months following the last vaccination in two study participants, one of whom had symptoms that predated vaccination. One case of acute thyroiditis was reported ~ 3 weeks following last vaccination; this subject also has symptoms consistent with this diagnosis that began before vaccination. One case of anaphylaxis was reported in the CDC vaccination campaigns which occurred within 30 minutes of the first BEXSERO vaccination, and was considered related to vaccination by both the investigator and the reviewer. There were no additional cases of anaphylaxis related to vaccination in the clinical trials evaluated as part of this BLA.

The safety data submitted indicate that local and systemic reactogenicity is common, and the observed frequency and severity following immunization with BEXSERO was greater than that seen following administration of a control or comparator vaccines. In the majority of individuals, local and systemic symptoms were mild and resolved. The type of unsolicited and severe adverse events reported in subjects 10 through 25 years of age were consistent with events commonly observed in adolescents and young adults in the US, and the one case of anaphylaxis, considered related to vaccination, did not occur at a frequency greater than that seen following other immunizations administered to this age group.

Subgroup Demographic Analyses
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.

Concomitant vaccination
Data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

The applicant has committed to 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 CRM_{197} Conjugate vaccine in persons 16 years through18 years of age.

8. Advisory Committee Meeting

An advisory committee meeting was not convened during the review of this original BLA. A VRBPAC meeting was held April 7, 2011, to discuss approaches to demonstrate effectiveness of meningococcal serogroup B vaccines. At this meeting, the committee concluded that serum bactericidal antibody levels induced by a meningococcal serogroup B vaccine as measured by hSBA assays are an appropriate measure of vaccine effectiveness. The committee agreed that 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 group B vaccines, such as BEXSERO, against the diverse population of circulating serogroup B strains. The committee discussed possible strategies for assessing breadth of coverage of a meningococcal serogroup B vaccine. Novartis will further address breadth of coverage as part of their confirmatory studies.

9. Other Relevant Regulatory Issues

Not Applicable

10. Labeling

The proprietary name BEXSERO was reviewed by the Advertising and Promotional Labeling Branch, CBER, and found acceptable.

The labels for the carton and container were reviewed. All issues, including required revisions, were resolved after exchange of information and discussions with the applicant.

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. Recommendations and Risk/ Benefit Assessment

a. Recommended Regulatory Action

The committee recommends approval of the BLA.

b. Risk/ Benefit Assessment

Based on the data submitted by the applicant to support the safety and effectiveness of BEXSERO that have been presented and discussed in this document, as well as the high degree of mortality and serious and permanent sequelae associated with meningococcal group B invasive disease, the review committee is in agreement that the risk/benefit profile for BEXSERO is favorable and supports approval of this BLA.

c. Recommendation for Postmarketing Risk Management Activities

The applicant will conduct routine surveillance reported in accordance with 21 CFR 600.80.

d. Recommendation for Postmarketing Activities

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 four 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 CRM_{197} Conjugate Vaccine in persons 16 years through 18 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 within 30 days prior to the last menstrual period or at any time during pregnancy. The applicant will submit annual reports as well as a three-year summary report.

12. References

1. WHO. 2011. *Meningococcal vaccines: WHO position paper, November 2011* [Online]. Available: http://www.who.int/wer/2011/wer8647.pdf [Accessed March 14, 2014 2014]
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.
4. Wang X, Cohn, A., Comanducci, M., et al. Prevalence and genetic diversity of candidate vaccine antigens among invasive *N. meningitidis* isolates in the United States. Vaccine 2011; 29:4739-4744.