Summary Basis for Regulatory Action

Date: October 29, 2014

From: Drusilla L Burns, Ph.D., Chair of the Review Committee

BLA/ STN#: 125549

Applicant Name: Wyeth Pharmaceuticals Inc.

Date of Submission: June 16, 2014

PDUFA Goal Date: February 13, 2015

Proprietary Name: Trumenba™

Established Name: Meningococcal Group B Vaccine

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

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Marion F. Gruber, 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	Lucia Lee, M.D.- October 29, 2014
Pharmacovigilance Review	Laura Polakowski, M.D., M.S.P.H.- October 21, 2014
Statistical Review	Barbara Krasnicka, Ph.D. (clinical immunogenicity) and Mridul Chowdhury, Ph.D. (clinical safety)- October 20, 2014 Tsai-Lien Lin, Ph.D. (assay)- October 23, 2014
Clinical Serology Assay Review	Freyja Lynn, B.S.- August 19, 2014
CMC Review	Tina Roecklein, M.S.- October 27, 2014 Freyja Lynn, B.S.- August 19, 2014 Alfred Del-Grosso, Ph.D.- October 8, 2014 Anil Choudhary, Ph.D. – September 23, 2014 Hyesuk Kong, Ph.D.- August 8, 2014
Facilities Review	Nancy Waites, M.S.- September 29, 2014 and October 15, 2014
Lot Release Protocol Template	Karen Campbell, M.S – October 28, 2014
Pharmacology/ Toxicology Review	Steven Kunder, Ph.D.- October 20, 2014
Bioresearch Monitoring Review	Lilian Ortega, M.P.H.- September 30, 2014
Advertising and Promotional Labeling	Michael Brony, Pharm. D.- August 6, 2014
Establishment Inspection Report	September 24, 2014
Inspection Waiver Memos	Nancy Waites, M.S.-June 4, 2014 for Drug Substance facility; July 7, 2014 for Drug Product labeling and packaging facility and Drug Product release testing facility
Advisory Committee Transcript	April 7, 2011
Approved Draft Labeling	N/A

1. Introduction

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc., submitted Biologics License Application (BLA) 125549 for licensure of Meningococcal Group B Vaccine. The proprietary name is Trumenba™. Trumenba is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Trumenba is intended for intramuscular injection administered as a three-dose series in individuals 10-25 years of age following a 0-, 2-, and 6-month schedule.

Trumenba is a sterile suspension of two recombinant lipidated factor H binding protein (fHBP) variants, one from each of two antigenically distinct fHBP subfamilies, subfamily A and subfamily B (A05 and B01, respectively). These proteins are also known as rLP2086 proteins. The proteins are individually produced in *Escherichia coli* and subsequently purified. Each 0.5 ml dose of Trumenba is formulated to contain 60 micrograms of each fHBP variant subtype (120 micrograms total protein), 0.018 mg of polysorbate 80, and 0.25 mg of Al^{3+} as $AlPO_4$ in 10 mM histidine buffered saline at pH 6.0.

Each prefilled syringe of Trumenba delivers a 0.5 ml dose of vaccine. Trumenba contains no preservative. Trumenba 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

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-135. Because of the poor immunogenicity of serogroup B polysaccharides, even when conjugated to immunogenic carrier proteins, as well as because of the similarity between serogroup B capsular polysaccharide and host polysaccharides, development of a vaccine based on serogroup B capsular polysaccharide was not possible. Thus meningococcal serogroup B vaccines were developed based on the discovery of immunogenic outer membrane proteins. Trumenba is based on one of these immunogenic bacterial surface proteins, fHBP. fHBP is a virulence factor that contributes to the ability of *Neisseria meningitidis* to avoid complement-mediated killing in the host. *N. meningitidis* serogroup B fHBPs can be categorized into two immunologically distinct subfamilies, subfamily A and subfamily B[1]. While a high degree of amino acid identity exists within a subfamily, thus favoring cross-reactivity, much more amino acid heterogeneity is observed between subfamilies. Trumenba consists of one representative fHBP variant from each of the two subfamilies.

