Summary Basis for Regulatory Action

Date: March 13, 2017

From: CDR Mike Smith, Ph.D., Chair of the Review Committee

BLA/ STN#: 125549/173

Applicant Name: Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.

Date of Submission: May 13, 2016

Goal Date: March 13, 2017

Proprietary Name/Established Name: Trumenba®/Meningococcal Group B Vaccine

Indication: 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:
The Review Committee recommends approval of this Clinical Efficacy Supplement to include data from two confirmatory clinical studies to verify and describe the clinical benefit of the three-dose schedule (a dose administered at 0, 1-2, and 6 months) of Trumenba. Also, we recommend approval of the Applicant's request to include data from a study to further describe the safety of Trumenba in persons 10 years to less than 26 years of age, and a study to assess the 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. We approved BLA STN 125549/0 on October 29, 2014, under 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills the Applicant's postmarketing requirements 1 and 2 for the three-dose schedule for Trumenba under 21 CFR 601.41 and their postmarketing commitments 6 and 7, identified in the October 29, 2014, approval letter for STN 125549/0 for Trumenba. Lastly, we also recommend approval of revisions to the package insert labeling to comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*.

Review Office Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, 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.

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
Clinical Review • *Clinical (OVRR/DVRPA)*	Suyoung (Tina) Chang, M.D. (3/12/2017)
Statistical Reviews • *Clinical data (OBE/VEB)* • *Non-clinical data* (OBE/VEB)	Lei Huang, Ph.D. (3/10/2017) Tsai-Lien Lin, Ph.D. (3/1/2017)
CMC Reviews • *Clinical serology (OVRR/DBPAP)* • *Clinical serology (OVRR/DBPAP)*	Leslie Wagner (2/22/2017) Freyja Williams (10/21/2016)

1. Introduction

   This Clinical Efficacy Supplement was submitted on May 13, 2016, to the Biologics License Application (BLA) for Trumenba to include the final Clinical Study Reports for the accelerated approval required studies: two confirmatory studies (B1971009 and B1971016), and two postmarketing commitments: a safety study (B1971014) and a concomitant use study with Adacel and Menactra (B1971015). These four studies were postmarketing requirements or commitments under the original approval of the three-dose schedule (a dose administered according to a 0, 2, and 6 month schedule).

2. Background

   Trumenba is a bivalent meningococcal group B vaccine that contains two factor H binding proteins (fHBP) from *Neisseria meningitidis (N. meningitidis)* serogroup B. fHBP is a conserved, outer membrane lipoprotein and a virulence factor that contributes to the ability of the bacteria to avoid host defenses.

   On June 16, 2014, Wyeth Pharmaceuticals, Inc. (U.S. license 0003), a subsidiary of Pfizer Inc., submitted BLA 125549 for licensure of Meningococcal Group B Vaccine (Trumenba). Trumenba was approved on October 29, 2014, under the accelerated approval regulations (21 CFR 601.4o-46) for active immunization to prevent invasive disease caused by *N. meningitidis* serogroup B in individuals 10 through 25 years of age. Under this approval, the Applicant was required to conduct adequate and well-controlled studies (B1971009 and B1971016) to verify and describe the clinical benefit attributable to this product by demonstration of effectiveness against diverse meningococcal group B strains. Additionally, the Applicant was required to conduct three pediatric studies and committed to conducting three postmarketing studies: to further describe the safety of Trumenba in persons 10 years to less than 26 years of age (B1971014), to assess the concomitant use of Trumenba with Menactra and Adacel and in persons 10

years to less than 13 years of age (B1971015) and a cohort study to examine pregnancy and birth outcomes following vaccination with Trumenba prior to or during pregnancy (B1971052).

On March 27, 2015, the Applicant submitted a Clinical Efficacy Supplement (STN 125549/17) to revise the dosing regimen. The FDA approved the supplement on April 14, 2016, to include a two-dose schedule (a dose administered at 0 and 6 months) under the regulations for accelerated approval, 21 CFR 601.40-46. The approval also included a modification of the three-dose schedule (that had been approved under the original BLA according to the regulations for accelerated approval) from administration at 0, 2, and 6 months to administration at 0, 1-2, and 6 months.

