Application Type	Biologics License Application
STN #	125549/17
CBER Received Date	March 27, 2015
PDUFA Goal Date	April 25, 2016
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Lucia Lee, M.D.
Review Completion Date / Stamped Date	April 14, 2016
Supervisory Concurrence	Jeff Roberts, M.D., Chief, CRB1
Applicant	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Established Name	Meningococcal Group B Vaccine
Trade Name	Trumenba
Pharmacologic Class	Vaccine
Formulation	Each 0.5mL dose contains recombinant lipidated factor H binding protein (fHBP) variants from *Neisseria meningitidis* serogroup B (60µg fHBP subfamily A and 60µg fHBP subfamily B), 0.25 mg aluminum as AlPO4.
Dosage Form and Route of Administration	Liquid suspension, intramuscular
Dosing Regimens	• Three dose schedule: administer at 0, 1-2, and 6 months. • Two dose schedule: administer at 0 and 6 months.
Indication and Intended Population	Active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 years through 25 years of age. (No change to the indication or intended population)
Orphan Designated	No

TABLE OF CONTENTS

GLOSSARY

BLA	Biologics license application
fHBP	factor H binding protein
HPV	Human papillomavirus
hSBA	serum bactericidal activity with human complement
LLOQ	Lower limit of quantitation
LOD	Lower limit of detection
MenB	Meningococcal serogroup B
PeRC	Pediatric Review Committee
PREA	Pediatric Research Equity Act
SUSAR	Sudden unexpected safety adverse reaction
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. **EXECUTIVE SUMMARY**

Trumenba is a bivalent meningococcal group B vaccine that contains two factor H binding protein (fHBP) antigens from *Neisseria meningitidis* serogroup B. fHBP is a conserved, outer membrane lipoprotein and a virulence factor that contributes to the ability of *N. meningitidis* to avoid host defenses. Trumenba was approved by the FDA in October 2014, for use as a 3-dose series (0, 2 and 6 month schedule), in accordance with the regulations for accelerated approval [21 CFR 601.41].

The applicant submitted this efficacy supplement (STN125549/17) to request changes to the Trumenba dosing regimen. The clinical data support accelerated approval of a

- 3-dose schedule: a 0.5 mL dose administered at 0, 1-2, and 6 months
- 2-dose schedule: a 0.5 mL dose administered at 0 and 6 months.

The schedules enable flexibility in vaccination intervals depending on the risk of exposure months 1 and 6, and the patient's susceptibility to *N. meningitidis* serogroup B disease.

Immunogenicity of Trumenba

For both schedules, bactericidal antibodies to fHBP were measured using serum bactericidal activity with human complement (hSBA) assays. Five endpoints were assessed one month after a 2-dose series, and in a subset of subjects, after a third dose:

- The percentage of subjects with a ≥4-fold increase in hSBA titer compared to pre-dose #1 (each of four primary strains)
- The percentage of subjects with a composite response (defined as the % of subjects with hSBA titer ≥LLOQ for all four meningococcal primary strains)

The MenB primary strains (PMB80, PMB2001, PMB2948, and PMB2707) express fHBP variants A22, A56, B24 and B44, respectively, which are among the prevalent fHBP variants in the US. The endpoints were analogous to the primary endpoints agreed upon by CBER for the confirmatory studies.

3-dose schedule (0, 1-2, and 6 months)

Retrospective analyses of data for the 3-dose schedule were provided from three studies (B1971012, B1971011 and B1971010) that enrolled individuals 11 to <19 years of age from Europe and the US, and were studies that were previously submitted in BLA (STN 125549/0). The analyses of the 5 endpoints were descriptive; nonetheless, hSBA responses were evaluated in a substantial number of evaluable participants (2300 Trumenba participants received doses at 0, 1 and 6 months or 0, 2 and 6 months, and an additional ~200 received 2 doses at 0 and 2 months).

- Dosing interval: the proportions of subjects with a ≥4-fold increase in hSBA titer from baseline (pre-dose #1), compared by individual strain, were similar when two doses of Trumenba were administered at 0 and 1 month or 0 and 2 months, and accounted for variations in baseline titer.

- Dosing regimen: hSBA responses after a third Trumenba dose were notably higher, especially for the subfamily B variant-expressing strains, than corresponding hSBA responses after two doses. The composite response estimate was approximately 50% after the second dose (administered at 0

and 1-2 months) and approximately 80% after a third dose, indicating that a third dose was necessary if the interval between the first two doses was separated by 1 month.

2-dose schedule (0 and 6 months)

- Study B1971012 was already completed at the time of the applicant's proposal for a 2-dose schedule administered at 0 and 6 months. Therefore, comparisons of hSBA responses following the 2-dose schedule [Group #3] to hSBA responses after the 3-dose schedule by the CBER clinical reviewer were described without pre-specified formal statistical hypothesis testing. A longer interval between administration of the first and second dose (i.e., 1-2 months compared with 6 months between 1st and 2nd doses) resulted in higher percentages of participants with a ≥4-fold increase in post-vaccination hSBA titer (64.5% to 90.1%, depending on the individual MenB strain) compared to corresponding titers reported at baseline. The composite response after the second dose given at 6 months was 72.9%.

Safety of Trumenba

Overall (7 studies), 4,282 subjects 11 to <26 years of age received at least one dose of Trumenba, of which 2,557 subjects were enrolled in controlled trials. A total of 3924 subjects received at least one dose of Trumenba in the 3 main studies (B1971012, B1971011 and B1971010). For the 3-dose schedule, *post-hoc* analyses of serious adverse events (SAEs) defined by time intervals after completion of a 2-dose series (0 and 1-2 months), after the third dose and safety follow-up post-dose #3 indicated that SAE rates from studies B1971011, B1971012 and B1971010 combined were similar to SAE rates reported in the 7 studies overall. Analyses of safety data for the 2-dose schedule (0 and 6 months) were the same as the analyses included in the individual study report for study B1971012. There were no new concerns identified from a review of the SAEs after either the 3-dose (0, 1-2 and 6 months) or a 2-dose schedule (0 and 6 months).

Safety and immunogenicity in other age groups

Extrapolation of the safety and immunogenicity (inferred effectiveness of Trumenba in adolescents to two age groups (10 to <11 and 19 to <26 years of age) is supported because the mechanism of protection against invasive meningococcal serogroup B disease, hSBA responses and safety profile following Trumenba vaccination are expected to be sufficiently similar in each of the age groups compared to adolescents. The confirmatory studies conducted as a requirement for accelerated approval of Trumenba includes all age groups (10 to <26 years of age).

Post-marketing Actions

- 3-dose schedule: a change in the existing 3-dose schedule did not result in additional post-marketing actions with regard to accelerated approval or PREA requirements. Please see the approval letter for STN 125549.0.
- 2-dose schedule: post-marketing requirements
  - In accordance with the accelerated approval regulations, a confirmatory study in the post-marketing period will be conducted to evaluate Trumenba further, to verify and describe the clinical benefit in individuals 10 to <26 years of age, by demonstrating the effectiveness of Trumenba against meningococcal B strains that represent an extended range of antigenically diverse fHBP variants.

- PREA: a study will be conducted in children 1 to <10 years to evaluate safety and immunogenicity of a 2-dose regimen (0 and 6 months) of Trumenba in children 1 year to less than 10 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

There were no notable differences in hSBA responses or SAE rates among female and male participants. No meaningful conclusions could be made about differences in immunogenicity or SAE rates by age, race or ethnicity since all of the participants were adolescents (11 to <19 years of age; no young adults 19 to <26 years ofage), mostly White and non-Hispanic/non-Latino.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition Studied

Neisseria meningitidis is a significant cause of endemic and epidemic invasive meningococcal disease worldwide. Six serogroups (A, B, C, W, X and Y) are responsible for the majority of clinical disease, which is commonly meningitis and septicemia. A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, and seizure disorder) and approximately 10% of cases are fatal.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Capsular polysaccharide vaccines and polysaccharide-protein conjugate vaccines are currently licensed and available in the US for prevention of meningococcal disease caused by serogroups A, C, Y and W. Two meningococcal protein vaccines (Trumenba, Wyeth Pharmaceuticals, Inc.; Bexsero, Novartis Vaccines and Diagnostics, Inc.) are licensed and available in the US for prevention of meningococcal serogroup B disease.

2.3 Safety and Efficacy of Pharmacologically Related Products

Please see section 2 of the clinical review for STN# 125549/0.

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

Trumenba is not licensed in countries outside the US.

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

Pertinent Regulatory history

- STN 125429\0: Trumenba administered as a 3-dose series (at 0, 2 and 6-months) was approved for use in in individuals 10 through 25 years of age.
  - The effectiveness of Trumenba was inferred based on the ability of the vaccine to induce bactericidal antibodies (surrogate marker) to fHBP, as measured by hSBA assays using a MenB test strain. Use of a serological marker to demonstrate effectiveness of MenB vaccines was discussed at a VRBPAC meeting held in April 2011; the committee advised that hSBA could provide evidence for inferring vaccine effectiveness.
  - Selection of four primary strains were based on fHBP surface expression levels on MenB invasive disease isolates, fHBP variants that were heterologous compared to vaccine antigen variants, and prevalent fHBP variants (variants B24 and A22) expressed on MenB disease isolates in the US.

Reviewer Comment: Regulatory review of hSBA responses to Trumenba (inferred effectiveness) administered as a 3-dose were based principally on analyses of hSBA post-vaccination #3 data; the assessment of certain adverse events (e.g., SAEs) were defined by time periods through the completion of the 3rd dose and the follow-up period thereafter.

- IND 13812: a proposal was submitted to the IND, in preparation for sBLA submission (STN 125549/17), to change the Trumenba dosing schedule from a 3-dose primary series to a 2-dose primary series at least one month apart and an optional booster dose given at least four months after the second dose. CBER requested additional immunogenicity and safety (SAEs only) analyses, updated statistical analysis plan and associated datasets/statistical programs to be included in the sBLA.

  Reviewer Comment: The immunogenicity data submitted in the sBLA (STN 125549/17) supported flexibility in the intervals between vaccinations in the 3-dose schedule, but not a change in the number of doses (i.e., third Trumenba dose was not optional) when the first two doses were administered at 0 and 1-2 months. The "booster" dose is hereafter referred to as the third Trumenba dose.

- During the review of this sBLA (STN 125549/17),
  Clinical review of the immunogenicity data provided in the sBLA did not support the initial proposed schedule. The immunogenicity data supported flexibility in the timing of the second dose administered, but not the number of doses in the existing 3-dose schedule (i.e., third dose was not optional) when the first two doses were administered at 0 and 1-2 months. Subsequently, the applicant restated the initial schedule as a 3-dose series administered at the same time points, and proposed a new 2-dose schedule (0 and 6 months) for the following reasons:
  - 3-dose schedule: 2 doses administered at least 1 month apart followed by a third dose given at least 4 months after the second dose. The applicant referred to this schedule as an "accelerated" schedule since a shorter vaccination interval between the first and second dose may be beneficial in certain situations when an individual might be at significantly high risk of exposure to serogroup B meningococci during the 1- and 6-month time period, such as during an ongoing outbreak of invasive meningococcal disease.
  - 2-dose schedule (0 and 6 months): The applicant referred to this schedule as the "standard" schedule intended to improve vaccination compliance in situations when a longer interval between vaccinations was possible without increasing the risk of exposure to serogroup B meningococci, such as immunization of the general population of adolescents and young adults who might be vaccinated with MenB vaccine at the discretion of the treating clinician.

  Reviewer Comments:
  - The applicant's proposed terms for standard and accelerated dosing regimens, respectively, for the 2-dose and 3-dose schedules were unsubstantiated since both schedules were completed at 6 months.
  - The accelerated approval of Trumenba administered at 0 and 6 months was assessed independently of accelerated approval of the 3-dose schedule. The criteria for accelerated approval of Trumenba administered at 0 and 6 months met the criteria in accordance with statutory regulations [21 CFR 601.41].