Invasive disease caused by *N. meningitidis* serogroup B strains can lead to permanent sequelae or death. While the incidence of meningococcal serogroup B disease in the United States is relatively low, recent outbreaks on several 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, such as fHBP, 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 Trumenba met the criteria for Breakthrough Therapy designation and granted that designation on March 19, 2014. Given the public health concerns about meningococcal serogroup B disease in the US, CBER agreed to consider licensing Trumenba under the accelerated approval regulations, 21 CFR 601 Subpart E. The Agency determined that it would be appropriate to use the accelerated approval pathway, 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 includes strains that express the two fHBP variants that are expressed by the most prevalent strains causing meningococcal serogroup B disease in the US. The breadth of coverage of Trumenba against diverse meningococcal group B strains would be confirmed in subsequent clinical studies that examine the ability of the vaccine to induce bactericidal antibodies against a larger panel of meningococcal serogroup B strains that represent a range of genetically diverse fHBP variants 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. Many issues regarding these topics were resolved before submission of the BLA. On June 16, 2014, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., submitted a BLA for Trumenba. The established name for this vaccine is Meningococcal Group B Vaccine.

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

Trumenba contains two meningococcal serogroup B (MnB) fHBP variants, one from subfamily A and one from subfamily B, as the active ingredients. The full composition of the Trumenba final drug product and the function of the ingredients are provided in Table 1 below.

Table 1: Composition of Trumenba Final Drug Product

Ingredient	Function	Amount/Dose
MnB fHBP subfamily A variant	Active ingredient	0.06 mg
MnB fHBP subfamily B variant	Active ingredient	0.06 mg
Sodium chloride	---(b)(4)---	(b)(4)
Histidine	pH control	0.78 mg
Polysorbate 80[a]	---(b)(4)---	0.018 mg
Aluminum phosphate	---(b)(4)---	0.25 mg
Water for injection	Diluent	(b)(4)

[a]Polysorbate 80 is part of the drug substance

Presentation and Packaging System

Trumenba is supplied in 1 ml pre-filled disposable syringes. A single dose of vaccine is 0.5 ml with no preservative. The syringes are pre-assembled with a Luer-Lok® adapter, a tip cap and a plastic rigid tip cap (PRTC) overseal. The tip cap is composed of ---(b)(4)--- latex-free -----(b)(4)------ rubber. The Luer-Lok adapter is composed of clear -----(b)(4)----- and the PRTC is composed of ------(b)(4)------. The Luer-Lok adapter and the PRTC do not have contact with the product.

Manufacturing Overview

Trumenba consists of two separate Drug Substances:

- Meningococcal serogroup B fHBP subfamily A variant (A05)
- Meningococcal serogroup B fHBP subfamily B variant (B01)

Both drug substances are manufactured at ----------(b)(4)----------

The drug product is manufactured (formulated, filled, and visually inspected) at Pfizer ----------(b)(4)---- (Pfizer, ---(b)(4)---). Aluminum phosphate ($AlPO_4$) is a non-novel, ----(b)(4)---- excipient which functions as a ---(b)(4)--- for this vaccine. The final vaccine is a sterile liquid suspension.

Drug Substance

The meningococcal serogroup B fHBP subfamily A and B variants are individually expressed in *Escherichia coli*. The fermentation and recovery processes are ----------(b)(4)----------. Commercial scale drug substance batches are fermented at a production culture scale of approximately ----------(b)(4)----------.

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

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The applicant performed process development and analytical methods development to establish the suitability of the drug substance. In-process tests for control and in-process tests for monitoring are implemented throughout the process to ensure consistency of the manufacturing process. The validation of the drug substance manufacturing process was performed for ----------
----------(b)(4)----------
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The specifications for drug substance are shown in Table 2. The tests performed for ---(b)(4)--- are footnoted. The acceptance criteria are ----------(b)(4)----------.

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

Drug Product

The Trumenba drug product contains the subfamily A and subfamily B variant proteins in 10 mM histidine buffer containing --(b)(4)-- NaCl, pH 6.0, and 0.50 mg/ml $AlPO_4$ with polysorbate 80 at a concentration defined by the ----(b)(4)----. During the manufacturing process for the drug product, ----------(b)(4)----------. The formulated drug product is filled into syringes to deliver a nominal dose of 0.5 ml. The filled syringes are

stored at 2-8°C until ready to be shipped from Pfizer, -(b)(4)- (commercial manufacturing site) to the labeling and packaging site, Pfizer, ----------(b)(4)----------.