3. Clinical/Statistical/Pharmacovigilance

a) **Clinical Program**

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

This supplement contains clinical data from four studies (B1971009, B1971016, B1971014 and B1971015) that were ongoing at the time of the original Trumenba BLA approval.

- Studies B1971009 and B1971016 were confirmatory Phase 3 studies that were conducted in subjects 10 to <18 years of age and 18 to <26 years of age, respectively, as postmarketing requirements (PMRs) for accelerated approval of the Trumenba three-dose schedule (0, 2, and 6 months). Lot consistency was also evaluated as part of study B1971009.

- Study B1971014 was a Phase 3 safety study conducted in persons 10 years to <26 years of age.

- Study B1971015 was a Phase 2 study that assessed concomitant use of Trumenba with Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (MCV4) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) in persons 10 years to <13 years of age.

All four studies, B1971009, B1971016, B1971014, and B1971015, were randomized, controlled, observer-blinded studies. Study B1971014 evaluated only safety while the other three studies evaluated safety and immunogenicity. Additionally, studies B1971009 and B1971016 were conducted in the U.S., Canada and Europe, study B1971014 was conducted in the U.S. and Europe, and study B1971015 was conducted only in the U.S.

Table 1. Clinical Trials

Study # (Region)	Study Objectives	Age (years)	Study Groups	Number of Randomized Subjects
B1971009 (U.S., Canada and Europe)	Safety and Immunogenicity of Trumenba Lot-to-lot consistency	10 to <19	Group 1: Lot 1 Trumenba Group 2: Lot 2 Trumenba Group 3: Lot 3 Trumenba Group 4: HAV/Saline	1509 600 589 898
B1971016 (U.S., Canada, and Europe)	Safety and immunogenicity of Trumenba	18 to <26	Group 1: Trumenba Group 2: Saline	2480 824
B1971014 (U.S. and Europe)	Safety of Trumenba	10 to <26	Group 1: Trumenba Group 2: HAV/Saline	3804 1908
B1971015 (U.S.)	Safety and Immunogenicity of MCV4 and Tdap co-administered with Trumenba	10 to <13	Group 1: MCV4+Tdap+Trumenba Group 2: MCV4+Tdap+Saline Group 3: Saline+Saline+Trumenba	888 878 882

MCV4 = Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra)
Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel)
HAV = Hepatitis A Vaccine, Inactivated (Havrix)

Immunogenicity

The effectiveness of Trumenba against diverse *N. meningitidis* serogroup B strains was inferred by human serum bactericidal activity (hSBA) responses using 14 test strains (four primary strains and 10 secondary strains) in the two confirmatory Phase 3 studies. As mentioned above, these studies were ongoing at the time the original Trumenba BLA was approved and conducted with the original three-dose schedule (a dose administered at 0, 2, and 6 months). These studies confirmed the effectiveness through an evaluation using the same four diverse strains that were evaluated in the Phase 2 studies reviewed under the original BLA as well as a further description of responses to an additional 10 strains to confirm breadth of coverage of the vaccine against this panel of diverse strains. The primary objectives and analyses for the Phase 3 studies were to assess the hSBA response to each primary strain and to all of the primary strains to provide pivotal evidence of effectiveness. We consider these studies as adequately designed for confirmation of effectiveness to support traditional approval of the vaccine.

Primary strains:

Evaluation of hSBA responses using four primary meningococcal serogroup B (MenB) strains expressing variants A22, A56, B24 and B44 was the primary objective for the confirmatory studies. The selection of the four primary strains included the most prevalent fHBP variants from each family in the U.S. (A22 and B24). The two additional primary strains represent genetically diverse fHBP variants. The five co-primary endpoints and corresponding data are summarized below. The pre-specified primary immunogenicity endpoints were met in both studies.

