Application Type	Clinical Efficacy Supplement
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Division / Office	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
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Review Completion Date / Stamped Date	
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Applicant	Wyeth Pharmaceutical Inc.
Established Name	Trumenba®
(Proposed) Trade Name	*Neisseria meningitidis* Serogroup B bivalent rLP2086 vaccine
Pharmacologic Class	Meningococcal serogroup B Vaccine
Formulation(s), including Adjuvants, etc	Sterile liquid suspension of 60 µg of subfamily A and 60 µg of subfamily B rLP2086 (120 µg total protein) per 0.5 mL dose
Dosage Form(s) and Route(s) of Administration	0.5 mL single-dose pre-filled syringes with 60 µg of subfamily A and 60 µg of subfamily B rLP2086 (120 µg total protein) per 0.5 mL dose, to be injected intramuscularly
Dosing Regimen	✓ Standard dosing: A series of 2 doses (0.5 mL each) administered at 0 and 6 months. ✓ Accelerated dosing: 2 doses (0.5 mL each) administered at least 1 month apart, followed by a third dose at least 4 months after the second dose.
Indication(s) and Intended Population(s)	For active immunization to prevent invasive meningococcal disease caused by N. *meningitidis* serogroup B in individuals aged 10 through 25 years.

Table of Contents

1. Executive Summary 6

1.1 Introduction 6
1.2 Brief Overview of sBLA Submission 6
1.3 Major Statistical Issues and Conclusions 7

2. Clinical and Regulatory Background 8

2.1 Background 8
2.2 Previous Human Experience with the Product 8
2.4 Regulatory Activity Related to the Submission 8

3. Submission Quality and Good Clinical Practices 9

3.1 Submission Quality and Completeness 9
3.2 Compliance with Good Clinical Practices and Data Integrity 9

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines 9

5. Sources of Clinical Data and Other Information Considered in the Review 9

5.1 Review Strategy 9
5.2 BLA Documents that Serve as the Basis for the Statistical Review 10
5.3 Overview of Clinical Trials/Studies 10

6. Discussion of Individual Studies/Clinical Trials 11

6.0 General Technical Statistical Information 11
6.1 Trial #1: B1971011 14
6.1.1 History of Study Protocol 14
6.1.2 Objectives 14
6.1.3 Design Overview 14
6.1.4 Population 15
6.1.5 Study Treatments or Agents Mandated by the Protocol 15
6.1.6 Sites and Centers 15
6.1.7 Surveillance/Monitoring 16
6.1.8 Endpoints and parameters 16
6.1.9 Statistical Considerations and Statistical Analysis Plan 17
6.1.10 Study Population and Disposition 17
6.1.11 Immunogenicity Analyses 18
6.1.12 Subgroup Analyses 20
6.1.13 Safety Analyses 21
6.2 Trial #2: B1971012 21
6.2.1 History of Study Protocol and Changes in the Conduct of the Study 22
6.2.2 Objectives 22
6.2.3 Design Overview 22
6.2.4 Population 23
6.2.5 Study Treatments or Agents Mandated by the Protocol 23
6.2.6 Sites and centers 23
6.2.7 Surveillance/Monitoring 23
6.2.8 Endpoints and Criteria Related to this Submission 24
6.2.9 Statistical Considerations and Statistical Analysis Plan 24

6.2.10 Study Population and Disposition....25
6.2.11 Immunogenicity Analyses....25
6.2.12 Subgroup Analyses....29
6.2.13 Safety Analyses....29
6.3 Trial #3: B1971010....30
6.3.1 History of Study Protocol....30
6.3.2 Objectives....31
6.3.3 Design Overview....31
6.3.4 Population....32
6.3.5 Study Treatments or Agents Mandated by the Protocol....32
6.3.6 Sites and Centers....32
6.3.7 Surveillance/Monitoring....32
6.3.8 Endpoints and Criteria for Study Success....32
6.3.9 Statistical Considerations and Statistical Analysis Plan....33
6.3.10 Study Population and Disposition....33
6.3.11 Immunogenicity Analyses....34
6.3.12 Subgroup Analyses....35
6.3.13 Safety Analyses....36