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 3.

Table 3: Trumenba Drug Product Specifications

Test	Method	Specification
Sterility[a]	---(b)(4)---	Meets requirements of the test No growth observed
Endotoxin	---(b)(4)---	---(b)(4)---
General Safety	(b)(4)	Passes Test/Meets Requirements
------(b)(4)--------	(b)(4)	Passes Test/Meets Requirements
Appearance[a]	Visual	Homogeneous, white suspension
Identity	---(b)(4)---	-------(b)(4)------- -------(b)(4)-------
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
---(b)(4)---Potency---(b)(4)-----	---(b)(4)---	---(b)(4)---
---(b)(4)---Potency---(b)(4)-----	---(b)(4)---	---(b)(4)---
Aluminum	---(b)(4)---	-----(b)(4)-----
---(b)(4)---	---(b)(4)---	------(b)(4)------
pH[a]	-----(b)(4)-----	6.0 (b)(4)
Polysorbate 80 -----(b)(4)------	---(b)(4)---	---(b)(4)---
Purity[a]	---(b)(4)---	---(b)(4)---
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
----------(b)(4)----------	---(b)(4)---	---(b)(4)---
Volume of Injection	-------(b)(4)--------	(b)(4) 0.5 ml
Container closure integrity[a,b]	---(b)(4)---	Pass

[a]These tests are performed for the stability assessment
[b]Not a release test; performed only annually on stability

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

To date 18 months of real-time stability data are available from the Pfizer, --(b)(4)-- process validation/primary stability lots. Up to --(b)(4)-- of real-time data are available from supportive stability lots. All data remained within the proposed commercial stability specifications. In addition, stability studies on drug product stored at the accelerated condition of --(b)(4)-- were conducted for (b)(4) stability lots. The studies are complete with 6 months of data. Data from all studies remained within the proposed commercial stability specifications. CBER determined that the totality of the data support a dating period of 24 months.

Among the Chemical, Manufacturing and Controls (CMC) issues that arose and were resolved during the BLA review were the following: 1) lack of adequate information concerning certain procedures including determination of ----------(b)(4)---------- drug substance, and purity determination of the drug product; 2) lack of data supporting adequacy of certain methodologies including methodologies to determine ----------(b)(4)----------; 3) inadequate data to support certain hold times in the manufacturing process; 4) the need for additional release testing for ----------(b)(4)----------, for -----(b)(4)----, and for general safety; and 4) the need

----------(b)(4)----------. 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 Trumenba were submitted in support of the BLA for lot release testing and were found to be acceptable. For routine lot release, the applicant will submit final container samples and a lot release protocol. Protocol review for Lot Release is performed for both the bulk and final container stages for Trumenba. Both the bulks and the final container will be released by CBER. A lot testing plan was developed by CBER and will be used for routine lot release.

c. Facilities Review/Inspection

The facilities involved in the manufacture of Trumenba along with their inspectional history are listed in Table 4. The activities conducted by each facility in the manufacture of Trumenba are included in the Table.

Table 4: Facilities Involved in the Manufacture of Trumenba and Their Inspection History

Name / Address	FEI	Inspection / Waiver	Results / Justification
Drug Substance			
---------(b)(4)---------- -------(b)(4)------- ----------(b)(4)---------- ---(b)(4)--- -----(b)(4)-----	----(b)(4)----	Waived	Waived based on acceptable FDA compliance history
Drug Product			
Pfizer -------(b)(4)------- ----------(b)(4)---------- ---(b)(4)--- -----(b)(4)-----	---(b)(4)----	Insp. ------(b)(4)------ TeamBio & Product Office	A pre-license inspection was performed for the manufacture, filling, and testing of the Drug Product. The result was VAI. All inspectional issues were adequately resolved.
Drug Product Labeling & Packaging			
Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc. ---(b)(4)--- ----------(b)(4)---------- ----------(b)(4)----------	---(b)(4)----	Waived	Waived based on acceptable FDA compliance history
Drug Product Release Testing			
Wyeth Pharmaceutical Division of Wyeth Holdings Corporation, a subsidiary of Pfizer Inc. ----------(b)(4)---------- ----------(b)(4)----------	---(b)(4)----	Waived	Waived based on acceptable FDA compliance history

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

d. Environmental Assessment

The applicant's request for a categorical exclusion was submitted to the file based on 21 CFR 25.31(c). The active ingredients of Trumenba are recognized as naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substances, their metabolites, or degradation in the environment. The request for a categorical exclusion was accepted.