Table 2. Study B1971009 and Study B1971016. Percentage of Participants with a ≥4-Fold Increase in hSBA Titer and Composite Response – Evaluable Immunogenicity Population.

	Subjects ≥10 to <19 years			Subjects 18 to <26 years of age		
	U.S. %[b] (95% CI)	U.S. + Europe %[b] (95% CI)	Pre-specified Lower Bound of 95% CI Threshold[d]	U.S. %[b] (95% CI)	U.S. + Europe %[b] (95% CI)	Pre-specified Lower Bound of 95% CI Threshold[d]
fHBP variant[a]						
A22	86.2 (83.1, 88.9)	83.2 (81.0, 85.2)	75%	81.1 (77.8, 84.0)	80.5 (78.6, 82.4)	55%
A56	92.0 (89.4, 94.2)	90.2 (88.4, 91.9)	85%	90.7 (88.1, 92.8)	90.0 (88.4, 91.4)	85%
B24	81.9 (78.5, 84.9)	79.8 (77.4, 82.0)	65%	83.9 (80.8, 86.7)	79.3 (77.3, 81.2)	50%
B44	88.3 (85.3, 90.8)	85.9 (83.8, 87.8)	60%	79.3 (76.0, 82.4)	79.6 (77.6, 81.5)	60%
Composite (≥LLOQ for all 4 variants)[c]	85.7 (82.4, 88.5)	83.5 (81.3, 85.6)	75%	82.4 (79.2, 85.3)	84.9 (83.1, 86.6)	60%

Source: Adapted from STN 125549/173; B1971009 study body report, Table 20, page 108, Table 21, page 109 and from B1971016 study body report, Table 18, page 97 and Table 19, page 98.
hSBA = serum bactericidal assay using human complement; N= the number of subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline; LLOQ = lower limit of quantitation; CI = confidence interval
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
[a] The strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively.
[b] ≥4-fold increase in hSBA titer: %=n/N = number of subjects with a hSBA fold rise ≥4 from baseline (pre-Vaccination #1) for the given strain/ number of subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline. A ≥4-fold increase in hSBA titer 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 hSBA 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] Composite hSBA response (hSBA ≥ LLOQ for all four primary strains: %=n/N = number of subjects with observed hSBA titer ≥ LLOQ for all four primary strains at the given time point/ number of subjects with valid and determinate hSBA results on all four strains at the given time point.

[d] If the lower bound of the 95% CI is greater than the corresponding threshold, the immunogenicity objective with respect to that endpoint is achieved. The primary study objective requires this criterion to be met for all five co-primary endpoints.

Secondary strains:

hSBA responses against the following 10 diverse meningococcal group B strains (secondary strains) was a descriptive, secondary objective in the two Phase 3 confirmatory studies: PMB3010 (A06), PMB3040 (A07), PMB824 (A12), PMB1672 (A15), PMB1989 (A19), PMB3175 (A29), PMB1256 (B03), PMB866 (B09), PMB431 (B15), and PMB648 (B16). The descriptive assessment of serum bactericidal antibodies against these additional strains further describes effectiveness against circulating strains expressing protein variants that differ from the primary strains.

For subjects 10 to <18 years of age (study B1971009), the proportion of subjects with a hSBA titer ≥LLOQ one month after Vaccination #3 with Trumenba were 76.1% to 98.9% for U.S. subjects and 75.1% to 98.6% for all subjects (U.S. and Europe), depending on the strain. For subjects 18 to <26 years of age (study B1971016), the proportion of subjects with a hSBA titer ≥LLOQ one month after Vaccination #3 with Trumenba was 66.7% to 98.8% for U.S. subjects and 71.3% to 99.3% for all subjects (U.S. and Europe), depending on the strain.

The hSBA responses to primary strains were not necessarily predictive of responses to secondary strains. Overall, the immunogenicity data from B1971009 and B1971016 verify and further describe the clinical benefit of Trumenba administered as a three-dose series (0, 1-2, and 6 months), to induce bactericidal antibodies against diverse MenB strains.