7. Integrated Overview of Efficacy....36

7.1 Background....36
7.2 Overview of Efficacy....37
7.3 Efficacy Conclusions....43

8. Integrated Overview of Safety....44

8.1 Safety Design, Data, and Subject Disposition....44
8.2 Safety Results....45
8.3 Safety Conclusions....47

9. Additional Statistical Issues....47

10. Conclusions....47

List of Tables

Table 1: General Information on the Submitted Studies **11**
Table 2: Time Periods (Study Phases) for Safety Analyses **13**
Table 3: Study B1971011 Design **15**
Table 4: Disposition of Randomized Subjects for Groups 1 and 2 ..... **18**
Table 5: Results for Immune Responses Utilizing Group 2 Data and 5 Key Parameters **19**
Table 6: Estimates of hSBA GMTs and Percentages of Subjects with hSBA ≥ LLOQ after 2-dose Series for Group 2 PP Population **20**
Table 7: Estimates of hSBA GMTs after the Third Dose for the Third Dose Group 2 PP Population **20**
Table 8: Summary of SAEs Reported for Each Analysis Time Period **21**
Table 9: Study B1971012 Design **23**
Table 10: Disposition of All Subjects (Vaccine Groups as Randomized) Considered in this Review **25**
Table 11: Immunogenicity Populations Considered for Analyses: Whole Study Duration **26**
Table 12: Results for Immune Responses Utilizing Groups 1 and 2 Data and 5 Key Parameters **27**
Table 13: Results for the 5 Key Immunogenicity Objectives for the 2-Dose Per-Schedule Evaluable Immunogenicity Population for Group 4 ..... **28**
Table 14: Summary of SAEs reported for Each Analysis Time Period: Groups 1 and 2 ..... **29**
Table 15: Summary of Subjects Reporting at Least 1 SAE during the Whole Study Period, Safety Population: Groups 1, 2, 3, and 4 ..... **30**
Table 16: Study B1971010 Design **31**
Table 17: Disposition of Randomized Subjects **34**
Table 18: Subjects achieving ≥ 4-Fold Rise in hSBA Titer After the 2-Dose Series and the Third Dose **35**
Table 19: Summary of SAEs reported for Each Analysis Time Period: Group 1 ..... **36**
Table 20: Estimates of Percentages of Subjects with hSBA ≥ LLOQ after the 2-dose Series and the Third Dose for Pooled Groups 1 and 2 Data: Post-Third Dose PP Population **38**
Table 21: Numbers (%) of Subjects with hSBA titer ≥ LLOQ Five Months after the 2-Dose Series: 2-Dose Per-Schedule Evaluable Immunogenicity Population (Group 4) **40**
Table 22: Results for the 5 Key Immunogenicity Parameters after the Third Dose (Groups 1 and 2) and the 2-Dose Series (Group 3) Based on the Relevant Evaluable Immunogenicity Populations **41**
Table 23: Percentage of Subjects with hSBA Titer ≥ LLOQ for Per-schedule Evaluable Immunogenicity Population (N= 183-209) **41**
Table 24: Proportions of Subjects Achieving Composite hSBA Response after the 2-Dose Series – Study Evaluable Population **43**
Table 25: Proportions of Subjects Achieving hSBA Titer 4-fold Rise after 2-Dose Series and Third Dose for PMB2707 [B44] Strain – PP Populations **43**
Table 26: Summary of SAEs Reported for Each Analysis Time Period **45**
Table 27: Subjects Reporting at Least 1 SAE for Each Analysis Interval – Pooled 7 Studies **46**
Table 28: List of Autoimmune Conditions **47**

Glossary

Abbreviation	Definition
AE	adverse event
BDR	blinded data review
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cLIA	competitive Luminex immunoassay
CRF	case report form
CRO	contract research organization
CSR	clinical study report
EDMC	external data monitoring committee
ET	early termination
EU	European Union
FDA	Food and Drug Administration (United States)
fHBP	factor H binding protein
GCP	Good Clinical Practice
GMR	geometric mean ratio
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
hSBA	serum bactericidal assay using human complement
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
MCAR	missing completely at random
MCV4	meningococcal conjugate vaccine
mITT	modified intent-to-treat
ML	maximum likelihood
MnB	*Neisseria meningitidis* serogroup B
OMV	outer membrane vesicle
rLP2086	recombinant lipoprotein 2086
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
Tdap	tetanus, diphtheria, and acellular pertussis
US; USA	United States; United States of America