2.6 Other Relevant Background Information

In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of MenB vaccines in certain groups of individuals ≥10 years of age who are at increased risk for serogroup B meningococcal disease, including individuals who are identified as being at risk to develop MenB disease during an ongoing MenB disease outbreak. In June 2015, the ACIP recommended that adolescents and young adults may be vaccinated with a MenB vaccine at the discretion of the treating clinician.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Immunogenicity and safety studies included for review in this supplemental application were conducted in accordance with Good Clinical Practice (GCP) and International Committee on Harmonization guidelines.

3.3 Financial Disclosures

The financial disclosure information for the studies included in this sBLA was reviewed in STN #125549/0.

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

4.1 Chemistry, Manufacturing, and Controls

n/a

4.2 Assay Validation

n/a

4.3 Nonclinical Pharmacology/Toxicology

n/a

4.4 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. The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with Trumenba is dependent on the antigenic similarity of the bacterial and vaccine fHBPs and the amount of fHBP expressed on the surface of the invading meningococci.

4.5 Statistical

The CBER statistical review memo highlighted the following limitations of the data submitted in the sBLA: the amended Statistical Analysis Plan (SAP) contained modified objectives that differed from the protocol-specified objectives; the data provided by the applicant in support of changing the 3-dose schedule were based on *post-hoc* analyses.

> *Reviewer Comment:* Analysis populations were defined retrospectively by the applicant to provide the appropriate analyses for the proposed change in the 3-dose schedule; immunogenicity data generated with 4 primary strains was a reasonable approach, from a clinical perspective, for assessment of alternatives to an existing schedule that is still approved in accordance with the regulations for accelerated approval (immunogenicity data from the confirmatory studies has not been submitted yet). Analyses of ≥4-fold increases in hSBA titer compared to baseline (individual primary strains) and composite hSBA response to all primary strains, though retrospective, were relevant to the review of the proposed schedules. Regulatory considerations for accelerated approval of the proposed schedules took into consideration the continued public health urgency for control of MenB outbreaks. The endpoints were analogous to the primary endpoints agreed upon by CBER for the confirmatory studies.

The study design of the Trumenba 2-dose confirmatory study was discussed at the January monthly committee meeting. The statistical justification included in the concept protocol was reviewed by the CBER statistical reviewer (see change in committee assignment), who had no comments for the applicant.

4.6 Pharmacovigilance

n/a

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

5.1 Review Strategy

An extensive review of the immunogenicity and safety data from phase 2 studies B1971012, B1971011 and B1971010 and safety data from 7 studies was included in the clinical review of the BLA (STN 125549/0). No changes were made to the individual study reports, including analyses of solicited AEs, non-serious unsolicited AEs and autoimmune and neuroinflammatory events in preparation for submission of this sBLA (STN 125549/17). Therefore, only the characteristics of the phase 2 studies relevant to the schedules proposed in this sBLA (STN 125549/17) are described in this memo.

Evaluation of Immunogenicity: Post-hoc analyses from studies B1971012, B1971011 and B1971010 were based on the evaluable (per-protocol), per-schedule evaluable (study B1971012 only) and mITT immunogenicity populations defined for timepoints 1 month after the 2-dose series and the third Trumenba dose. Please see Section 6.0 (General Technical Statistical Information) of the CBER statistical review for further details.

Five main endpoints were evaluated

- For each of 4 primary strains, the proportion of participants with a ≥4-fold increase in hSBA titer (after the 2-dose series and after the dose #3) compared to pre-dose #1. Primary strains PMB80,

PMB2001, PMB2948, and PMB2707 correspond to strains expressing variant A22, A56, B24, and B44.

- Composite response, defined as the proportion of participants with hSBA response ≥ the lower limits of quantitation (LLOQs) for all 4 primary strains.

Evaluation of Safety: The number and percentage of subjects reporting at least one SAE were defined for 4 time periods.

- 2-dose series: All subjects who received at least 1 dose of the investigational product and for whom safety information was available from study entry through the post-vaccination #2 visit.
- 2-dose series follow-up: All subjects who received at least 1 dose of investigational product and for whom safety information was available from the post-vaccination #2 visit (i.e., 1 month after vaccination 2) to before the third dose visit.
- Third dose: All subjects who received the first 2 vaccinations and a third dose, and for whom safety information was available within 1 month after the third dose visit.
- Third dose follow-up: All subjects who received the first 2 vaccinations and a third dose, and for whom safety information was available from 1 month after the third dose visit to the post-dose #3 follow-up visit. Subjects were included in the analyses according to the investigational product received.

5.2 sBLA Documents That Serve as the Basis for the Clinical Review

All information in the following modules (m) and sections (s) of the sBLA were reviewed:
Amendment 0: m1 (s1.9 Pediatric study plan, Requests for partial waiver and deferral of pediatric studies, s1.4 Labeling); m2 (s2.5 Clinical overview, s2.7 Clinical summary).
Amendment 1: m1 (s1.11 Responses to CBER information requests [IR] dated 18-March-2015 [part 1] for analysis populations and immunogenicity data); m5 (s5.3.5.3 Statistical analysis plan addendum).
Amendment 2: m1 (s1.11 Responses to CBER IR dated 18-March-2015 [part 2] for safety populations and safety data, s1.4 Labeling).
Amendment 3: m1 (s1.9 revised Pediatric Study Plan, Requests for partial waiver and deferral of pediatric studies).
Amendment 4: m1 (s1.11 Responses to CBER IR dated 28 July 2015 for study B1971012).
Amendments 5-8: m1 (s1.4 Labeling).
Amendment 9: m1 (s1.11 Responses to CBER IR dated 05-Nov-2015, Question #1: justification for new dosing regimen [0- and 6-month schedule])
Amendment 10: m1 (s1.9 updated requests for partial waiver and deferral of pediatric studies, s1.4 Labeling; s1.11 Responses to CBER IR dated 05-Nov-2015, Question #2-4: status for antibody persistence data, PREA requirements- additional details).
Amendment 12: m1 (s1.11 Responses to CBER IR dated 13-Jan-2016: additional information for concept protocol).
Amendment 13: m1 (s1.4 Labeling).

5.3 Table of Studies/Clinical Trials

Overview of Clinical Trials
The main immunogenicity studies are summarized in the following table:

Table 1. Overview of Immunogenicity Studies

Study # (Region)	Study Objectives	Age (years)	Vaccination Schedule (months [m]) Study Group	Number of Randomized Trumenba Subjects
B1971011 (US)	Safety and immunogenicity of HPV4 co-administered with Trumenba, and Trumenba without HPV	11 to <18	Trumenba + HPV4 at 0, 2 and 6m Trumenba + saline at 0, 2 and 6m	999 998
B1971012 (Europe)	Safety and immunogenicity of Trumenba administered according to 2- or 3-dose schedules	11 to <19	Group #1: 0, 1 and 6m Group #2: 0, 2 and 6m Group #3: 0 and 6m Group #4: 0 and 2m	427 430 427 286
B1971010 (Europe)	Safety and immunogenicity of DTaP-IPV co-administered with Trumenba	11 to <19	Trumenba (0, 2 and 6m) + dTaP-IPV (0m; saline at 2 and 6m)	373

HPV4= Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [Gardasil].
dTap-IPV= Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) [Repevax].

Safety: In 7 studies, a total of 4335 subjects received at least one dose of Trumenba, of which 4282 subjects were 11 to ≤25 years of age. Detailed descriptions of the studies (B1971003, B1971004, B1971005, B1971010, B1971011, B1971012 and B1971042) were included in Section 6 of the clinical review for STN 125549/0.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study B1971012

NCT# 01299480

Title: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Bivalent rLP2086 Vaccine When Administered in Either 2- or 3-Dose Regimens in Healthy Subjects Aged ≥11 to <19 Years.

Study B1971012 was conducted in Europe (Czech Republic, Denmark, Finland, Germany, Poland, Spain and Sweden).

6.1.1 Objectives (Primary, Secondary, Exploratory)

The protocol-specified primary objectives were to assess hSBA responses when Trumenba was administered at 0, 1 and 6 months (Group 1) or at 0, 2 and 6 months (Group 2), as measured by hSBA assay performed with four MenB primary strains after the 3rd Trumenba vaccination. The proportion of subjects with hSBA titer ≥LLOQ, for each strain, were the primary endpoints.

> *Reviewer comment:* The hypotheses tested for Groups 1 and 2 were not relevant to clinical development of Trumenba in the US, since the primary endpoints for phase 3 studies were not based on the proportion of subjects with a hSBA titer ≥LLOQ.

The protocol-specified secondary objectives were to describe hSBA responses (GMTs, distribution of titers) among study groups who received a 2-dose series [Groups #3 and #4] or a 3-dose series [Groups

#1 and #2]. The exploratory objectives were to describe the hSBA responses (% of subjects with a ≥4-fold response for each strain and composite response to all strains) for all study groups. The secondary and exploratory endpoints were assessed using hSBA assays performed with the four MenB primary strains.

Reviewer comment:
Additional exploratory objectives to describe hSBA responses to Trumenba (Groups #1 and #2) after a 2-dose series and after a booster (3rd) dose were included in an amended SAP (SAP for 2-dose series related analyses, version 1.0, dated 22-Apr-2015). The protocol objectives were not changed since the study had already been completed at the time the SAP was amended.

In the context of this sBLA, the main endpoints were:

- ≥4-fold response
  For each of the 4 primary strains, (1) For subjects with a baseline hSBA titer <1:4, a ≥4-fold increase was defined as an hSBA titer ≥1:16. (2) For subjects with a baseline hSBA titer ≥1:4, a ≥4-fold increase was defined as an hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer.
- Composite response
  The % of subjects achieving a composite hSBA response, defined as hSBA titer ≥LLOQ for all 4 primary strains, for each post-vaccination time point.

Primary strains: PMB80 [A22], PMB2948 [B24], PMB2001 [A56] and PMB2707 [B44].
LLOQ = hSBA titer of 1:16 for A22; 1:8 for A56, B24, and B44.

6.1.2 Design Overview

Table 2. Study B1971012. Study Design

Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Description	Injection #1 and Blood Draw	Injection #2	Injection #3 and Blood Draw	Blood Draw	Injection #4	Blood Draw	Telephone call
Approximate Month	Month 0	Month 1	Month 2	Month 3	Month 6	Month 7	6m after last study vaccination
Visit window prior to study pause (per-schedule)	Day 1	28 to 42d After Visit 1	56 to 70d After Visit 1*	28 to 42d After Visit 3	105 to 126d After Visit 3	28 to 42d After Visit 5	
Visit window after study pause	Day 1	28 to 132d After Visit 1	56 to 160d After Visit 1*	28 to 42d After Visit 3	105 to 156d After Visit 3	28 to 42d After Visit 5	168 to 196d After Visit 5
Group 1	Trumenba	Trumenba	Saline		Trumenba		
Group 2	Trumenba	Saline	Trumenba		Trumenba		
Group 3	Trumenba	Saline	Saline		Trumenba		
Group 4	Trumenba	Saline	Trumenba		Saline		

*Visit 3 must be at least 21 days after vaccination at Visit 2.

Subjects were randomized in a 3:3:3:2 ratio to the following study groups and vaccination schedules: Group #1 (0, 1 and 6 months): Group #2 (0, 2 and 6 months): Group #3 (0 and 6 months): Group #4 (0 and 2

months).Study participants, but not the study investigator and the applicant, were blinded to their allocated vaccine group (i.e. single blinded).

Vaccine composition: Trumenba (0.5 mL dose): contains 60ug of fHBP from subfamily A and 60ug of fHBP from subfamily B, polysorbate 80 (in [redacted]), 0.25 mg of aluminum as AlPO4 (stabilizer). Packaged as a liquid in a pre-filled syringe. Administered intramuscularly (IM).