Lot consistency

The lot consistency was evaluated in study B1971009 and the objective was met. The 2-sided 95% CIs on the hSBA GMT ratios between any 2 of the 3 Trumenba lots using MenB strains PMB80 (A22) and PMB2948 (B24) were tested with a 2-fold margin and the results were within the pre-specified interval (0.5, 2.0), one month after Vaccination #3.

Concomitant vaccination

No immunological interference with meningococcal hSBA responses was observed when Trumenba was administered concomitantly with Menactra and Adacel vaccines compared to hSBA responses when Trumenba was

administered alone (study B1971015). Immune responses were evaluated by comparisons of GMTs for each of the Menactra and Adacel antigens one month after the first Trumenba vaccination, and hSBA GMTs using two MenB strains (variants A22 and B24) one month after the third Trumenba vaccination. The non-inferiority criteria for the comparisons of GMTs (lower limit of the 2-sided 95% CI of the GMT ratio (Group 1/Group 3 for MenB strains and Group 1/Group 2 for MCV4 and Tdap) > 0.67) were met for all antigens.

Clinical serology assays

The performance of each serological assay was evaluated and deemed appropriate for its intended use in the studies submitted to this application.

- The primary strains were validated and the secondary strains were qualified for the hSBA assays.
- Serum bactericidal assays (using (b) (4) complement (rSBA) and the (b) (4) IgG assay) were used to assess the responses to the polysaccharides in Menactra.
- The (b) (4) IgG assay was used to quantitate antibodies against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) to assess the responses to the polysaccharides in Adacel.

Statistical

There were no major statistical issues related to the submission. Primary results were confirmed by independent analyses from the statistical reviewer. The pre-specified immunogenicity objectives in the studies were met and supported the approval of the vaccine.

b) Pediatrics

This supplement did not contain a pediatric assessment.

4. Chemistry, Manufacturing and Controls (CMC)

   The product has not changed since the original BLA was approved and no new CMC information was submitted to this supplement.

5. Nonclinical Pharmacology/Toxicology

   N/A

6. Clinical Pharmacology

N/A

7. Safety

(*Extracted in part from Dr. Tina Chang's clinical review*)

The safety of Trumenba was evaluated in four randomized, controlled studies (B1971009, B1971016, B1971014, and B1971015) in this supplement. A total of 10,718 subjects received at least one dose of Trumenba and 4,497 subjects were included in control groups. The control group in studies B1971009 and B1971014 received hepatitis A virus vaccine (at 0 and 6 months) and saline (at 2 months). The control group in study B1971016 received 3 saline injections (at 0, 2 and 6 months). In study B1971015, Group 2 received 3 saline injections (at 0, 2, and 6 months) with Menactra and Adacel at 0 months. Solicited local reactions and systemic events were recorded on an e-diary in all studies except in the phase 3 study B1971014. Because the purpose of study B1971014 was to detect rare safety events, e-diaries were not used; therefore, reactogenicity events were reported as unsolicited adverse events (AEs).

Among the 10,718 subjects who received at least one dose of Trumenba, 48.0% of subjects were male and 84.3% were Caucasian, 11.6% were African-American, 1.4% were Asian, and 2.7% were characterized as "other."

In general, Trumenba was more reactogenic than the comparator (saline, HAV/saline or Menactra +Adacel, depending on the study) for local adverse reactions and systemic adverse reactions. The most common solicited adverse reactions in adolescents and young adults that occurred in ≥30% were pain at the injection site (≥85%), fatigue (≥60%), headache (≥55%) and muscle pain (≥35%).

In study B1971009, the proportion of subjects reporting AEs that led to study withdrawal was 0.82% in the combined Trumenba groups (receiving lots 1, 2 and 3) and 0.33% in the HAV/saline group. In study B1971016, the proportion of subjects reporting AEs that led to study withdrawal was 1.01% in the Trumenba group and 0.73% in the saline group. In study B1971014, the proportion of subjects reporting AEs that led to study withdrawal was 1.19% in the Trumenba group and 0.52% in the HAV/Saline group. In study B1971015, the proportion of subjects reporting AEs that led to study withdrawal was 1.4% in Group 1 (Menactra+Adacel+Trumenba) 0.6% in Group 2 (Menactra+Adacel+saline), and 0.7% in Group 3 (saline+saline+Trumenba).