1. Executive Summary

1.1 Introduction

Pfizer submitted the original Biologics License Application (BLA) STN 125549/0 on June 14, 2014. The application was submitted under the Accelerated Approval licensure pathway for licensing the bivalent rLP2086 vaccine (Trumenba®). On October 29, 2014, the Agency granted approval for Trumenba® to be administered in 3 doses on the 0, 2, and 6-month schedule. The vaccine is intended for active immunization of individuals 10 through 25 years of age to prevent invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroup B.

On March 27, 2015, the applicant submitted this efficacy supplement (STN 125549/17), requesting a change in the Trumenba® dosing regimen.

1.2 Brief Overview of sBLA Submission

The objective of this sBLA review is to assess the applicant's request for a change in the Trumenba® vaccine administration. The change of the Trumenba® schedule was proposed in the initial application of this supplement and revised in Amendment STN 125549/17.9, specifically:

1. First, the applicant proposed administration of two doses given at least one month apart and an optional booster (the third dose) given four months later.
2. Next, the applicant proposed the second Trumenba® dosing regimen consisting of:
   - ✓ Standard dosing: A series of 2 doses (0.5 mL each) administered at 0 and 6 months.
   - ✓ Accelerated dosing: 2 doses (0.5 mL each) administered at least 1 month apart followed by the third dose given at least 4 months after the second dose.

The second proposal was needed because data submitted in the supplement did not support a schedule in which the third dose of Trumenba® is optional.

Additionally, the applicant acknowledged that the accelerated schedule may be needed for individuals at increased risk of disease (e.g., microbiology laboratory workers) and in a situation of outbreak control. Meanwhile, a 0, 6 month schedule may be adequate for routine vaccination.

Justification for the applicant's proposed dosing regimen was based on a retrospective review of the immunogenicity and safety data generated by three Phase 2 studies (B1971010, B1971011, and B1971012) previously submitted to the Biologics License Application STN 125549/0. Evaluations of the immune responses to Trumenba® 1 month after the 2-dose series and the third dose in the relevant populations utilized 5 key parameters or 4-fold titer increase defined in Section 6.0 of this review. It was agreed that the safety assessment of Trumenba®

is to be based only on consideration of serious adverse events (SAEs) in each study for 4 phases/periods of time defined in Section 6.0 of this review (Table 2).

Assessment of the immune responses induced by Trumenba® utilized measurements of serum bactericidal assays using human complement (hSBA), performed for *Neisseria meningitidis* serogroup B (MnB) primary (indicator) strains expressing lipoprotein 2086 (LP2086) subfamily A and B proteins. Measurements were to be performed one month after the 2-dose series and the third dose vaccinations. Assessments were based on 5 key parameters which are defined in Section 6.0 of this review.

1.3 Major Statistical Issues and Conclusions

To support a change in the Trumenba® administration, the applicant submitted to this sBLA data generated by three clinical trials -- B1971011, B1971012, and B1971010 -- designed to evaluate Trumenba® administration **only** as a 3-dose series on the 0-, 2-, and 6-month schedule. After careful evaluation of the submitted material, substantial concerns related to validation of the proposed change are to be mentioned:

- The new objective of the modified Trumenba® dosing regimen in the population aged 10 to 25 years was formulated retrospectively.
- The use of vaccine was tested only in the population aged 11 to 19 years.
- Assessments of the immunogenicity data were performed using *post-hoc* statistical analyses.
- Evaluation of immune responses to the vaccine after standard and/or accelerated dosing was based only on tests for 4 primary MnB strains. Therefore, data generated by the submitted studies do not provide information on the breath of protection against MnB meningococcal disease.

Safety evaluations taking into account only SAE data indicated that the overall rates of SAEs for Trumenba® vaccinees assessed based on the pooled data from the 3 studies B1971011, -1010, and -1012 for four safety phases were consistent with the rates of SAEs estimated for the pooled seven studies.