4. Nonclinical Pharmacology/Toxicology

Two repeat-dose toxicology studies and two reproductive toxicology studies were submitted to provide nonclinical support for this BLA. For specifics regarding study design and outcomes, reference is made to the toxicology review document. No significant safety issues were noted in the review of the toxicology studies.

Reproduction studies were performed in rabbits at a dose approximately 17 times the human dose (on a mg/kg basis) and revealed no evidence of impaired fertility or harm to the fetus due to Trumenba. Based on the data derived from these studies, Trumenba received a pregnancy Category B designation which will be reflected in the Prescribing Information for Trumenba under Section 8.1: Pregnancy.

5. Clinical Pharmacology

Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent bactericidal killing of *N. meningitidis*. Bactericidal antibodies as measured by hSBA assays were used to assess the effectiveness of Trumenba.

fHBP is one of many proteins found on the surface of meningococci and contributes to the ability of the bacterium to avoid host defenses. fHBPs can be categorized into two immunologically distinct subfamilies, A and B[1]. The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with Trumenba is dependent on both the antigenic similarity of the bacterial and vaccine fHBPs, as well as the amount of fHBP expressed on the surface of the invading meningococci.

6. Clinical/Statistical-Efficacy

(Extracted in part from Dr. Lee's clinical review)

General Description of Clinical Studies

Trumenba was evaluated in 7 clinical studies (4 randomized controlled and 3 supportive non-controlled studies) conducted in the US, Europe and Australia. These studies are listed in Table 5.

Table 5: Overview of Trumenba Clinical Studies

Study	Age (years)	Number of subjects receiving final formulation of Trumenba (120 µg protein)	Region	Study design
B1971003 Safety and Immunogenicity	≥ 18 to ≤ 40	60	Australia	Single-arm, open-label study
B1971004 Safety and Immunogenicity	≥ 18 to ≤ 40	12	US	Randomized, open-label, active- and placebo-controlled study
B1971005 Safety and Immunogenicity	≥ 11 to ≤ 18	198	Europe Australia	Randomized, single-blind, placebo-controlled study
B1971010 Safety and Immunogenicity	≥ 11 to < 19	374	Europe	Randomized, placebo-controlled, single-blind study
B1971011 Safety and Immunogenicity Concomitant vaccination with Gardasil®	≥ 11 to < 18	1982	US	Randomized, active-controlled, observer-blinded study
B1971012 Safety and Immunogenicity	≥ 11 to < 19	1696	Europe	Randomized, placebo-controlled[a], single-blind study
B1971042 Safety and Immunogenicity	≥ 18 to ≤ 65	13	US	Single-arm, open-label study

[a] Saline was administered to maintain the study blind at each injection visit (i.e., same number of injections was administered at each visit for each study group). The study was designed to assess the safety and immunogenicity of Trumenba when administered as a 2- or 3-dose schedule, rather than to compare the safety and immunogenicity of Trumenba to a control group comprised of the same subjects who received a saline injection at all visits; in this regard, the study was not a controlled study.

Vaccine Effectiveness

At the time of Trumenba development, efficacy studies using clinical disease outcomes were not feasible due to low incidence and sporadic occurrence of cases of disease in the US. At the VRBPAC meeting held April 7, 2011, the committee supported the use of serum bactericidal activity with human complement (hSBA) to evaluate effectiveness of protein-based meningococcal B vaccines. However, genetic diversity and variable expression of meningococcal surface proteins limits generalizations of vaccine-induced protection to meningococcal group B strains antigenically similar to the strain tested in the hSBA assay.