The percentage of subjects with at least 1 SAE occurring during the time period from the first study vaccination through 6 months after last study vaccination was 1.89% in the HAV/saline group and 2.45% in the combined Trumenba groups in study B1971009 and 1.34% in the Trumenba group and 1.34% in the saline group for study B1971016. In study B1971014, 1.55% of subjects in Group 1

and 2.52% subjects in Group 2 reported serious adverse events (SAEs) throughout the study. In study B1971009 and B1971015, none of the SAEs were assessed as related to study vaccination by the investigators. In study B1971016, there were 3 (0.12%) SAEs (pyrexia, multiple sclerosis, and dystonia) in the Trumenba group and no SAEs in the saline group that were assessed as possibly related to study vaccination by the investigators. In study B1971014, there were 2 (0.05%) SAEs (neutropenia and anaphylactic reaction) in the Trumenba group and 2 (0.10%) SAEs (demyelination and spontaneous abortion) in HAV/saline group that were assessed as possibly related to study vaccination by the investigators.

Solicited local reactions within 7 days of vaccination

In adolescents in study B1971009, subjects in the combined Trumenba group (Lots #1-3) (93.0%) reported more local reactions than subjects receiving either HAV or saline (58.8%). Pain at the injection site was the most commonly reported local reaction and was reported in a higher proportion of subjects in the combined Trumenba group compared to the HAV/saline group after Vaccination #1 (86.7% and 47.0%, respectively), Vaccination #2 (77.7% and 15.2%, respectively), and Vaccination #3 (76.0% and 34.0%, respectively). Most cases were mild to moderate in severity. Redness at the injection site was reported in a higher proportion of subjects in the combined Trumenba group compared to the HAV/saline group after Vaccination #1 (16.2% and 1.3%, respectively), Vaccination #2 (12.5% and 0.6%, respectively), and Vaccination #3 (13.9% and 1.1%, respectively). Swelling at the injection site was reported in a higher proportion of subjects in the combined Trumenba group compared to the HAV/saline group after Vaccination #1 (18.0% and 2.2%, respectively), Vaccination #2 (13.9% and 0.6%, respectively), and Vaccination #3 (15.4% and 0.9%, respectively). In Study 1, mean duration of pain was 2.4 to 2.6 days (range 1-17 days), for redness 2.0 to 2.2 days (range 1-12 days) and for swelling 2.0 to 2.1 days (range 1-21 days) in the combined Trumenba group.

In young adults in study B1971016, subjects in the Trumenba group (90.0%) reported more local reactions within 7 days after each vaccination than subjects receiving saline (19.2%). Again, pain at the injection site was the most commonly reported local reaction and was reported in a higher proportion of subjects in the Trumenba group compared to the saline group after Vaccination #1 (84.2% and 11.8%, respectively), Vaccination #2 (79.3% and 7.8%, respectively), and Vaccination #3 (80.4% and 6.7%, respectively). Most cases were mild to moderate in severity. Redness at the injection site was reported in a higher proportion of subjects in Group 1 compared to Group 2 after Vaccination #1 (13.8% and 0.6%), Vaccination #2 (11.8% and 0.3%), and Vaccination #3 (17.1% and 0.2%). Swelling at the injection site was reported in a higher proportion of subjects in Group 1 compared to Group 2 after Vaccination #1 (15.5% and 0.6%), Vaccination #2 (14.0% and 0.4%), and Vaccination #3 (16.6% and 0.3%). In Study 2, mean duration of pain was 2.6 to 2.8 days (range 1-67 days), for redness

2.2 to 2.5 days (range 1-13 days) and for swelling 2.1 to 2.6 days (range 1-70 days) in the Trumenba group.