It is worth noting that eleven (11) Trumenba® vaccinees were diagnosed with autoimmune conditions during the three Phase 2 studies. As per the applicant, all 11 autoimmune conditions were considered not related to vaccination.

Conclusions related to the immunogenicity and safety

Data generated by the three studies included in this submission do not support changing the Trumenba® dosing regimen from a 3-dose series to a 2-dose series given at least 1 month apart, potentially followed by a third dose administered any time after at least 4 months. However, the applicant's modified proposal to change Trumenba® administration from a 3-dose regimen (0, 2, and 6-month schedule) to standard and accelerated dosing may be acceptable under the Accelerated Approval licensure pathway.

Based on the available data submitted in this sBLA, a safety imbalance between the Trumenba® vaccinees and controls was not established.

The statistical reviewer defers to the clinical reviewer on the final assessment of the clinical relevance of the immunogenicity and safety issues reported in this review.

2. Clinical and Regulatory Background

2.1 Background

The applicant developed a novel investigational vaccine based on the bacterial surface-expressed, outer-membrane lipoprotein LP2086, which is also a factor H binding protein (fHBP). Development of the bivalent rLP2086 (Trumenba®) vaccine was conducted under IND 13812. Extensive discussions took place between Pfizer and CBER throughout the program development, and CBER's input and guidance were incorporated into the Phase 2 clinical development program. The candidate bivalent rLP2086 (Trumenba®) vaccine is currently being evaluated in Phase 3 clinical trials under IND 13812.

2.2 Previous Human Experience with the Product

The clinical development of the bivalent rLP2086 vaccine began in 2006 with three early Phase 1 studies -- B1971007, B1971006, and 6108A1-500 -- conducted in subjects aged 18 months to 36 months (99 subjects enrolled), 8 to 14 years (127 subjects enrolled), and 18 to 25 years (103 subjects enrolled), respectively. Later, in three Phase 2 studies -- B1971010, B1971011, and B1971012 -- 4056 subjects received at least 1 dose of the bivalent rLP2086 vaccine (Trumenba®). Additionally, in four Phase 1 and 2 small clinical trials, 524 subjects received at least one dose of the bivalent rLP2086. On October 29, 2014, based on data from 7 clinical trials, the Agency granted approval for Trumenba® to be administered in 3 doses on the 0, 2, and 6-month schedule for active immunization of individuals 10 through 25 years of age.

2.4 Regulatory Activity Related to the Submission

In February and March 2015, many discussions and communications took place between Pfizer and CBER in an effort to reach agreement on materials, datasets, and programs needed for a revision of the Dosage and Administration section of the current PI (Product Information) for Trumenba®.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The efficacy supplement BLA 125549/17, submitted on March 27, 2015, did not contain the required documentation and datasets. Therefore, the submission was not reviewable. After CBER's IR letters and teleconference, the applicant provided all requested materials (e.g., SAP addendum for three Phase 2 clinical trials, corresponding datasets, and analysis programs) in Amendments STN 125549/17.1 (May 1, 2015), STN 125549/17.2 (May 20, 2015), and STN 125549/17.4 (August 6, 2015).

After the second Amendment (17.2), the submitted materials were sufficient to enable statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

As per the applicant, data submitted to this efficacy supplement were generated by three clinical studies conducted in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

This section is not applicable to the statistical review.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The use of Trumenba® for individuals aged 10 to 25 years as the 3-dose regimen (on the 0-, 2-, and 6-month schedule) was granted by CBER based mainly on data collected in trials B1971011, B1971012, and B1971010, which the applicant considered as the pivotal studies in the original BLA STN125549/0 submission. Now, data generated by the same Phase 2 studies are to be utilized to support a change of the current Dosage and Administration instruction for the use of Trumenba® which is stated in the current USPI (United States Product Information). Statistical analyses regarding the 2-dose series plus the third dose schedule appear to be similar to the ones performed for the 3-dose schedule, but they should not be performed in the context of a 3-dose schedule. Instead, they are to be performed in the context of the 2-dose series (primary vaccination) plus potential third dose schedule. As it was shown that data submitted in the supplement did not support a schedule in which the third dose of Trumenba® is optional, the applicant has proposed to consider a Trumenba® dosing regimen consisting of Standard Dosing schedule (for routine vaccination) and Accelerated Dosing schedule (for vaccination in the case of outbreak control and for individuals at increased risk of disease).