CBER determined that the Trumenba qualified for submission of a biologics license application (BLA) under the accelerated approval pathway. Trumenba is intended to prevent invasive meningococcal serogroup B disease, which is a serious condition. At present, no meningococcal B vaccine is licensed or available in the US. Available therapy for adolescents and young adults for prevention of invasive meningococcal disease includes antibiotic chemoprophylaxis. However, disease manifestations (*e.g.*, meningitis, sepsis) are prevented only if individuals at risk are identified in a timely manner. Data to demonstrate vaccine effectiveness in the context of accelerated approval comes from clinical studies in which the ability of Trumenba to elicit serum bactericidal antibodies was assessed using hSBA assays that measure bactericidal activity against four individual primary meningococcal group B strains that represent the most prevalent strains that cause meningococcal group B disease in the US.

In accordance with the accelerated approval regulations, post-marketing confirmatory studies will be conducted to further verify and describe the effectiveness of Trumenba, which will be evaluated by post-vaccination hSBA responses using an additional panel of secondary strains. The secondary strains represent meningococcal serogroup B disease isolates in the US which express fHBP variants that are genetically diverse. Collectively, clinical evaluation of hSBA responses with the four primary strains and with the panel of secondary strains will provide data to confirm the effectiveness of Trumenba against diverse meningococcal serogroup B strains that are epidemiologically relevant for US adolescents and young adults.

Clinical Studies Effectiveness Data

The evaluation of effectiveness of Trumenba was based on the immune responses elicited by the vaccine to meningococcal serogroup B strains as measured by serum bactericidal antibodies using hSBA assays. The primary meningococcal serogroup B strains used for this analysis included two subfamily A strains, one expressing fHBP variant A22 and one expressing variant A56, and two subfamily B strains, one expressing fHBP variant B24 and one expressing variant B44. In the US, strains that express variants A22 and B24 are the most prevalent strains that cause meningococcal serogroup B disease.

The immunogenicity of Trumenba was supported by data from three adolescent (inclusive of individuals 11 to $\leq$18 years of age) phase 2 studies, which were conducted in the US and Europe. In the context of the accelerated approval pathway, analyses of the following endpoints, which were agreed to by CBER, using the four primary meningococcal serogroup B strains were most relevant to US licensure: the proportion of participants with a $\geq$4-fold hSBA response to each of the four strains and the proportion of participants with a hSBA response $\geq$ the lower limit of quantitation (LLOQ) of the assay for all of the primary strains (composite response). The analyses for these endpoints were descriptive; however, hSBA responses were evaluated in a substantial number of participants (*i.e.*, the evaluable immunogenicity population of approximately 2300 subjects in the three studies received Trumenba at 0, 2 and 6 months). The 4-fold and composite endpoints described above are analogous to the primary endpoints in the confirmatory phase 3 studies being conducted with Trumenba which were agreed upon by CBER.

In US study B1971011, adolescents 11 to <18 years of age were assigned randomly into three groups: Group 1 received Trumenba + Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV4, Gardasil®), Group 2 received Trumenba + Saline, and Group 3 received Saline + HPV4. The hSBA responses achieved after the third dose of Trumenba (Groups 1 and 2) are shown in Table 6.

Table 6-a. hSBA Responses to Trumenba in US Study B1971011 4-fold Response[a,b]

fHBP Variant[c]	**Group 1, Trumenba + HPV4** % achieving ≥ 4-fold response (95% CI)	**Group 2, Trumenba + Saline** % achieving ≥ 4-fold response (95% CI)
A22	85.3 (82.6-87.7)	86.4 (83.8-88.7)
A56	95.0 (93.2-96.5)	95.3 (93.6-96.8)
B24	83.4 (80.5-85.9)	84.8 (82.0-87.2)
B44	77.0 (73.9-79.9)	80.7 (77.8-83.4)

Table 6-b. Composite Response[a] (hSBA ≥ LLOQ[d] for all 4 strains)

	Group 1, Trumenba + HPV4 % achieving composite response (95% CI)	**Group 2, Trumenba + Saline** % achieving composite response (95% CI)
	81.0 (78.0-83.7)	83.9 (81.1-86.4)

[a]Serum was obtained approximately 1 month after dose 3
[b]The 4-fold increase is defined as follows: (1) for subjects with a baseline hSBA titer <1:4, a response was defined as an hSBA titer ≥1:16; (2) for subjects with a baseline titer ≥1:4, a 4-fold response was defined as an hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer, whichever was higher
[c]The strains expressing variant A22, A56, B24, B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively
[d]LLOQ = 1:16 for PMB80 (A22); 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)