Solicited systemic reaction within 7 days of vaccination

In adolescents in study B1971009, a higher proportion of subjects in the combined Trumenba group reported any systemic events within 7 days compared to the HAV/saline group after Vaccination #1 (74.2% vs 60.4%, respectively), Vaccination #2 (59.4% vs 42.7%, respectively) and Vaccination #3 (55.7% vs 41.4%, respectively). A higher proportion of subjects reported systemic events after Vaccination #1 in the combined Trumenba group compared to the HAV/saline group (the control group received an injection of HAV) for fever (6.4% vs 1.9%), headache (51.8% vs 37.2%), fatigue (54.0% vs 40.3%), chills (25.3% vs 17.2%), muscle pain (24.4% vs 19.2%), joint pain (21.9% vs 13.6%), and a similar proportion of subjects reported vomiting (3.7% vs 1.9%) and diarrhea (10.6% vs 12.1%). After Vaccination #2, a higher proportion of systemic events was observed for the combined Trumenba group compared to the HAV/saline group (the control group received an injection of saline) for headache (37.8% vs 28.1%), fatigue (38.3% vs 26.3%), chills (16.0% vs 10.3%), muscle pain (17.8% vs 10.3%), and joint pain (16.7% vs 9.1%) and a similar proportion for fever (2.0% vs 1.5%), vomiting (2.2% vs 1.4%) and diarrhea (7.6% vs 9.1%). After Vaccination #3, a higher proportion of systemic events was observed for the combined Trumenba group compared to the HAV/saline group (the control group received an injection of HAV) for headache (35.4% vs 24.8%), fatigue (35.9% vs 24.4%), chills (13.1% vs 8.3%), muscle pain (17.6% vs 11.1%), joint pain (16.0% vs 8.9%), and a similar proportion for fever (2.7% vs 2.3%), vomiting (1.7% vs 2.2%), and diarrhea (7.7% vs 7.6%). Headache and fatigue were the most commonly reported systemic events in both groups. Overall a low rate of fever and a low rate of antipyretic use were reported in subjects receiving Trumenba and subjects receiving HAV vaccine/saline. The mean duration of systemic events was generally similar between the subjects receiving Trumenba and subjects receiving HAV/saline.

In young adults in study B1971016, a higher proportion of subjects in the Trumenba group reported any systemic events within 7 days compared to the saline group after Vaccination #1 (71.6% vs 60.5%, respectively), Vaccination #2 (56.8% vs 43.6%, respectively) and Vaccination #3 (56.9% vs 36.7%, respectively). Fatigue and headache were the most frequently reported systemic events in Group 1 and Group 2. After Vaccination #1, a higher incidence of systemic events was observed for Group 1 compared with Group 2 for headache (43.9% vs 36.2%), fatigue (50.9% vs 39.8%), chills (18.1% vs 9.8%), muscle pain (25.9% vs 14.5%), and joint pain (19.6% vs 10.9%). After Vaccination #2, a higher incidence of systemic events was observed for Group 1 compared with Group 2 for headache (33.1% vs 24.9%), fatigue (39.2% vs 27.3%), chills (12.4% vs 8.5%), muscle pain (15.6% vs 8.5%), and joint pain (15.1% vs 6.5%). After Vaccination #3, a higher incidence of systemic events was observed for Group 1 compared with Group 2 for fever (2.0% vs 0.6%), headache (32.5% vs 21.6%), fatigue (39.3% vs 24.5%),

chills (12.6% vs 6.4%), muscle pain (16.9% vs 7.5%), and joint pain (12.6% vs 5.3%). Overall, a low rate of fever and a low rate of antipyretic use were reported in subjects from Group 1 and 2 (2.7% and 0.6%, respectively). The mean durations of systemic events were generally similar between the subjects in Group 1 and Group 2.