6.1.3 Population

(Healthy individuals ≥11 to <19 years of age.)

6.1.4 Surveillance/Monitoring

The safety evaluation included an assessment of immediate adverse reactions (20 minutes or longer, depending on the study site) solicited local and systemic reactions (within 7 days after each vaccination); general non-serious, AEs (through one month after the 3rd vaccination); SAEs, medically attended AEs (defined as a non-serious AE that resulted in an evaluation at a medical facility) and newly diagnosed chronic medical conditions (including neuroinflammatory and autoimmune conditions) through 6 months after the last vaccination.

6.1.5 Statistical Considerations & Statistical Analysis Plan

Primary Hypotheses (based on the protocol-specified primary objectives)
The percentage of subjects with ≥LLOQ is >50% for each of the 4 strains (Groups #1 and #2).

Reviewer comment: The hypotheses tested for Groups #1 and #2 were not relevant to clinical development of Trumenba in the US, since the primary endpoints for phase 3 studies in support of US licensure were not based on the proportion of subjects with a hSBA titer ≥LLOQ.

Pertinent changes

- Study B1971012 SAP, version 3, dated 10-Sept-2012
  Study enrollment and further vaccinations were paused during a review of a SUSAR (a 15-year old participant experienced vertigo associated with ataxia, chills and headache 1 hour after the 2nd dose of Trumenba) by the external data monitoring committee (EDMC). The study resumed 2 to 3 months later; the protocol (amendment 2, dated 25-Jul-2011) and the SAP ("Study B1971012 SAP", version 3, dated 10-Sept-2012) were amended to extend the time period for vaccination at Visits 2 and 3 (Month 1 and 2, respectively) by 90 days and by 30 days for Visit 5 (Month 6).

  Sensitivity analyses were performed by the applicant to assess any effect of delayed vaccination (all study groups) on the hSBA responses observed among participants who received Trumenba as randomized and according to the vaccination windows defined before (per-schedule) and after (out-of-schedule) the study pause.

  Per-schedule immunogenicity populations
  - Group #1: Subjects were included in the analysis of the 0, 1, 6m schedule if they received dose #2 within 28-42 days after dose #1 and dose #3 within 161-196 days after dose #1 (i.e. 0, interval of 28-42 days between the first and second dose and an interval of 161-196 days between the first and third dose).

- Group #2: Subjects were included in the analysis of the 0, 2, 6m schedule if they received dose #2 within 56-70 days after dose #1 and dose #3 within 105-126 days after dose #2 (i.e. 0, 56-70 days and 161-196 days).

- SAP for 2-dose series related analyses, version 1.0, dated 22-Apr-2015
  Included additional exploratory objectives (see Reviewer comment in the Objectives section); included the following analysis populations for Group #1 and Group #2:

hSBA post-vaccination #2

- Evaluable immunogenicity population: randomized subjects who were eligible for the study (through one month post-vaccination #2), received the 1st two doses of Trumenba at the corresponding scheduled visit, had blood samples obtained pre-vaccination #1 and 28-42 days after vaccination #2, at least one valid and determinate assay result for the post-vaccination #2 analyses, received no prohibited vaccines or treatment through 1 month post vaccination #2, and had no major protocol violations through 1 month post vaccination #2.

- Modified intent-to-treat (mITT) immunogenicity population: subjects who were randomized and had at least one valid and determinate assay result for the 2-dose series analyses.

hSBA post-vaccination #3

- Evaluable immunogenicity population: randomized subjects who were eligible for the study (through one month after the third dose), received all 3 doses of Trumenba at the corresponding scheduled visit, had blood samples obtained pre-vaccination #1 and 28-42 days after vaccination #3, at least one valid and determinate assay result for the third dose analyses, received no prohibited vaccines or treatment through 1 month after the third dose, had no major protocol violations through 1 month after the third dose.

- mITT immunogenicity population: subjects who were randomized, received two doses of investigational product, and had at least one valid and determinate assay result for the third dose analyses.

Reviewer Comment: Sensitivity analyses for the populations defined in the SAP dated 22-Apr-2015 were also performed by the applicant for Groups #1 and #2 to assess any effect of delayed vaccination of the 2nd and 3rd doses on the hSBA responses observed among participants who received Trumenba as randomized and according to the vaccination windows defined before (per-schedule) the study pause.

Group 4, by design, received only 2 doses of vaccine. Thus, the definitions of the evaluable and mITT immunogenicity populations, and populations for the sensitivity analyses (e.g., per-schedule evaluable immunogenicity population), as defined in Study B1971012 SAP v3 (dated 10-Sept-2012), were unchanged.

For all analyses of the evaluable populations, subjects were included as randomized.

Safety populations (Groups #1 and #2)

- 2-dose series: All subjects who received at least 1 dose of the investigational product and for whom safety information was available from study entry through the post-vaccination #2 visit.

- 2-dose series follow-up: All subjects who received at least 1 dose of investigational product and for whom safety information was available from the post-vaccination #2 visit (i.e., 1 month after vaccination 2) to before the booster dose visit.
- Vaccination #3: All subjects who received the first 2 vaccinations and a booster (3rd) dose and for whom safety information was available within 1 month after the booster (3rd) dose visit.
- Vaccination #3 follow-up: All subjects who received the first 2 vaccinations and a booster (3rd) dose and for whom safety information was available from 1 month after the booster (3rd) dose visit to the booster (3rd) dose follow-up visit. Subjects were included in the analyses according to the investigational product received.

6.1.6 Study Population

With regard to a shortened interval for the first two doses (i.e., change from 2 months to at least 1 month) results from Groups #1, 2 and 4 were taken into consideration for the proposed change.

6.1.6.1 Populations Analyzed

Table 3. Study B1971012. Immunogenicity Populations[a]

Population	Group 1 (0, 1 and 6 months) n(%)	Group 2 (0, 2 and 6 months) n(%)	Group 3 (0 and 6 months) n(%)	Group 4 (0 and 2 months) n(%)
Randomized	427 (100)	430 (100)	427 (100)	286 (100)
mITT[b]	426 (99.8)	430 (100)	426 (99.8)	286 (100)
Evaluable immunogenicity population	365 (85.5)	360 (83.7)	371 (86.9)	241 (84.3)
Per-schedule evaluable immunogenicity population[c]	**193 (45.2)**	**165 (38.4)**	**209 (48.9)**	**173 (60.5)**

Source: Response Document dated 05-Aug-2015.pdf, Table 1, page 6; Study B1971012 report body.pdf , Table 13, page 70.
[a] number (and %) of subjects in the last dose in the 3-dose (Groups #1 and #2) or 2-dose series (Groups #3 and #4).
[b] 2-dose series mITT population: Group #1 n (%)= 395 (92.5%), Group #2 n (%)= 383 (89.7%).
[c] 2-dose series Per-Schedule evaluable population: Group #1 n (%)= 197 (46.1%), Group #2 n (%)= 246 (57.2%).

Reviewer Comment: A substantial number of subjects were excluded from the evaluable immunogenicity population because the administration of the second and third vaccinations was temporarily paused during a safety review. The results from sensitivity analyses for study groups described above (Groups #1, #2 and #4) indicated that the delay in vaccinations did not have an effect on the observed hSBA responses (See section 6.1.7 of this review).

Table 4. Study B1971012. Summary of Subjects Reporting at Least 1 Serious Adverse Event for Each Analysis Interval- Safety Populations

Population	Group 1	Group 2	Group 3	Group 4
2-Dose series vaccination phase	426	414	451	277
2-Dose series follow-up phase	426	414	437	271
Third dose vaccination phase	383	382	NA	NA
Third dose follow-up phase	383	382	NA	NA

Source: Response Document dated 15-May-2015.pdf, Table 10, pages 41-42; Study B1971012 report body.pdf , Table 32, pages 185-186.

6.1.6.1.1 Demographic and other Baseline Characteristics

The overall safety population (all study groups) consisted of 50.8% male participants and 49.2% female participants; the median age was 14 years (36.6% of participants were 11 to <14 years age and 63.4% were age 14 to <19 years). The population overall were 99.0% White, 0.1% Black, 0.3% Asian, and 0.6% of participants were classified as 'other'. The demographic and other baseline characteristics of the per-schedule evaluable immunogenicity population and the population who received study products as administered were similar to the randomized population.

Reviewer Comment
The subjects in this trial were largely White, which differs from the racial composition of the U.S. population. The number of subjects in the Black, Asian and 'other' groups were too small to make meaningful conclusions about the effect of race on the immunogenicity of Trumenba.

6.1.6.1.2 Subject Disposition

Table 5. Study B1971012. Subject Disposition (Study Groups as Randomized)

Disposition of Subjects	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	Group 4 n(%)
Randomized	427	430	427	286
Withdrawn before vaccination	0	0	1 (0.2)	1 (0.3)
2-Dose series vaccination phase - completed	401 (93.9)	405 (94.2)	386 (90.4)	266 (93.0)
2-Dose series vaccination phase - withdrawn	26 (6.1)	25 (5.8)	40 (10.0)	19 (6.6)
2-Dose series follow-up phase - completed	386 (90.4)	396 (92.1)	386 (90.4)	261 (91.3)
2-Dose series follow-up phase - withdrawn	15 (3.5)	9 (2.1)	0.0 (0.0)	5 (1.7)
Third dose vaccination phase - completed	385 (90.2)	395 (91.9)	NA	NA
Third dose vaccination phase - withdrawn	1 (0.2)	1 (0.2)	NA	NA
Third dose follow-up phase - completed	385 (90.2)	395 (91.9)	NA	NA
Third dose follow-up phase - withdrawn	0 (0.0)	0 (0.0)	NA	NA
Completed the 6 Month follow-up contact	412 (96.5)	419 (97.4)	405 (94.8)	273 (95.5)

Source: Response document (dated 15-May-2015).pdf, Tables 8 and 9, pages 35, 36, 38 and 39; Study B1971012 report body.pdf , Table 9, page 57-59.
n = Number of subjects with the specified characteristic.
2-Dose series vaccination phase = vaccination #1 Visit to 1 month after the vaccination #2 Visit.
2-Dose series follow-up phase = 1 month after the Visit vaccination 2 to the vaccination #3 Visit.
Third dose vaccination phase = through 1 month after the Visit for vaccination #3.
Third dose follow-up phase = 1 month after the Visit for vaccination #3 through the end of the study.

6.1.7 Immunogenicity Results

% of participants with a ≥4-Fold Rise in hSBA Titer and Composite Response

Table 6. B1971012. Percentage of Participants with ≥4-Fold Increase in hSBA Titer and Composite Response (Per-Schedule Evaluable Immunogenicity Population)

	Group 1 (0, 1 and 6 months)	Group 2 (0,2 and 6 months)	Group 3 (0 and 6 months)
≥4-fold increase in hSBA titer[b] fHBP variant[c] Time point	**%[d] (95% CI)**	**%[d] (95% CI)**	**%[d] (95% CI)**
A22			
Post-dose #2	58.8 (51.4, 66.0)	72.5 (66.4, 78.0)	82.3 (76.3, 87.3)
Post-dose #3	77.6 (70.9, 83.4)	87.7 (81.6, 92.3)	N/A
A56			
Post-dose #2	87.8 (82.2, 92.2)	90.7 (86.2, 94.1)	90.1 (85.1, 93.8)
Post-dose #3	91.2 (86.1, 94.9)	93.8 (88.8, 97.0)	N/A
B24			
Post-dose #2	51.1 (43.6, 58.5)	54.2 (47.7, 60.7)	64.5 (57.4, 71.1)
Post-dose #3	74.1 (67.1, 80.2)	78.3 (71.1, 84.4)	N/A
B44			
Post-dose #2	48.1 (40.7, 55.6)	53.4 (46.8, 59.9)	66.0 (58.9, 72.6)
Post-dose #3	80.9 (74.5, 86.2)	78.6 (71.4, 84.7)	N/A
Composite response (hSBA titer ≥LLOQ for all 4 primary strains)	**%[d] (95% CI)**	**%[d] (95% CI)**	**%[d] (95% CI)**
Before dose #1	4.6 (2.0, 8.8)	2.2 (0.7, 5.0)	1.5 (0.3, 4.4)
Post-dose #2	52.0 (44.3, 59.7)	52.0 (45.3, 58.6)	72.9 (65.9, 79.1)
Post-dose #3	80.3 (73.7, 85.9)	81.8 (74.9, 87.4)	N/A

Source: Response document (dated 30-Apr-2015): Table 20, pages 53-54; Response Document (dated 05-Aug-2015): Table 2, page 8; Study B1971012 addendum report body.pdf , Table 6.30, pages 128-129.

hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; CI= confidence interval

[a] ≥4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titer <1:4, a ≥4-fold increase was defined as a hSBA titer ≥1:16. (2) For subjects with a baseline hSBA titer ≥1:4, a ≥4-fold increase was defined as a hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer.