These immunogenicity data support the use of Trumenba as a 3-dose series. The proportions of subjects with a hSBA titer ≥1:8 (1:16 for A22) to each strain also supported vaccine-induced immunogenicity. No substantial differences in hSBA responses were observed by gender or age. The hSBA data from the two studies in Europe were consistent with data from the US study. Immunogenicity data with other meningococcal serogroup B strains and preliminary hSBA data using the four primary strains in young adults (19 to ≤25 years of age) supported the immunogenicity of Trumenba in this population. Immune responses to Trumenba vaccination in individuals 10 years of age are expected to be similar to the immunogenicity in adolescents.

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 discussed extensively during clinical development of the vaccine. The performance of the hSBA assays was supported with detailed methodologies and validation reports. The assays were found to perform adequately for their intended use.

Bioresearch Monitoring
Bioresearch Monitoring data audit inspections of three clinical investigators were conducted in support of this BLA. The inspections focused on Protocol B1971011, the pivotal phase 2 US safety and immunogenicity study. The inspections did not reveal significant problems that impact the data submitted in this BLA.

Pediatric Research Equity Act (PREA)
In accordance with PREA, the requirement for studies in children ages 0 to <12 months was waived because safety data from a clinical study in infants vaccinated with a reduced dosage formulation showed an unacceptably high incidence of fever after a single dose. Studies in children ages 1 to <10 years were deferred because regulatory approval was ready for use in adolescents and young adults before studies in children age 1 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

(Extracted in part from Dr. Lee's and Dr. Polakowski's reviews)

Safety of Trumenba
The safety of Trumenba was evaluated in 7 studies. A total of 4335 subjects received at least one dose of Trumenba (120 µg protein). At the time of enrollment, 58.1%, 40% and 2% of subjects were age 11-14 years, 15-18 years and >18 years of age, respectively. The median age was 14 years. Of the 4335 subjects, 4282 were 11 to ≤25 years of age. Overall, 56% of subjects were male. 90.6% were Caucasian, 6.3% were African American, 0.9% were Asian and 2.2% of participants were characterized as "other".

- Subjects from 4 randomized, controlled studies (B1971004, B1971005 Stage 1, B1971010, and B1971011) comprised the core safety database of subjects who received Trumenba according to vaccination schedule (0, 2 and 6 months) intended for US licensure: 2557 subjects age 11 to ≤25 years received at least 1 dose of Trumenba and 1004 subjects were included in control groups; 1994 and 513 subjects, respectively, were enrolled at US sites.
- In 3 non-randomized, non-controlled studies (B1971003, B1971012, and B1971042), a total of 1725 participants received Trumenba, which was administered according to a 2-dose or a 3-dose schedule.

Among adolescents in US study B1971011, common solicited adverse reactions following bivalent rLP2086 vaccination were pain at the injection site (≥ 85%), fatigue (≥40%),

headache (≥35%), generalized muscle pain (≥30%) and chills (≥15%) with the majority of these being mild to moderate. Trumenba was associated with more local reactions than saline placebo and generally was more reactogenic than the comparator for systemic adverse reactions (saline, Tdap-containing vaccine or HPV4 vaccine, depending on the study).

In the 7 studies, the rates of unsolicited adverse events reported within 30 days were similar among subjects receiving Trumenba compared to participants in the control groups (25.3% vs. 31.7%, respectively). The nature and frequency of events reported were consistent with events that are common in an adolescent and young adult population. The rates of serious adverse events (through 6 months after the last vaccination) were 2.0% among subjects receiving Trumenba and 1.6% among participants in the control groups. The safety profile of Trumenba in adults was similar to adolescents.