Autoimmune and neuroinflammatory conditions

Twelve of 10,718 subjects (0.11%) who received Trumenba reported an autoimmune condition and 7 of 10,718 (0.07%) Trumenba recipients reported a neuroinflammatory condition. Six of 4,497 (0.13%) subjects categorized as controls reported an autoimmune condition and 4 of 4497 (0.09%) subjects categorized as controls reported a neuroinflammatory condition for comparison. Based on clinical review of individual cases, there was no conclusive evidence of excess risk of autoimmune or neuroinflammatory conditions among the overall population of Trumenba recipients. Five of the 12 subjects with autoimmune conditions had evidence of pre-existing disease prior to vaccination with Trumenba. In all, autoimmune and neuroinflammatory conditions reported in Trumenba recipients did not suggest a pattern of a common pathophysiological mechanism.

8. Advisory Committee Meeting

A Vaccines and Related Biologics Products Advisory Committee meeting was not held for this supplement, as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

9. Other Relevant Regulatory Issues

The two-dose schedule (a dose administered at 0 and 6 months) was approved on April 14, 2016, also under the accelerated approval regulations. As both the two-dose and three-dose schedules are mentioned in the package insert (PI), it is important to refer to the specific schedule that is being confirmed under this supplement (as the two-dose schedule has yet to be verified and further described).

The Applicant submitted post-dose 2 clinical data obtained after month two within the three-dose schedule. However, because this supplement was to confirm the original three-dose schedule, the immunogenicity data obtained after the second dose were not incorporated into the Trumenba PI. Only immunogenicity data obtained after the final dose in the series were included in the PI.

10. Labeling

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

During the review of this supplement, changes were made to the following sections of the Trumenba PI: Dosage and Administration (2.0), Adverse Reactions (6.0), Clinical Trials Experience (6.1), Pregnancy (8.1), Lactation (8.2), Immunogenicity (14.1), and Concomitant Vaccine Administration (14.2). No changes were made to the carton and container labeling. The notable changes in the specific subsections are described below.

The following statement was added under the Dosage and Administration section to provide guidance regarding the two-dose schedule: "If the second dose is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose." Revisions were made to the Adverse Reactions section to describe the most common solicited adverse reactions in adolescents and young adults (from studies B1971009 and B1971016). The safety results of two Phase 3 confirmatory studies (B1971009 and B1971016) replaced the Phase 2 data in the Clinical Trials Experience section (i.e., four new tables containing local and systemic adverse reactions replaced two comparable tables). Revisions were made to the Pregnancy and Lactation sections to be compliant with the format established by the 2014 Pregnancy and Lactation Labeling (PLLR) rule. The immunogenicity results of two Phase 3 confirmatory studies replaced the Phase 2 data in the Immunogenicity section (i.e., two new tables containing immunogenicity data replaced a comparable table). Additional descriptive information was added in the Concomitant Vaccine Administration section to describe 1) study 4 (B1971011) with respect to the administration of Trumenba with Gardasil that was reviewed under the original BLA and 2) study 5 (B1971015) with respect to the administration of Trumenba with Menactra and Adacel that was reviewed under this supplement. The final draft PI dated March 10, 2017, was reviewed by the review committee and found to be acceptable.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The immunogenicity data from two confirmatory clinical studies B1971009 and B1971016 confirm the clinical benefit of Trumenba for the primary strains and the breadth of coverage against a panel of diverse meningococcal group B strains. Thus, this supplement supports a recommendation for conversion of the Trumenba three-dose schedule (administered at 0, 1-2, and 6 months) from accelerated approval status to traditional approval, and removal of the following language from the highlights section of the PI: "the effectiveness of Trumenba against diverse serogroup B strains has not been confirmed." In contrast, since the two-dose schedule (a dose administered at 0 and 6 months) is still approved under the accelerated approval regulations, the following language will be

retained in the highlights section of the PI: "The effectiveness of the two-dose schedule of Trumenba against diverse *N. meningitidis* serogroup B strains has not been confirmed."

b) Risk/Benefit Assessment

The risk/benefit assessment of the three dose schedule of Trumenba is unchanged.

c) Recommendation for Postmarketing Activities

The review team made a determination that no new postmarketing commitments or postmarketing requirements were needed.