[b] Strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively. LLOQ = 1:16 for A22 and 1:8 for A56, B24 and B44.

[c] %= n/N= number of subjects with a ≥4-fold increase 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.

Group 1 (0, 1, and 6 months): N=173-187 after dose 2 and N=178-188 after dose 3, depending on the strain.
Group 2 (0, 2, and 6 months): N=229-240 after dose 2 and N=159-162 after dose 3, depending on the strain.
Group 3 (0 and 6 months): N=188-203 after dose 2.

[d] Composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains): %=n/N= number of subjects with observed hSBA titer ≥ LLOQ for all 4 primary strains at the given time point/ number of subjects with valid and determinate hSBA results on all 4 strains at the given time point.

Group 1 (0, 1, and 6 months): N=184 pre-dose 1, N=174 after dose 2 and N=173 after dose 3.
Group 2 (0, 2, and 6 months): N=157 pre-dose 1, N=152 after dose 2 and N=157 after dose 3.
Group 3 (0 and 6 months): pre-dose 1 N=237 and N=201 after dose 2.

Reviewer Comment:

Group #1: 87.4% of Group #1 subjects received the second dose at 28 to 42 days after the first dose. Comparisons of the hSBA antibody responses based on the evaluable and per-schedule evaluable populations indicate that the delay (i.e., vaccination window for the third dose was extended by 30 days) between the first and third doses did not have an effect on the observed hSBA responses.

Group #2: Comparison of the hSBA antibody responses based on the evaluable and per-schedule evaluable populations indicate that the delay (vaccination window for the 2nd dose extended by 90 days) between the 1st and 2nd doses, and delay (i.e., vaccination window extended by 30 days) between the 2nd and 3rd doses did not appear to have a negative effect on the observed hSBA responses following completion of the 3-dose series.

Descriptive comparisons of hSBA responses in Group #3 to responses in Groups #1 and #2 indicate that the proportions of subjects with a ≥4-fold increase in hSBA titer after 2 doses at 0 and 6 months were lower, especially with the B strains, than the corresponding hSBA responses after either of the 3-dose schedules (with one exception: ≥4-fold response using A22 in Group #1 subjects). However, the 95% CIs for the proportions of subjects with a ≥4-fold Increase in hSBA titer and for the composite response were mostly overlapping between Group#3 (0,6m) and 3-dose schedules (Groups #1 and #2).

Group 4 (0 and 2 months)

Per-Schedule Evaluable Immunogenicity population: The percentages of subjects in Group #4 with a ≥ 4-fold increase in hSBA titer (post-dose #2 compared to pre-dose #1) were 74.3% for A22, 93.3% for A56, 56.1% for B24 and 57.2% for B44. The percentage of subjects with a composite hSBA response (hSBA titer ≥LLOQ for all 4 primary strains) before and after the 2nd dose was 5.6% and 57.8%, respectively.

Reviewer Comment: The results for the 2-dose series in Group #4 (0 and 2 month schedule) were consistent with corresponding results for Group #2 (0, 2, and 6 month schedule).

Other Endpoints

% of hSBA titer ≥ LLOQ Pre-dose #1

Per-Schedule Evaluable Immunogenicity population; LLOQ= 1:16 for A22 and 1:8 for A56, B24 and B44.
Group #1: 30.2% (A22), 24.3% (A56),17.5% (B24) and 5.6% (B44).
Group #2: 19.8% (A22), 22.2% (A56),13.6% (B24) and 4.1% (B44).
Group #3: 22.5% (A22), 19.3% (A56),12.9% (B24) and 5.2% (B44).
Group #4: 22.5% (A22), 17.9% (A56),13.2% (B24) and 8.8% (B44).

6.1.8 Safety Results

6.1.8.1 Deaths

None.

6.1.8.2 Serious Adverse Events

A total of 37 subjects reported 40 SAEs during the study period:

- During the 2-dose series vaccination phase, 3 SAEs (3 subjects [0.7%]) were reported in Group #1 (leg fracture, migraine, deep venous thrombosis [attributed to another etiology]), 11 SAEs (8 subjects [1.9%]) were reported in Group #2 (chills, fever, vomiting, headache, vertigo, localized infection, UTI, appendicitis (2 subjects), cough, head injury), 4 SAEs (4 subjects [0.9%]) were

reported in Group #3 (abdominal pain, alcohol ingestion, decreased appetite, Type 2 diabetes mellitus), 5 SAEs (4 subjects [1.6%]) were reported in Group #4 (sinusitis, viral infection, concussion, fracture + contusion).

Study enrollment and vaccinations were paused during a review of a sudden unexpected safety adverse reaction (SUSAR): a 15-year old participant (Group #2) was hospitalized after experiencing vertigo associated with ataxia, chills and headache 1 hour after the 2nd dose of Trumenba. She was treated with ibuprofen and loratidine. All symptoms resolved by the second hospital day.

Review Comment: In this reviewer's opinion, the short timing of event onset relative to vaccination suggests a temporal relationship without a defined etiologic cause for the events.

An 11-year old female reported moderate swelling/mild pain at the injection site on the day of the first Trumenba vaccination. The next day, she was hospitalized for fever and vomiting, which were associated with headache, fatigue, chills, and muscle pain. Except for fatigue, the symptoms resolved within 72 hours following treatment with IV fluids, ibuprofen and acetaminophen.

Review Comment: In this reviewer's opinion, the short timing of event onset relative to vaccination suggests a temporal relationship without a defined etiologic cause for the events.

- During the 2-dose series follow-up phase, 6 SAEs (5 subjects [1.2%] were reported in Group #1 (aphthous stomatitis, Crohn's disease, constipation, viral gastroenteritis, tonsillitis, dermatitis), 1 SAE (1 subjects [0.2%]) was reported in Group #2 (spontaneous abortion), 6 SAEs (4 subjects [0.9%]) were reported in Group #3 (appendicitis, hyperbilirubinemia, urethritis, concussion, ovarian cyst) and 2 SAEs (2 subjects [2.2%]) were reported in Group #4 (hand fracture, sympathetic posterior cervical syndrome).

  Spontaneous abortion: occurred 84 days post-vaccination (gestational age unknown), which was considered by the study investigator to be unrelated to Trumenba vaccination.

- During the third dose phase, no SAEs were reported by subjects [0.0%] in Group #1, and 2 SAEs (2 subjects [0.5%]) were reported in Group #2 (poisoning, headache).

- During the third dose follow-up phase, 4 SAEs (4 subjects [1.0%]) were reported in Group #1 (gastroenteritis, concussion, removal of foreign body, urticaria), and 3 SAEs (2 subjects [0.8%]) were reported in Group #2 (gastritis, alcohol ingestion, extremity fracture).

Reported SAEs were most commonly categorized in the system organ class (SOC) of infections and infestations and Injury, poisoning and procedural complications. A case narrative for the subject who was diagnosed with Crohn's disease (not attributed to vaccination) was included in section 8.4.6 (Neuroinflammatory and Autoimmune Conditions) of the clinical review for STN 125549/0.

6.1.9 Study Summary and Conclusions

Study B1971012 was a safety and immunogenicity study to assess hSBA responses following Trumenba administered according to 2-dose and 3-dose schedules.

Of note, the analyses of 4-fold responses using each of the 4 primary strains and composite response (hSBA response to all primary strains) in this study were descriptive and performed *post-hoc*. Nonetheless, 5 endpoints were consistent with the co-primary endpoints in the Trumenba confirmatory

studies to fulfill statutory requirements for accelerated approval. For the 3-dose schedule, the overall number of participants for which hSBA responses were evaluated using primary strains, including Trumenba participants in this study, was substantial (in the context of this sBLA, ~2300 evaluable participants overall received three doses of Trumenba (0,1 and 6 months or 0,2 and 6 months) and an additional~200 evaluable participants received two doses of Trumenba (0 and 2 months). The evaluation of the proposed 2-dose schedule (0 and 6 months) was based on hSBA responses from subjects in Group #3.

Immunogenicity
3-dose schedule (0, 1-2 and 6 months)
hSBA responses (comparison by individual MenB test strain) were similar following two doses administered at a shortened interval (0 and 1 months vs. 0 and 2 months) and following administration of the third dose (at 6 months) regardless if the interval between the first two doses was 1 or 2 months apart.
Dosing regimen: Two doses administered at 1 or 2 months apart were notably lower, especially for the subfamily B variant-expressing strains, than corresponding hSBA responses in a subset of subjects who received a third Trumenba dose. The estimated composite response after the second dose was approximately 50%, indicating that a third dose was necessary if the interval between the first two doses was separated by 1 month.

2-dose schedule (0 and 6 months)
As expected, the proportion of participants with ≥4-fold and composite responses after dose #2 were higher when Trumenba was administered at longer intervals (0 and 6 months vs. 0 and 1-2 months between the first and second doses). Trumenba administered as a 2-dose series at 0 and 6 months was immunogenic for all MenB test strains. In the context of accelerated approval, Trumenba administered at 0 and 6 months has an effect on surrogate endpoints that is reasonably likely to predict clinical benefit compared to participants who received no MenB vaccine.

Overall, the schedules enable flexibility in vaccination intervals depending on the risk of exposure during months 1 and 6, the patient's susceptibility to MenB disease, and the geographic distribution of MenB subfamily A and B strains.

Safety
Study enrollment and vaccinations were paused during a review of a sudden unexpected safety adverse reaction in a 15 year old participant (Group #2), who was hospitalized after vertigo associated with ataxia, chills and headache 1 hour after the 2nd dose of Trumenba. All symptoms resolved by the second hospital day. In this reviewer's opinion, the short timing of event onset relative to vaccination suggests a temporal relationship without a defined etiologic cause for the events.

No new concerns were identified from the analyses of SAEs by 4 time intervals.

6.2 Study B1971011

NCT# 01461993

Title: A Phase 2, Randomized, Placebo-Controlled, Observer-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Gardasil (HPV4) and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 to <18 Years.

6.2.1 Objectives (Primary, Secondary, Exploratory)

The protocol-specified primary objectives pertained to the evaluation of IgG antibody responses to all vaccine types in HPV4 and hSBA responses to Trumenba using 2 primary strains, as measured by GMTs.

Other protocol-specified objectives included a description of the proportion of subjects with a ≥4-fold increase in post-vaccination hSBA titer compared to pre-dose #1 titer (each of 4 primary strains) and composite responses (all 4 strains), measured one month after the second and third Trumenba vaccinations; the definitions of 4-fold response and composite response, description of primary strains and corresponding LLOQs for the hSBA assay were included in section 6.1.1 of the clinical review for this sBLA.