Detailed information about clinical trials B1971012, B1971010, and B1971011 was originally submitted to support BLA STN BL 125549/0 under the Accelerated Approval licensure pathway for licensing Trumenba® for individuals 10 through 25 years of age as a 3-dose regimen. The extensive review of data generated by these clinical trials was provided in the statistical review of the original submission BLA 125549/0. Therefore, in the current review, as no changes were introduced into the CSRs of these three studies, only the synopses of studies and the most important results of the immunogenicity and safety assessments relevant to the objective of this submission, i.e., relevant to the proposed vaccine administration change, are presented.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

The complete submission that contained the Summary of Clinical Efficacy document, SAS datasets, and other related materials was supplied by the applicant mainly in three steps on March 3, May 1, and May 15, 2015, and is located in the EDR under STN 125549/17.0, STN 125549/17.1, and 125549/17.2.

Evaluations of Trumenba® described in this statistical review are based on the above mentioned complete submission and the statistical reviewer's analyses performed on the supplied SAS datasets.

For preparation of this review, the following volumes were mainly used:

From Amendment 17.1:
- ✓ Module 1.11.3: Clinical Information Amendment (Response and Summary)
- ✓ Module 5.3.5.:
  - Revised statistical analysis plans for B1971010, B1971011, and B1971012 studies.
  - Datasets and SAS programs.

From Amendment 17.2:
- ✓ Module 1: Administrative information and labeling.
- ✓ Module 5.3.5.:
  - All requested safety data
  - Immunogenicity disposition data and SAS programs.

From Amendment 17.4:
- ✓ Module 1.11.3: Response to statistical IR letter (regarding study B1971012).

From Amendment 17.9:
- ✓ Module 1.11.3: Response to statistical IR letter (regarding study B1971012).

5.3 Overview of Clinical Trials/Studies

Basic information about the studies included in the efficacy supplement is summarized in Table 1.

Table 1: General Information on the Submitted Studies

Study (Region)	Study Objectives	Study Population	Vaccine Schedule	# of subjects randomized
B1971010 (EU)	To assess safety and immunogenicity of Trumenba when used with Repevax	Adolescents 11 to 19 years old	Trumenba at 0, 2, 6-month. Repevax at 0-month (saline at 2, 6-month)	749
B1971011 (US)	To assess safety and immune response to HPV without and with Trumenba and to assess Trumenba alone	Adolescents 11 to 18 years old	Trumenba at 0, 2, 6-month. HPV at 0, 2 ,6--month	2499
B1971012 (EU)	To assess safety and immunogenicity of Trumenba	Adolescents 11 to 19 years old	Trumenba at 0, 1, 6-month; 0, 2, 6-month; 0, 4-month; 0, 6-month;	1713

Source The statistical reviewer's table based on the studies protocols

All three studies under consideration presented safety and immunogenicity data after the second dose of Trumenba®. However, only the post-vaccination 3 data were used previously for the primary statistical analyses of the immune responses to Trumenba®. As per Table 1, the main objectives of Phase 2 studies B1971010 and B1971011 were evaluations of Trumenba® administered concomitantly with other vaccines. Data generated by study B1971012 provided information on immune responses to Trumenba® alone after the second dose and under different vaccine schedules. Immune responses to Trumenba® after the second dose were previously evaluated as the secondary and/or exploratory objectives, and the statistical analyses were performed in the context of a 3-dose schedule.

6. Discussion of Individual Studies/Clinical Trials

6.0 General Technical Statistical Information

As the studies have already been closed, in order to support and justify the proposed change to the Dosage and Administration section of the label, instead of creating additional amendments to study protocols, the applicant proposed, after discussions with CBER, to introduce additional exploratory objectives and description of analyses in a SAP addendum. The *post-hoc* exploratory objectives to assess the new proposed Trumenba® dosing regimen, the details of the analysis populations, and the planned exploratory analyses were defined in the "Statistical Analysis Plan Addendum for 2-dose Series Related Analyses" (dated April 22, 2015) and in Amendment 17.9.