Among the 4576 subjects who received bivalent fHBP-containing vaccine (any dosage or schedule, age 11 to 65 years of age), 13 subjects reported an autoimmune (AI) condition and 1 subject reported a neuroinflammatory (NI) condition, compared to no conditions reported among 1028 subjects in a control group. Of these, 8 cases (1-psoriasis, 1-rheumatoid arthritis, 1-hyperthyroidism, 2-celiac disease, 3-hypothyroidism) were determined to have an onset before vaccination, 3 cases (1-post infectious arthritis caused by group A streptococcal disease, 1-Sydenham's chorea caused by group A streptococcal disease, 1-Bell's palsy caused by Lyme disease) had etiologies unrelated to vaccination, and 1 (IgA nephropathy) was not considered to have a possible vaccine etiology since the onset was only one day post-dose 1 of vaccine. Thus, only two cases were considered to have a possible vaccine etiology. For these two cases, the rates observed were either lower than the background rate or the corresponding 95% CI includes the 95% CI of the background rate for these conditions in the general population of adolescents and young adults. Also, no significant imbalance of new AI cases with possible vaccine etiology was observed between Trumenba vaccines and controls (95% CI lower bound of the relative risk ratio was 0.08 for all 7 BLA studies and 0.03 for the 4 core safety studies; both are substantially <1.0, suggesting there is no significant difference between groups).

As noted above, the majority (8) of the cases were conditions that were present prior to study entry. The possibility that Trumenba vaccination exacerbated or "unmasked" symptoms of AI/NI disease in individuals who were asymptomatic at the time of study entry was considered. However, no sufficient evidence suggesting an elevated risk of exacerbation or "unmasking" of asymptomatic AI disease occurring among Trumenba vaccinees was found (see Dr. Polakowski's review for more details).

Even assuming a maximum number of 14 AI/NI cases either caused or exacerbated by Trumenba vaccination with no cases among control vaccinees, the 95% CI lower bound of the relative risk was 0.92, again suggesting no excess risk among Trumenba vaccinees. Additionally, there is no single plausible disease mechanism that could explain exacerbation of all 8 pre-existing AI cases. These cases likely represent sporadic occurrences of different AI diseases at rates comparable to those typically seen in this age population.

The safety profile of Trumenba was deemed adequate to support the use of a 3-dose series. Four ongoing studies will contribute an additional 15,000 subjects to the safety database, with approximately 10,000 receiving Trumenba.

Concomitant vaccination
No immunological interference with hSBA responses was observed when Trumenba was administered concomitantly with human papillomavirus vaccine, HPV4 (Gardasil; types 6, 11, 16 and 18), compared to hSBA responses when Trumenba was administered alone. When HPV4 was co-administered with Trumenba or alone, the statistical criteria for three of the four HPV types were met. For HPV-18, the lower bound of the 95% CI for the GMT ratio was 0.62, which was only slightly below the statistical criteria for no interference (>0.67). In both study groups, the HPV seroconversion rate was ≥99% for each respective HPV type.

The applicant committed to submit safety and immunogenicity data from a study to support co-administration of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (TdaP), Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Trumenba.

8. Advisory Committee Meeting

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, such as fHBP, among meningococcal group B strains adds an additional challenge to ascertaining effectiveness of meningococcal group B vaccines, such as Trumenba, against the diverse population of circulating serogroup B strains. The committee discussed possible strategies for assessing breath of coverage of a meningococcal serogroup B vaccine. Pfizer will further address breadth of coverage as part of their confirmatory studies.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

The proprietary name Trumenba 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 Trumenba 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 Trumenba 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 evaluate the ability of the vaccine to elicit hSBA responses against the four primary strains and hSBA responses against an additional panel of secondary strains to provide additional clinical data to confirm effectiveness of Trumemba against diverse meningococcal group B strains that are epidemiologically relevant in US adolescents and young adults.
- Studies in children 1 to <10 years of age will be conducted to fulfill PREA requirements

Post-marketing Commitments

- The applicant will submit the clinical study report from an ongoing large scale phase 3 safety study in order to further describe the safety profile of Trumenba. This study is being conducted in individuals 10 years to less than 26 years of age
- The applicant will submit the clinical study report from a phase 2 study to assess concomitant use of Trumenba with Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed in persons 10 years to less than 13 years of age.
- The applicant committed to conduct a cohort study to examine pregnancy and birth outcomes following vaccination with Trumenba prior to or during pregnancy

12. Reference

1. Wang X, Cohn, A., Comanducci, M., et al. Prevalence and genetic diversity of candidate vaccine antigens among invasive *Neisseria meningitidis* isolates in the United States. Vaccine 2011; 29:4739-4744.