Reviewer comment: Additional exploratory objectives to describe hSBA responses to Trumenba (Groups 1 and 2) after a 2-dose series and after a booster (3rd) dose were included in an amended SAP (SAP for 2-dose series related analyses, version 1.0, dated 22-Apr-2015). The protocol objectives were not changed since the study had already been completed at the time the SAP was amended.

6.2.2 Design Overview

Phase 2, randomized, active-controlled, observer-blinded trial conducted in the US. Individuals 11 to < 18 years of age were randomly assigned (2:2:1 ratio) to 1 of 3 groups, as described below:

Table 7. Study B1971011. Study Design

Study Group	Vaccination schedule		
	Month 0	Month 2	Month 6
1	HPV4 + Trumenba	HPV4 + Trumenba	HPV4 + Trumenba
2	Trumenba + saline	Trumenba + saline	Trumenba+ saline
3	HPV4 + saline	HPV4 + saline	HPV4 + saline

HPV4= Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [Gardasil].

The study participants, study investigators and the applicant were blinded to the treatment allocation (i.e. observer-blinded). Persons dispensing and administrating study vaccine were not blinded to the treatment assignment (appearance of both vaccines and saline differed). Study personnel collecting safety information were separate from personnel dispensing/administering study vaccine. Laboratory personnel involved in tested the sera were blinded to the treatment assignment.

6.2.3 Population

(Healthy individuals ≥11 to <18 years of age.)

6.2.4 Surveillance/Monitoring

The safety evaluation included an assessment of solicited local and systemic reactions; general non-serious AEs; SAEs, medically attended AEs and newly diagnosed chronic medical conditions (including neuroinflammatory and autoimmune conditions).

6.2.5 Statistical Considerations & Statistical Analysis Plan

Pertinent changes

- SAP for 2-dose series related analyses v1.0, dated 22-Apr-2015

Included additional exploratory objectives (see Reviewer comment in the Design section); included the following analysis populations:

Immunogenicity

- Post-vaccination #2 mITT and evaluable immunogenicity populations: were defined similarly to the post-vaccination #2 populations in study B1971012, except for one criterion (the criterion to include subjects who received the 1st two doses of Trumenba at the corresponding scheduled visit was not applicable since subjects in study B1971011 received Trumenba at all visits for which an injection was administered).
- Post-vaccination #3 mITT and evaluable populations were defined similarly to the post-vaccination #3 populations in study B1971011, except for one criterion (included criterion that subjects in this study who received all 3 doses of Trumenba at the corresponding scheduled visit was not applicable since subjects in study B1971011 received Trumenba at all visits for which an injection was administered).

Safety

- The definitions for the 2-dose series, 2-dose series follow-up, Vaccination #3 and Vaccination #3 follow-up safety populations were as for Study B1971012 (see section 6.1.5 of this review).

6.2.6 Study Population

6.2.6.1 Populations Analyzed

Immunogenicity

Of 999 subjects randomized to Group #1(Trumenba + HPV4)

- 901 (90.2%) and 861 (86.2%) subjects were included in the post-vaccination #2 and post-vaccination #3 mITT populations, respectively.
- 857 (85.8%) and 814 (81.5%) subjects were included in the post-vaccination #2 and post-vaccination #3 evaluable immunogenicity populations, respectively.

  Subjects were excluded mainly because participants did not attend a scheduled pre-vaccination #1 or designated post-vaccination (i.e., post-vaccination #2, post-vaccination #3) blood draw, did not have a valid and determinate hSBA result for the pre-vaccination #1 or designated post-vaccination time point (i.e., post-vaccination #2, post-vaccination #3) or did not receive all study vaccines as randomized at the designated visit (post-vaccination #2 population: at the first and second vaccination visits; post-vaccination #3 population: at all vaccination visits).

Of 998 subjects randomized to Group #2 (Trumenba + saline)

- 909 (91.1%) and 812 (81.4%) subjects were included in the post-vaccination #2 and post-vaccination #3 mITT populations, respectively.
- 849 (85.1%) and 812 (81.4%) subjects were included in the post-vaccination #2 and post-vaccination #3 evaluable immunogenicity populations, respectively.
  The main reasons for exclusion from the evaluable populations in Group #2 were the same as for Group #1.

Safety

Table 8.Study B1971011. Summary of Subjects Reporting at Least 1 Serious Adverse Event for Each Analysis Interval- Safety Populations

Population	Group 1 (Trumenba + HPV4)	Group 2 (Trumenba + saline)	Group 3 (HPV4 + saline)
2-Dose series vaccination phase	992	990	501
2-Dose series follow-up phase	992	990	501
Third dose vaccination phase	871	869	452
Third dose follow-up phase	848	845	439

Source: Response Document (dated 15-May-2015).pdf, Table 4, page 25.

6.2.6.1.1 Demographic and Other Baseline Characteristics

In total, 66.5% of subjects were male (Group 1: 66.0%, Group 2: 67.0%, Group 3: 66.3%) and 33.5% were female. 65.9% of participants were 11 to <14 years age and 34.1% were 15 to <18 years of age; the age distribution was similar among the three study groups. The population overall was 81.6% Caucasian, 13% African American, 1.2% Asian, and 4.3% participants that were classified as 'other'. The applicant attributed enrollment of a higher proportion of males aged 11 to <14 years in the study was due to updated recommendations by the Advisory Committee on Immunization Practices (ACIP) in late 2009 for the prevention of HPV disease to include routine HPV vaccination in males at age 11 or 12 years.

6.2.6.1.3 Subject Disposition

Table 9. Study B1971011. Subject Disposition

Disposition of Subjects	Group 1 (Trumenba + HPV4) n(%)	Group 2 (Trumenba + saline) n(%)	Group 3 (HPV4 + saline) n(%)
Randomized	999	998	502
Withdrawn before vaccination	6 (0.6)	8 (0.8)	1 (0.2)
2-Dose series vaccination phase - completed	904 (90.5)	912 (91.4)	471 (93.8)
2-Dose series vaccination phase - withdrawn	89 (8.9)	78 (7.8)	30 (6.0)
2-Dose series follow-up phase - completed	872 (87.3)	869 (87.1)	452 (90.0)
2-Dose series follow-up phase - withdrawn	32 (3.2)	43 (4.3)	19 (3.8)
Third dose vaccination phase - completed	864 (86.5)	860 (86.2)	448 (89.2)
Third dose vaccination phase - withdrawn	8 (0.8)	9 (0.9)	4 (0.8)
Third dose follow-up phase - completed	848 (84.9)	841 (84.3)	438 (87.3)
Third dose follow-up phase - withdrawn	16 (1.6)	19 (1.9)	10 (2.0)
Completed the 6 Month follow-up contact	875 (87.6)	879 (88.1)	448 (89.2)

Source: Response document (dated 15-May-2015).pdf, Table 2, pages 17-19.
n = Number of subjects with the specified characteristic.
2-Dose series vaccination phase = vaccination #1 Visit to 1 month after the vaccination #2 Visit.
2-Dose series follow-up phase = 1 month after the Visit vaccination 2 to the vaccination #3 Visit.
Third dose vaccination phase = through 1 month after the Visit for vaccination #3.
Third dose follow-up phase = 1 month after the Visit for vaccination #3 through the end of the study.

For all study groups, the reasons for premature discontinuation were mainly due to lost-to-follow-up or voluntary withdrawal of consent.

6.2.7 Immunogenicity Results

Please see Table 12 in Section 7 (Integrated Summary of Efficacy) for a summary of 4-fold responses for each primary strain and composite response (% of subjects ≥LLOQ for all 4 primary strains).

Other Endpoints

% of hSBA titer ≥ LLOQ pre-dose #1

Evaluable Immunogenicity population; LLOQ= 1:16 for A22 and 1:8 for A56, B24 and B44.
Group #1: 13.8% (A22), 9.0% (A56),5.1% (B24) and 1.5% (B44).
Group #2: 16.5% (A22), 9.1% (A56),7.0% (B24) and 2.6% (B44).

6.2.8 Safety Results

6.2.8.3 Deaths

None.

6.2.8.4 Serious Adverse Events

A total of 32 (1.3%) subjects reported 34 SAEs during the study period:

During the 2-dose series vaccination phase

- 4 SAEs (4 subjects [0.4%]) reported in Group #1, including lymphoid tissue hyperplasia and psychiatric disorders.
- 4 SAEs (4 subjects [0.4%]) reported in Group #2: appendicitis, cellulitis, leg fracture, psychiatric disorder.
- 1 SAE (1 subject [0.2%]) reported in Group #3:migraine.

During the 2-dose series follow-up phase

- 2 SAEs (2 subjects [0.2%] reported in Group #1: migraine, depression.
- 4 SAEs (4 subjects [0.4%] reported in Group #2: abdominal pain, weakness of extremities, depression, asthma.
- 1 SAE (1 subject [0.2%]) reported in Group #3:thymic disorder.

During the third dose phase

- 2 SAEs (2 subjects [0.2%]) reported in Group #1: appendicitis, first degree burn.
- 1 SAE (1 subject [0.1%]) reported in Group #2: psychiatric disorder.
- 0 SAEs reported in Group #3

During the third dose follow-up phase

- 5 SAEs (4 subjects [0.5%]) reported in Group #1: appendicitis, 2 unintentional injuries, 2 psychiatric disorders.
- 8 SAEs (7 subjects [0.8%]) reported in Group #2: 5 unintentional injuries (e.g. wrist fracture), nodular fasciitis, epiphysiolysis, bipolar disorder.
- 2 SAEs (2 subjects [0.5%]) reported in Group #3: hemorrhoids, biliary dyskinesia

Reviewer Comment: In this reviewer's opinion, none of the events were considered related to vaccination.

6.2.9 Study Summary and Conclusions

Study B1971011 was one of the main adolescent immunogenicity and safety studies to support the immunogenicity (inferred effectiveness) of Trumenba administered as a 3-dose schedule (0, 2 and 6

month) [STN125549/0]. In this sBLA, additional descriptive analyses of the 5 main endpoints were presented in support of a change in dosing regimen.

Immunogenicity
Five endpoints were analogous to the primary endpoints in the Trumenba confirmatory studies that were conducted to fulfill FDA requirements for accelerated approval: the proportion of participants with a ≥4-fold response to each of the four MenB primary strains and the proportion of participants with a hSBA response ≥LLOQ to all of the primary strains (composite response). The analyses for the endpoints in this study were descriptive; nonetheless, the hSBA responses were evaluated in a substantial number of US participants (Group 1 n=999, Group 2 n=998).

- First two doses (2 months apart): An increase in hSBA titer post-vaccination relative to baseline (prior to dose #1) was observed for each of the primary strains. A higher proportion of subjects had a ≥4-fold rise increase in post-vaccination hSBA titer for each of the strains expressing sub-family A variants compared to the proportion of subjects with a ≥4-fold rise increase in post-vaccination hSBA titer each of the strains expressing sub-family B variants. When 2 doses were administered 2 months apart, the proportions of Trumenba subjects with a ≥4-fold increase in post-vaccination hSBA titer compared to baseline were 63.5% and 48.8% for strains expressing variant B24 and B44, respectively, and 74.0% and 92.7% for strains expressing variant A22 and A56, respectively. The composite response, measured by the proportion of participants with hSBA titer ≥ LLOQ to all 4 primary MenB strains (composite response), was 52.6% after the 2nd vaccination.

- Third dose: The proportion of participants with hSBA titer ≥ LLOQ to all 4 primary MenB strains (composite response) was >82% after receipt of the third dose of Trumenba, and >75% of subjects had a ≥4-fold increase in hSBA titer to each of the 4 primary MenB strains.

Safety
The frequencies of SAEs among participants who received Trumenba with HPV4 (Group #1) or with HPV4 (Group #2) was <1% for each of the 4 time intervals. Many of the events were unintentional injuries (e.g. fracture), and none of the SAEs were considered by this reviewer to be related to vaccination. No new concerns were identified from the analyses of SAEs by 4 time intervals.