Evaluation of Immunogenicity

The following three regimens were considered and evaluated using the descriptive *post-hoc* analyses:

- Two doses administered 1 month apart and optionally followed by a third dose (the third dose is called "booster" by the applicant) at least 4 months after the second dose,
- Two doses administered at 0 and 6 months (referred to as "standard dosing") for routine vaccination,

- Two doses administered at least 1 month apart, followed by the third dose given at least 4 months after the second dose (referred to as "accelerated dosing") in the case of outbreak control and for individuals at increased risk of disease.

For evaluations of immune responses to Trumenba® (1 month after the 2-dose series and the third dose) observed in three clinical trials, special Per Protocol and mITT populations were defined in the following way:

For the 2-dose series:

- Evaluable immunogenicity Per-Protocol population consisting of all subjects who were eligible for the study, have been randomized, have received all investigational products at the first 2 vaccination visits as scheduled and randomized, have blood drawn prior to the first dose of vaccine (pre-vaccination draw) and within 28-42 days after vaccination 2 (post-vaccination 2 draw), have valid and determinate assay results for the post-vaccination 2 analysis, have received no prohibited vaccines or treatment through 1 month post-vaccination 2, and have no other major protocol violations through 1 month post-vaccination 2.
- The mITT population comprising all subjects who have been randomized and have at least one valid and determinate assay result for the post-vaccination 2 analysis.

For the third dose:

- Per-Protocol evaluable immunogenicity population consisting of all subjects who were eligible for the study, have been randomized, have received all investigational products at the 3 vaccination visits as scheduled and randomized, have blood drawn prior to the first dose of vaccine (pre-vaccination draw) and post-booster vaccination blood drawn within 28-42 days after the third dose vaccination, have valid and determinate assay results for the third dose analysis, have received no prohibited vaccines or treatment through 1 month post-third dose, and have no other major protocol violations through 1 month post- third dose.
- The mITT population comprising all subjects who have been randomized, have received the 2-dose series, and have at least one valid and determinate assay result for the post-third dose analysis.

Note: Definitions of the immunogenicity PP and mITT populations can be slightly different for different clinical trials due to the differences in the study designs.

For the three studies B1971010, B1971011, and B1971012, and for the evaluation of the immune responses to Trumenba® 1 month after the 2-dose series and the third dose, the following 5 key parameters were used:

(1) - (4) For each of four primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], proportion of subjects achieving at least 4-fold increase in hSBA titer from baseline to one month post 2-dose series and the third dose,

(5) Proportion of subjects achieving a composite hSBA response defined as hSBA titer ≥ LLOQ for all 4 primary strains combined at one month after the 2-dose series and the third dose.

Per definition, the 4-fold increase took place if:

- hSBA titer after vaccination was ≥ 1:16, for subjects with a baseline hSBA titer below LOD (i.e., with baseline hSBA titer < 1:4),
- hSBA titer after vaccination was greater than or equal to four times the LLOQ, for subjects with a baseline hSBA titer ≥ LOD (i.e., with baseline hSBA titer ≥ 1:4) but < LLOQ,
- hSBA titer after vaccination was greater than or equal to four times the baseline titer, for subjects with a baseline hSBA titer ≥ LLOQ.

Evaluation of Safety

For evaluations of the safety profile in this submission, only serious adverse events (SAEs) were considered. The safety profile was characterized by frequency of SAEs for two time periods for each: 2-dose series of Trumenba® and the third dose.

For studies B1971010 (Group 1 and Group 2), B1971011 (Group 1, 2, and 3), and B1971012 (Group 1 and 2), SAEs were summarized for 4 time periods (4 phases of study) defined in Table 2. The percentage of subjects reporting at least one SAE and the number of episodes were estimated for each group of a given study for each of the 4 time periods.