6.3 Study B1971010

NCT# 01323270

Title: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability and Immunogenicity of Repevax and Bivalent rLP2085 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 To <19 Years.

Study B1971010 was conducted in Europe (Finland, Germany and Poland).

6.3.1 Objectives (Primary, Secondary, Exploratory)

The protocol-specified primary objectives pertained to immunogenicity evaluations of antigens contained in dTap-IPV (Sanofi-Pasteur MSD) [Repevax]. One of the secondary objectives was to describe the proportion of subjects with a ≥4-fold increase in hSBA titer, using 4 primary MenB test strains, as measured 1 month after the second and the third Trumenba vaccinations. The definitions of 4-fold response, description of primary strains and corresponding LLOQs for the hSBA assay were included in section 6.1.1 of the clinical review for this sBLA.

Reviewer comment: The statistical analysis plan, but not the protocol objectives, was amended to include exploratory objectives to describe hSBA responses to Trumenba after a 2-dose series and after the 3rd dose. The protocol remained unchanged since the study had already been completed at the time the SAP, entitled "SAP for 2-dose series related analyses" (version 1.0, dated 22-Apr-2015), was written.

6.3.2 Design Overview

The study was designed as a phase 2, randomized, placebo-controlled, single-blind trial. Individuals 11 to <19 years of age were randomly assigned to 1 of 2 groups (1:1 ratio).

Table 10. Study B1971010. Study Design

Study Group	Vaccination schedule		
	Month 0	**Month 2**	**Month 6**
1	Trumenba + dTap-IPV	Trumenba	Trumenba
2	saline + dTap-IPV	Saline	Saline

dTap-IPV (Sanofi-Pasteur MSD): Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) [Repevax].

Study participants, but not the study investigator and the applicant, were blinded to their allocated vaccine group (i.e. single blinded). The safety parameters, data collection methods were the same as for study B1971012. The observation period for immediate adverse reactions was at least 20 minutes (or longer depending on the site).

6.3.3 Population

(Healthy individuals ≥11 to <19 years of age.)

6.3.4 Surveillance/Monitoring

Safety
Solicited local and systemic adverse reactions were assessed after each vaccination visit. The safety parameters and data collection methods were the same as for study B1971012. The observation period for immediate adverse reactions was at least 20 minutes (or longer depending on the site).

Immunogenicity
Sera from a 50% of subjects (50% subjects from Group #1 and 50% subjects from Group #2) were tested with hSBA assays using strains expressing variants A22 and B24, and sera from the other 50% of subjects were tested with hSBA assays using strains expressing variants A56 and B44.
Primary strains: PMB80 [A22], PMB2948 [B24], PMB2001 [A56] and PMB2707 [B44].

Reviewer comment: A composite response (i.e., the proportions of participants with a hSBA response ≥ LLOQ to all of the primary strains) was not evaluated in this study because sera from each subset population were not tested for all 4 primary strains.

6.3.5 Statistical Considerations & Statistical Analysis Plan

Pertinent changes

- SAP for 2-dose series related analyses, version 1.0, dated 22-Apr-2015: Included additional exploratory objectives (see Reviewer comment in the Design section); included mITT and evaluable populations for both the post-vaccination #2 and post-vaccination #3 time points and four safety populations, which were all defined in the same manner as the populations described in study B1971011 (see section 6.2 of this review).

6.3.6 Study Population

6.3.6.1 Populations Analyzed

Immunogenicity
Of the 373 subjects randomized to Group #1, the mITT immunogenicity hSBA post-vaccination #2 and post-vaccination #3 populations included 91.2% and 88.2% of subjects, respectively. The evaluable immunogenicity post-vaccination #2 and post-vaccination #3 populations included 315 (84.5%) and 307 (82.3%) subjects, respectively.

Safety
Subjects Reporting at Least 1 Serious Adverse Event for Each Analysis Interval- Safety Populations: Group #1 included 374 subjects each for the 2-dose series vaccination and follow-up phases, 331 for the third dose phase, and 330 for the third dose follow-up phase. Group #2 included 378 subjects each for the 2-dose series vaccination and follow-up phases, 351 for the third dose phase, and 349 for the third dose follow-up phase.

6.3.6.1.1 Demographic and other Baseline Characteristics

Overall, the safety population (vaccine as administered) was comprised of 51.1% male and 48.9% female; the median age at the time of the first vaccination was 13 years (57.8% of participants were 11 to <14 years age and 42.2% were age 14 to <19 years). The population overall were 98.9% Caucasian, 0.1% African American, 0.8% Asian, and 0.1% of participants were classified as 'other'. The demographic and other baseline characteristics of the evaluable immunogenicity population were similar to the randomized population.

6.3.6.1.2 Subject Disposition

Table 11. Study B1971010. Subject Disposition

Disposition of Subjects	**Group 1** (Trumenba + dTap-IPV) n(%)	**Group 2** (saline + dTap-IPV) n(%)
Randomized	373	376
Withdrawn before vaccination	1 (0.3)	0 (0.0)
2-Dose series vaccination phase - completed	342 (91.7)	354 (94.1)
2-Dose series vaccination phase - withdrawn	30 (8.0)	22 (5.9)
2-Dose series follow-up phase - completed	331 (88.7)	351 (93.4)
2-Dose series follow-up phase - withdrawn	11 (2.9)	3 (0.8)
Third dose vaccination phase - completed	331 (88.7)	348 (92.6)
Third dose vaccination phase - withdrawn	0 (0.0)	3 (0.8)
Third dose follow-up phase - completed	330 (88.5)	347 (92.3)

Third dose follow-up phase - withdrawn	1 (0.3)	1 (0.3)
Completed the 6 Month follow-up contact	358 (96.0)	366 (97.3)

Source: Response document (dated 15-May-2015).pdf, Table 1, pages 13-15.
n = Number of subjects with the specified characteristic.
2-Dose series vaccination phase = vaccination #1 Visit to 1 month after the vaccination #2 Visit.
2-Dose series follow-up phase = 1 month after the Visit vaccination 2 to the vaccination #3 Visit.
Third dose vaccination phase = through 1 month after the Visit for vaccination #3.
Third dose follow-up phase = 1 month after the Visit for vaccination #3 through the end of the study.

6.3.7 Immunogenicity Results

Please see Table 12 in Section 7 (Integrated Summary of Efficacy) for a summary of 4-fold responses for each primary strain and composite response (% of subjects ≥LLOQ for all 4 primary strains).

Other Endpoints
% of hSBA titer ≥ LLOQ pre-dose #1
Evaluable Immunogenicity population; LLOQ= 1:16 for A22 and 1:8 for A56, B24 and B44.
Group #1 (Trumenba+dTap-IPV): 13.8% (A22), 17.8% (A56), 11.0% (B24) and 6.1% (B44).
Group #2 (saline + dTap-IPV): 23.8% (A22), 21.1% (A56), 13.0% (B24) and 6.7% (B44).

6.3.8 Safety Results

6.3.8.3 Deaths

One subject (Group #1) died in a motor vehicle accident.

6.3.8.4 Nonfatal Serious Adverse Events

A total of 25 subjects reported 28 SAEs during the study period.

- During the 2-dose series vaccination phase, 5 SAEs (5 subjects [1.3%]) were reported in Group #1 (post-infectious reactive arthritis [attributed to another etiology], cellulitis, and gastroenteritis, motor vehicle accident, depression) and 4 SAEs (3 subjects [0.8%]) were reported in Group #2 (appendicitis and peritonsillar abscess, hip fracture, drug abuse).
- During the 2-dose series follow-up phase, 5 SAEs (5 subjects [1.3%]) were reported in Group #1 (positional vertigo, sinusitis, tonsillitis, hydrocephalus [pre-existing condition], depression) and 1 SAE (1 subject [0.3%]) was reported in Group #2 (joint dislocation).
- During the third dose phase, 2 SAEs (2 subjects [0.6%]) were reported in each study group (Group #1: headache and idiopathic thrombocytopenic purpura; Group #2: syncope and ovarian cyst rupture).
- During the third dose follow-up phase, 3 SAEs (1 subject [0.3%]) were reported in Group #1 (appendicitis with subsequent perforation, abdominal abscess) and 6 SAEs (6 subjects [1.7%]) were reported in Group #2 (syndactyly [pre-existing condition], appendicitis, UTI, non-accidental injury, depression, dyspnea).

Reviewer Comment: In this reviewer's opinion, none of the events were considered related to vaccination.

For both study groups, reported SAEs were most commonly categorized in the system organ class (SOC) of Infections and Infestations. For the 2 subjects who reported SAEs (post-infectious reactive arthritis and ITP, respectively) that were identified as an autoimmune condition, case narratives were included in section 8.4.6 (Neuroinflammatory and Autoimmune Conditions) of the clinical review for STN 125549/0.

6.3.9 Study Summary and Conclusions

Study B1971010 was a non-IND study conducted in Europe, and one of the main immunogenicity studies submitted by the applicant in support of the proposed change in dosing regimen. Adolescents ≥11 to <19 years of age received the first two doses 2 months apart then a third dose 6 months after the first dose (0, 2 and 6 month schedule).

Immunogenicity
The analyses of 4-fold responses using each of the 4 primary strains and composite response (hSBA response to all primary strains) in this study were descriptive. The proportion of adolescents with a ≥4-fold response was higher after a third dose (at 6 months) than after a two dose series (0 and 2 months), especially for subfamily B strains (post-dose #2: B24: 59.4%, B44: 50.7%; post-dose #3 B24: 80.8%, B44:77.6%). A composite response was not assessed in this study because hSBA responses to 2 of the primary strains (expressing variant A22 and B24) and hSBA responses to the remaining 2 primary strains (expressing A56 and B44) were measured in separate subsets of participants.

Safety
The frequencies of SAEs reported for each time interval was low for both groups (range: 0.3% to 1.7%, depending on the time point and duration of the time interval). The events were consistent with conditions commonly observed in an adolescent population.

7. INTEGRATED OVERVIEW OF EFFICACY

The applicant provided *post-hoc* analyses from 3 studies (B1971011, B1971012 and B1971010) that were previously submitted to the BLA (STN 125549/0). The analysis populations were described in section 6.2 of this review. Whereas the immunogenicity data following the completion of a 0, 2 and 6 month schedule were used for the primary statistical analyses in the BLA, the primary analyses in this sBLA were presented in the context of other vaccination schedules (two doses administered at least 1 month apart followed by a third dose, 2 doses administered at 0 and 6 months). Evaluations of hSBA responses for the Trumenba 2-dose (0 and 6 months) schedule were based on study B1971012.

Main endpoints: measured one month after the 2-dose series, and, in a subset of subjects after the third dose

- For each of the 4 primary strains, a ≥4-fold increase in hSBA titer compared to baseline (pre-dose#1) was defined as follows:
  For subjects with a baseline hSBA titer <1:4, a ≥4-fold increase was defined as an hSBA titer ≥1:16.
  For subjects with a baseline hSBA titer ≥1:4, a ≥4-fold increase was defined as an hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer.
- Composite response: The % of subjects with a hSBA titer ≥LLOQ for all 4 primary strains.

The primary strains [variant] are PMB80 [A22], PMB2948 [B24], PMB2001 [A56] and PMB2707 [B44]. A hSBA titer ≥1:8 was viewed by CBER as a conservative threshold of protection, provided that the hSBA

assay could accurately quantify a titer at this level. The LLOQ for the hSBA assay using the strain expressing A22 was 1:16.LLOQs: hSBA titer of 1:16 [A22], and 1:8 for A56, B24 and B44.