Table 2: Time Periods (Study Phases) for Safety Analyses

Analysis Interval	Interval Start date (inclusive)	Interval Stop (inclusive)
The 2-dose series vaccination phase	Vaccination date	Post-vaccination 2 visit (or withdrawal date if date of
The 2-dose series follow-up phase	If the third dose date exists: post-vaccination 2 visit +1 month If no the third dose given: withdrawal date +1 if withdrawal occurred before planned the third dose date	The third dose vaccination date (-1 day) if the third dose date exists If no the third dose date exists: 6 month follow-up date
Third dose phase	The third dose vaccination date	Post-third dose visit (or withdrawal date if withdrawal after the third dose and 1 month following the third dose date)
Third dose follow-up phase	Post-third dose visit date +1 (or withdrawal date+1 if between the third dose and 1 month after the third dose date	6 mon h follow-up date

Source Table based on the applicant's table included in Statistical Analysis Plan Addendum (page #10)

6.1 Trial #1: B1971011

Title of the clinical trial: "*A Phase 2, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of Gardasil (HPV) Vaccine and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥ 11 to <18"*

Study Initiation Date: September 28, 2011 (the first subject visit)
Study Completion Date: May 6, 2013 (the last subject visit)
Final Serology Date: December 18, 2013

6.1.1 History of Study Protocol

As a result of extensive communications between CBER and the applicant regarding the B1971011 protocol, the applicant introduced several important changes into the protocol and the Statistical Analysis Plan (SAP). Revisions of the study design included changes in the immunogenicity and safety endpoints, as well as modifications of statistical evaluations.

6.1.2 Objectives

The main objective of study B1971011 was to assess the safety, tolerability, and immunogenicity of Gardasil administered concomitantly with Trumenba® (bivalent rLP2086 vaccine) as compared to safety, tolerability, and immunogenicity of Gardasil® or Trumenba® vaccines administered alone.

Detailed information on the study objectives and endpoints was given in Section 6.1 of the Statistical Review of STN 125549/0.

6.1.3 Design Overview

Study B1971011 was a Phase 2, randomized, active-controlled, observer-blinded, multicenter clinical trial carried out in the US. Subjects were enrolled into the study if in good health, as judged by physical assessment and medical history, and if they met all inclusion criteria and none of the exclusion criteria. It was planned that approximately 2500 healthy adolescents age ≥ 11 to < 18 years at the time of study entry would be enrolled and randomized to one of 3 groups (Group 1, Group 2, Group 3) in a 2:2:1 ratio to receive Trumenba® + Gardasil®, Trumenba® + saline, and saline + Gardasil®, respectively. Vaccination schedules for each group are presented in Table 3.

Table 3: Study B1971011 Design

Month #	Month 0	Month 2	Month 3	Month 6	Month 7	Month 12
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Group 1	Trumenba+ Gardasil	Trumenba+ Gardasil		Trumenba + Gardasil		Phone contact
Group 2	Trumenba + Saline	Trumenba + Saline		Trumenba + Saline		Phone contact
Group 3	Saline + Gardasil	Saline + Gardasil		Saline + Gardasil		Phone contact
Blood draw (all groups)	~20 mL		~20 mL		~20 mL	

Source The statistical reviewer's Table based on the study protocol

All vaccinations were administered using the 0-, 2-, 6-month schedule.

6.1.4 Population

At the time of enrollment (baseline), the study population consisted of 11-18 year-old females and males:

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and/or a legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

6.1.5 Study Treatments or Agents Mandated by the Protocol

The vaccination groups and the vaccination plan per study group are presented in Table 3 of this review.

The investigational products were supplied by the applicant and they were:

- ✓ Trumenba® - a 0.5-mL dose formulated to contain 60 μg (total 120 μg) each of a purified subfamily A and a purified subfamily B rLP2086 protein, [redacted] polysorbate 80, and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0.
- ✓ Gardasil® - Human Papillomavirus (HPV) Quadrivalent (Types 6, 11, 16, 18) Recombinant vaccine - a 0.5-mL dose.
- ✓ Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose.

6.1.6 Sites and Centers

Multiple (63) sites in the US participated in the study. One additional site (#1018) received investigational product but did not enroll any subjects.

6.1.7 Surveillance/Monitoring

The final protocol, all amendments, and informed consent document (ICD) were reviewed and approved by the institutional review board(s) (IRBs) and/or independent ethics committee(s) (IECs) for each investigational center participating in the study.