A total of 3923 subjects in studies B1971012 (Groups #1-4), B1971011 (Group #1) and B1971010 (Group #1) received at least one dose of Trumenba. Of the 3923 Trumenba-vaccinated subjects, 2846 (72.5%) and 2291 (58.5%) were included in the evaluable immunogenicity populations (per-schedule evaluable population for study B1971012) for the 2-dose series and the third dose, respectively; 1706 (43.5%) and 1626 (41.4%) were US subjects. There were no substantial differences in subgroup analyses of hSBA responses among female and male participants. The study population was comprised largely of White (90%) and non-Hispanic/non-Latino (90.7%) subjects, and the number of subjects in other categories of race and ethnicity were too small to make meaningful conclusions about the effect of race or ethnicity on the immunogenicity of Trumenba.

Table 12. ISE. Subjects Achieving ≥4-Fold Increase in hSBA Titer and Composite Response

Study #, Geographic Region, Age group	≥4-Fold Increase in hSBA titer								Composite Response (hSBA titer ≥LLOQ for all 4 primary strains)	
	PMB80 (A22)		PMB2001 (A56)		PMB2948 (B24)		PMB2707 (B44)			
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
B1971012 EU 11 to <18 years of age[a,bc,] Group 1: Trumenba (0, 1, 6 month schedule)										
Post-vaccination #2	58.8	(51.4, 66.0)	87.8	(82.2, 92.2)	51.1	(43.6, 58.5)	48.1	(40.7, 55.6)	52.0	(44.3, 59.7)
Post-vaccination #3	77.6	(70.9, 83.4)	91.2	(86.1, 94.9)	74.1	(67.1, 80.2)	80.9	(74.5, 86.2)	80.3	(73.7, 85.9)
Group 2: Trumenba (0, 2, 6 month schedule)										
Post-vaccination #2	72.5	(66.4, 78.0)	90.7	(86.2, 94.1)	54.2	(47.7, 60.7)	53.4	(46.8, 59.9)	52.0	(46.8, 59.9)
Post-vaccination #3	87.7	(81.6, 92.3)	93.8	(88.8, 97.0)	78.3	(71.1, 84.4)	78.6	(71.4, 84.7)	81.8	(74.9, 87.4)
Group #3: Trumenba (0 and 6 months)										
Post-vaccination #2	82.3	(76.3, 87.3)	90.1	(85.1, 93.8)	64.5	(57.4, 71.1)	66.0	(58.9, 72.6)	72.9	(65.9, 79.1)
B1971011, US, 11 to <17 years of age[d] Group 1: Trumenba + HPV4 (0, 2, 6 month schedule)										
Post-vaccination #2	73.3	(70.2, 76.4)	92.8	(90.8, 94.5)	61.8	(58.4, 65.2)	46.0	(42.5, 49.5)	50.1	(46.5, 53.8)
Post-vaccination #3	85.3	(82.6, 87.7)	95.0	(93.2, 96.5)	83.4	(80.5, 85.9)	77.0	(73.9, 79.9)	81.0	(78.0, 83.7)
Group 2: Trumenba+Saline (0, 2 , 6 month schedule)										
Post-vaccination #2	74.0	(70.9, 77.0)	92.7	(90.7, 94.5)	63.5	(60.1, 66.9)	48.8	(45.3, 52.3)	52.6	(48.9, 56.2)
Post-vaccination #3	86.4	(83.8, 88.7)	95.3	(93.6, 96.8)	84.8	(82.0, 87.2)	80.7	(77.8, 83.4)	83.9	(81.1, 86.4)
Groups #1 and #2 (combined)										
Post-vaccination #2	73.7	(71.5, 75.8)	92.8	(91.4, 94.0)	62.7	(60.2, 65.1)	47.4	(44.9, 49.8)	51.4	(48.8, 53.9)

Post-vaccination #3	85.9	(84.0, 87.6)	95.2	(94.0, 96.2)	84.1	(82.1, 85.8)	78.9	(76.8, 80.9)	82.4	(80.4, 84.3)
B1971010, EU, 11 to <18 years of age[e] Group 1: Trumenba+ dTap-IPV (0, 2, 6 month schedule)										
Post-vaccination #2	69.7	(61.8, 76.8)	86.7	(79.7, 91.9)	59.4	(51.3, 67.1)	50.7	(42.2, 59.1)	N/A[f]	N/A
Post-vaccination #3	87.6	(81.3, 92.4)	92.6	(86.9, 96.4)	80.8	(73.7, 86.6)	77.6	(69.9, 84.2)	N/A[f]	N/A

Source: Response document (dated 30-April-2015).pdf, Tables 31 and 32, pages 83 and 85.

hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; CI= confidence interval; NA = not applicable.
LLOQ = 1:16 for strain PMB80 (A22) and 1:8 for strains PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).
The 4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titer <1:4, a 4-fold 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.

[a] Study B1971012: Per-schedule evaluable immunogenicity population: Group 1 (0, 1 and 6 month schedule): dose #2 N= 173-187, dose #3 N=178-188; Group 2 (0, 2 and 6 month schedule): dose #2 N= 229-240, dose #3 N=159-162; Group 3 (0 and 6 month schedule): dose #2 N= 188-203.
[b] Study B1971012: Percentage of subjects with ≥LLOQ for A22 prior to dose #1: Group 1: 30.2% (95% CI 23.7, 37.2); Group 2: 19.8% (95% CI 15.0, 25.4).
[c] Study B1971012: Composite response pre-dose #1: Group 1: 4.6 (95% CI 2.0, 8.8); Group 2: 2.2 (95% CI 0.7, 5.0); Group 3: 1.5 (95% CI 0.3, 4.4).
[d] Study B1971011: Evaluable Immunogenicity population: Group 1: dose #2 N=778-818, dose #3 N=742-792; Group 2: dose #2 N=757-827, dose #3 N=730-788.
[e] Study B1971010: Evaluable Immunogenicity population: Group 1: dose #2 N=135-160, dose #3 N=136-156.
[f] A composite response was not assessed because sera from each subset population were not tested for all 4 strains.

Main points:

When two doses of Trumenba were administered 1 or 2 months apart,

- The proportion of participants with a ≥4-fold response after the second dose was similar, when responses were compared by strain.

  Reviewer Comment: In study B1971012, the proportion of participants with a ≥4-fold response prior to dose #1 for the A22 variant-expressing strain was higher in Group #1 (0 and 1 month schedule) than in Group #2 (0 and 2 month schedule), which might have contributed to post-vaccination responses that were lower in Group #1 (58.8% (95% CI 51.4%, 66.0%)) than Group #2 (72.5% (95% CI 66.4%, 78.0%)).

- The proportions of participants with ≥4-fold responses after the second dose were higher for subfamily A (86.5% to 92.8% for A56 and 58.8% to 74.0% for A22) than subfamily B strains (51.1% to 63.5% for B24 and 46.0% to 53.4% for B44).

- The composite response (% with hSBA titer ≥LLOQ) after the second dose was approximately 50%.

After a third dose of Trumenba was administered to participants who previously received a 2-dose series at 0 and 1-2 months,

- When compared by strain, the proportion of participants with a ≥4-fold response after the third dose was similar regardless if the vaccination interval for the first two doses was 1 or 2 months.

- For the subfamily B strains, the proportions of subjects with ≥4-fold responses were 20-30% higher after the third dose than after the 2-dose series.

Composite response after the third dose was approximately 80%, compared with 50% after the 2-dose series.

When two doses of Trumenba were administered 6 months apart,

- The proportions of participants with ≥4-fold responses after the second dose were similar to corresponding responses after a 3-dose schedule (0, 1-2 and 6 months) for the subfamily A strains but lower for the subfamily B strains.

- The composite responses after two doses given at 0 and 6 months or three doses given at 0, 1-2 and 6 months was similar (73% vs. ~80%).

- The proportion of subjects with pre-vaccination #1 hSBA titers for at least one of the 4 primary MenB test strains was generally 5-10% higher among adolescents in Europe than in the US.

Immunogenicity Conclusions

3-dose schedule (0, 1-2 and 6 months)

- Dosing interval: After the third dose, the percentages of participants with a ≥4-fold increase in post-vaccination hSBA titer, compared by strain, were similar, indicating that differences in hSBA response due to a shortened interval between the first two doses were minimal after the third dose.
- Dosing regimen: Two doses administered at 1 or 2 months apart resulted in notably lower, especially for the subfamily B variant-expressing strains, than corresponding hSBA responses in subset of

subjects who received a third Trumenba dose. The estimated composite response after the second dose was approximately 50%, indicating that a third dose was necessary if the interval between the first two doses was separated by 1 month.

2-dose schedule (0 and 6 months)

- Dosing interval: As expected, the proportion of participants with ≥4-fold and composite responses after dose #2 were higher when Trumenba was administered at longer intervals (0 and 6 months vs. 0 and 1-2 months between the first and second doses).
- Dosing regimen: Trumenba administered as a 2-dose series at 0 and 6 months was immunogenic for all test strains. After completion of the 2-dose schedule, hSBA responses were similar to hSBA responses reported after three doses of Trumenba, administered at 0, 1-2 and 6 months, for subfamily A strains and approximately 10-15% lower for subfamily B strains.

Factors to take into consideration with regard to the choice of schedule include geographic distribution of MenB subfamily A and B strains, risk of exposure during 6 month interval, and the patient's susceptibility to MenB disease.

In the context of accelerated approval, Trumenba administered by either schedule has an effect on surrogate endpoints that is reasonably likely to predict clinical benefit compared to participants who received no meningococcal B vaccine. Confirmatory studies, for both the 3-dose and 2-dose schedules, in the post-marketing period will be conducted to evaluate Trumenba further, to verify and describe the clinical benefit in individuals 10 to <26 years of age, by demonstrating the effectiveness of Trumenba against MenB strains that represent an extended range of antigenically diverse fHBP variants.

At present, comparisons of hSBA responses following a 3-dose (0, 1-2 and 6 months) and 2-dose (0 and 6 months) schedules were limited to four MenB test strains. For each schedule, studies to evaluate hSBA responses using an extended range of antigenically diverse fHBP variants and persistence of hSBA antibodies to the primary test strains are being planned or are ongoing.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The primary safety assessment consisted of analyses of SAEs categorized into 4 time periods (vaccination phase for 2-dose series, 2-dose series follow-up phase, post-vaccination #3 phase and post-vaccination #3 follow-up phase). For the 2-dose schedule administered at 0 and 6 months, the analyses of safety data were the same as the analyses included in the individual study report for B1971012.

Demographic and baseline characteristics, and subgroup analyses (age, gender) and other safety assessments (solicited AEs and non-serious unsolicited AEs within 30 days after each vaccination and autoimmune and neuroinflammatory events through 6 months after the last vaccination for the 3-dose schedule were unchanged from the data submitted in BLA and are described in section 8 of the clinical review for STN 125549/0.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The rates of SAEs that were reported in Trumenba subjects pooled from 3 studies (B1971012, B1971011 and B1971010) were compared to pooled data from control groups that received HPV4 (study B1971011) or Tdap-IPV (Study B1971010) without Trumenba, and data from Trumenba subjects pooled from 7 studies that were previously submitted to the BLA (STN 125549/0).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the 3 main studies (B1971012, B1971011 and B1971010), a total of 3924 subjects received at least one dose of Trumenba, with the following characteristics: sex (female 41.4%, male 58.6%), Race (White 90.0%, Black 0.6%, Asian 2.2%, other 7.2%), ethnicity (Non-Hispanic/Non-Latino 90.7%, Hispanic/Latino 9.3%), age (11 to <19 years of age 100%). There were no notable differences in the rate of SAEs by sex. The study population was comprised largely of White (90%) and non-Hispanic/non-Latino (90.7%) subjects, and the number of subjects in other categories of race and ethnicity were too small to make meaningful conclusions about the effect of race or ethnicity on the immunogenicity of Trumenba. The effect of age on the safety of Trumenba was not assessed since all of the subjects in the three studies were 11 to <19 years of age.

Overall (7 studies), 4282 subjects 11 to ≤25 years of age received at least one dose of Trumenba; 99.3% of subjects were ages 11 to ≤18 years (adolescent) and 0.7% were ages 19 to ≤25 years (adult) at the time of enrollment. Please see section 8 (Integrated Summary of Safety) in the clinical review for STN 125549/0.

8.3 Safety Results

8.3.1 Deaths

One subject (Study B1971010, Group 1) died in a motor vehicle accident.

8.3.2 Nonfatal Serious Adverse Events

Of 4282 subjects 11 through 25 years of age received at least one dose of Trumenba, SAEs were reported by 88 (2.0%) subjects. SAEs were reported by 59 of 4282 (1.38%) subjects after 2 doses of Trumenba and by 29 of 3055 (0.95%) subjects after a third dose of Trumenba.

Table 13. Integrated Summary of Safety. Percentage of Subjects 11 to <26 Years of Age Reporting at Least One SAE

Time Interval	7 studies[a]	3 Studies[b]	
	Trumenba	Trumenba	Control
	N= 3004-4282	N= 1965-2004	N=788-879
	% (n/N)	% (n/N)	% (n/N)
2-dose series vaccination phase[c]	0.77%	0.91%	0.40%
2-dose series follow-up phase[d]	0.65%	0.68%	0.40%
Third dose phase[e]	0.26%	0.77%	0.33%
Third dose follow-up phase[f]	0.70%	0.59%	0.88
Vaccination #1 through follow-up phase (2-dose series or third dose, as	2.06%	1.72%	1.59%

applicable)			

Source: Response Document dated 15-May-2015.pdf, Tables 11 and 13, pages 45 and 48.
n = Number of subjects with at least 1 event for the specified analysis interval.
N = number of subjects who are in the safety population for the specified analysis interval.
[a] Subjects Who Received at Least 1 Dose of Trumenba (any dosage, any schedule) in studies B1971003, -1004, -1005, -1010, -1011, -1012 and -1042.
[b] Subjects Who Received at Least 1 Dose of Trumenba (120ug) in studies B1971012 (at 0, 1-2 and 6 months [Groups #1 and #2]), B1971011 (at 0, 2 and 6 months [Group #2]) and B1971010 (at 0, 2 and 6 months + dTap-IPV at month 0, saline at months 2 and 6 [Group #1]). Control groups: pooled data from subjects in B1971011 (HPV4 + saline at 0, 2 and 6 months [Group #3]) and B1971010 (dTap-IPV month 0, saline at months 2 and 6 [Group #2])
[c] 2-Dose series vaccination phase = Vaccination #1 visit to 1 month after Vaccination #2 visit.
[d] 2-Dose series follow-up phase = 1 month after Vaccination #2 visit to the Vaccination #3 visit.
[e] Vaccination #3 phase = through 1 month after vaccination #3 visit.
[f] Vaccination #3 follow-up phase = through the end of the study.

8.4 Safety Conclusions

No new concerns were identified from the analyses of SAEs by 4 time intervals.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Please see clinical review for STN 125549/0.

9.1.2 Use During Lactation

n/a

9.1.3 Pediatric Use and PREA Considerations

3-dose (0, 1-2 and 6 months): not viewed by PeRC as a change in the dosing interval, and therefore not subject to PREA. The pediatric study plan remains unchanged from the plan outlined in STN 125549/0.

2-dose (0 and 6 months)

- 0 to <12 months of age: The requirement for studies age was waived due to adverse safety outcomes observed in infants (same data as for the 3-dose schedule).
- 1 year to <10 years of age: The applicant plans to conduct a safety and immunogenicity study in children 1 year to <10 years of age; the requirement for studies in this age group was deferred because Trumenba is ready for approval for use in individuals 10 to <26 years of age before the pediatric study is completed.
- 10 years of age: Extrapolation of safety and immunogenicity to children age 10 years is supported by the safety and immunogenicity profile observed in children ages 11 to <18 years.
- 11 to <18 years of age: supported by safety and immunogenicity data from studies included in this sBLA.

9.1.4 Immunocompromised Patients

n/a

9.1.5 Geriatric Use

n/a

10. CONCLUSIONS

The clinical data support accelerated approval of a

- 3-dose schedule: a 0.5 mL dose administered at 0, 1-2, and 6 months.

  The applicant initially requested a change the dosing regimen from a 3-dose schedule (administered at 0, 2 and 6 months) to a 2-dose series given at least one month apart, followed by an optional booster (3rd) dose at least 4 months after the second dose. The immunogenicity and safety data provided in the sBLA support alternatives in vaccination interval between the first and second doses, but not a change in the number of doses in the primary immunization series (3 doses). Hence, in this reviewer's opinion, the resultant change in the vaccination interval constitutes a change in the existing 3-dose schedule rather than a new dosing regimen. Accordingly, the postmarketing requirements to fulfill requirements for accelerated approval for the 3-dose schedule are unchanged from the PMRs in the approval letter for STN 125549/0.

- 2-dose schedule: a 0.5 mL dose administered at 0 and 6 months.

The immunogenicity of Trumenba administered at 0 and 6 months was assessed independently from the 3-dose schedule. The clinical data support accelerated approval of Trumenba in accordance with statutory regulations [21 CFR 601.41]. The 4-fold and composite response endpoints were analogous to the primary endpoints agreed upon by CBER for the confirmatory study for the 2-dose schedule, in which the effectiveness of Trumenba, when administered at 0 and 6 months, will be evaluated further using 10 additional MenB strains.

The schedules enable flexibility in vaccination intervals depending on the risk of exposure during months 1 and 6, and the patient's susceptibility to meningococcal serogroup B disease.

There were no new concerns identified following a review of the SAEs re-categorized by 4 time intervals.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 14. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Neisseria meningitidis* is a significant cause of meningitis and sepsis worldwide; the majority of meningococcal disease is caused by 5 serogroups, including serogroup B. A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss) and approximately 10% of cases are fatal. • The incidence of invasive meningococcal disease is highest in infants, and second peak occurs in adolescents and young adults.	• Invasive disease due to serogroup B *Neisseria meningitidis* is a serious and potentially life-threatening condition. • Adolescents and young adults are at risk to develop invasive meningococcal disease.
Unmet Medical Need	• Control of an outbreak of meningococcal B disease may be facilitated if the first two doses of the vaccination series can be administered in a shorter interval (e.g., one month between the first two doses instead of two months). • A reduced dose schedule administered at a longer interval (0 and 6 months) may possibly improve vaccination compliance without increasing the risk of exposure to serogroup B meningococci, such as immunization of the general population of adolescents and young adults who might be vaccinated with MenB vaccine at the discretion of the treating clinician.	• Flexibility in the Trumenba vaccination schedules may be beneficial depending on the risk of exposure during months #1 and #6 and the patient's susceptibility to meningococcal serogroup B disease.
Clinical Benefit	• The hSBA assay is a functional assay that measures the serum's capacity for bacterial killing and is well-accepted as the likely mechanism of protection against meningococci. • 3-dose schedule: Retrospective analyses of immunogenicity data showed that the ≥4-fold and composite responses after two Trumenba doses were similar when the first two doses were administered 1 or 2 months apart; in subset of participants who receivd a third dose of Trumenba, post-dose #3 hSBA responses were similar regardless if the interval between the first two doses was 1 or 2 months. • 2-dose schedule (0 and 6 months): Immunogenicity data show ≥4-fold increase in hSBA titers, for each MenB primary strain, relative to hSBA titers prior to vaccination.	• The results from analyses included in the sBLA support a change in the vaccination intervals for the existing 3-dose schedule (0, 1-2 and 6 months), and accelerated approval of a new 2-dose schedule (administered at 0 and 6 months).
Risk	• 3-dose schedule: Analyses of safety data by 4 time intervals indicated that the frequency of SAEs among the 7 studies overall was consistent with the SAE rates reported in the 4 controlled trials.	• No new concerns were identified following a review of the SAEs categorized by 4 time intervals.
Risk Management	• The Risk Management Plan is unchanged from the Plan approved in STN 125549.0. The overall clinical benefit of the proposed Trumenba vaccination schedules is favorable compared to the risks associated with vaccination.	• The risks for the 3-dose and 2-dose schedules are adequately described in the label and the pharmacovigilance plan. adequate for continued assessment of safety in the post-marketing period.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of the 3-dose (0, 1-2 and 6 months) and the 2-dose (0,6m) schedules is favorable compared to the risks associated with vaccination. The safety of Trumenba is adequately described in the package insert, and the pharmcovigilance plan is unchanged from the plan approved in STN 125549.0.

11.3 Discussion of Regulatory Options

Flexibility in the intervals between the first two doses in the 3-dose series (0, 1-2 and 6 months) may be beneficial in certain situations when a person is at significantly high risk of exposure to MenB disease (e.g., during an outbreak of invasive meningococcal B disease) during months 1 and 6; control of MenB disease might be facilitated by vaccination with Trumenba when the first two doses can be administered at a shorter interval (0 and 1 months) vs. waiting for a 2 month time period before being able to administer the second dose.

Completion of a vaccination series given at 0 and 6 months may be beneficial if compliance can be improved with schedule consisting of a fewer number of doses and a longer interval between the first and second vaccinations was possible without the risk of exposure to serogroup B meningococci during months 1 and 6.

Regulatory considerations for accelerated approval of the proposed schedules took into consideration the continued public health urgency for control of MenB outbreaks. Immunogenicity evaluations of the 3-dose and 2-dose schedules were based on endpoints that were analogous to the primary endpoints agreed upon by CBER for the confirmatory studies, and Trumenba administered by each schedule shows an effect that is reasonably likely to predict clinical benefit. Similar to the requirements for accelerated approval of the 3-dose schedule (0, 1-2 and 6 months), a confirmatory study will be conducted to verify and further describe the clinical benefit of the Trumenba 2-dose schedule.

Extrapolation of the safety and immunogenicity (inferred effectiveness of Trumenba in adolescents to two age groups (10 to <11 and 19 to <26 years of age) is supported because the mechanism of protection against invasive meningococcal serogroup B disease, hSBA responses and safety profile following Trumenba vaccination are expected to be sufficiently similar in each of the age groups compared to adolescents. The confirmatory studies conducted as a requirement for accelerated approval of Trumenba includes all age groups (10 to <26 years of age).

11.4 Recommendations on Regulatory Actions

The immunogenicity and safety data submitted in this application support accelerated approval of the following Trumenba vaccination schedules

- Three-dose schedule: a dose (0.5mL) administered at 0, 1-2, and 6 months.
- Two-dose schedule: a dose (0,5mL) administered at 0 and 6 months.

11.5 Labeling Review and Recommendations

Main changes

- Dosage and Administration: changed from “Three doses (0.5 mL each) by intramuscular injection according to a 0, 2, and 6 month schedule” to

"Three-dose schedule: Administered a dose (0.5mL) at 0, 1-2, and 6 months.
Two-dose schedule: Administer a dose (0.5mL) at 0 and 6 months"

- Adverse Reactions and Clinical studies (sections 6 and 14, respectively): updated with information from study B1971012 (general description local and systemic reactions for the 2-dose schedule, and hSBA responses for the 3-dose and 2-dose schedules).

Please see the regulatory project manager's review memo for a detailed description of the changes to the package insert.

11.6 Recommendations on Postmarketing Actions

For the 3-dose schedule, the postmarketing studies are unchanged from the studies included in the approval letter for STN 125549/0.

For the 2-dose schedule, postmarketing requirements are as follows

- In accordance with the accelerated approval regulations, a confirmatory study in the post-marketing period will be conducted to verify and describe further the clinical benefit of a two-dose schedule (0 and 6 months) against diverse meningococcal B strains in the US. The study will be conducted in individuals 10 to <26 years of age.
- In accordance with PREA requirements, a study is being conducted to assess the safety and immunogenicity in children 1 year to 10 years of age.