6.1.8 Endpoints and parameters

In order to assess the immune responses to Trumenba® vaccine (Group 1 and Group 2) using hSBA, blood samples (approximately 20 mL each) were drawn from each subject immediately before Vaccination 1, 28 to 42 days after the second dose (Vaccination 2), and 28 to 42 days after the third dose (Vaccination 3).

Study endpoints and parameters related to this submission

Immunogenicity endpoints were:

- ✓ Titers at baseline and 1 month after the 2-dose series and the third dose vaccinations
- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the 2-dose series and the third dose vaccinations.
- ✓ Proportion of subjects achieving a composite hSBA response defined as hSBA titer ≥ LLOQ for all 4 primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], PMB2707 [B44] combined.
- ✓ hSBA geometric mean titers (GMTs) for each of the 4 primary strains 1 month after the 2-dose series and the third dose vaccinations.
- ✓ Proportion of subjects with hSBA titer ≥ LLOQ for each primary strain.

Safety endpoints/parameters

In this submission, assessments of vaccine safety were carried out during the 2-dose series, and after the third dose vaccination and follow-up phases, and took into consideration only occurrences of SAEs. As stated in Section 6.0 of this review, the percentages of subjects reporting at least one SAE and the numbers of episodes were summarized for each group in each of the 4 periods of time.

More information on immunogenicity and safety endpoints and parameters considered in in the original study protocol can be found in Section 6.1.8 of the Statistical Review of STN 125549/0.

6.1.9 Statistical Considerations and Statistical Analysis Plan

Hypotheses

Information on the original hypotheses for the primary objectives and their evaluations can be found in the Statistical Review of STN 125549/0.

Statistical analysis

For the purpose of descriptive evaluations of immune responses to Trumenba® 1 month after the 2-dose series and the third dose, 5 key parameters defined in Section 6.0 of this review, GMTs, and percent of subjects with titers ≥ LLOQ for each of four primary strains and the corresponding 95% CIs were estimated for Groups 1 and 2, using corresponding populations.

Safety data collected during the study course were evaluated utilizing frequencies of events during the 2-dose series and the third dose periods.

6.1.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects were balanced across the three vaccination study groups. Males and females constituted 66.5% and 33.5% of the subjects, respectively, and these gender ratios were similar across the vaccine groups. The majority of subjects were white (81.6%). The younger age group (11 to < 15 years old) constituted 65.9% of the subjects. The mean age (± SD) at the first vaccination was 13.6 (±1.92) years, while ages ranged from 11 to 17 years.

Disposition of subjects

A total of 2499 subjects were randomized and included in the Intent-To-Treat (ITT) population. A summary of the randomized subjects' disposition is presented in Table 4 only for Groups 1 and 2, as the statistical analyses related to the objective of this submission were performed only on these two groups' data.

Table 4: Disposition of Randomized Subjects for Groups 1 and 2

Disposition of Subjects	**Group 1** Trumenba + Gardasil n(%)	**Group 2** Trumenba + Saline n(%)
Randomized	999	998
Withdrawn before vaccination	6 (0.6)	8 (0.8)
2-Dose series vaccination phase[a] – completed	904 (90.5)	912 (91.4)
2-Dose series vaccination phase– withdrawn	89 (9)	78 (8)
2-Dose series follow-up phase[b] - completed	**872 (87.3)**	**869 (87)**
2-Dose series follow-up phase - withdrawn	32 (3)	43 (4)
Third dose vaccination phase[c] – completed	864 (86.5)	860 (86.2)
Third dose vaccination phase– withdrawn	8 (1)	9 (1)
Third dose follow-up phase[d] - completed	**848 (84.9)**	**841 (84.3)**
Third dose follow-up phase – withdrawn	16 (2)	19 (2)
Completed the 6 Month follow-up contact[e]	875 (87.6)	879 (88.1)

Source Table based on the applicant's table (Response Document, Page 18)

Note 2-Dose series = vaccination at Day 1 (Visit 1) and Month 2 (Visit 2). Booster dose = vaccination at Month 6 (Visit 4).

a. 2-Dose series vaccination phase = from Vaccination 1 to 1 month after Vaccination 2.

b. 2-Dose series follow-up phase = from 1 month after Vaccination 2 to the third dose.

c. Third dose phase = from booster dose through 1 month after the third dose.

d. Third dose follow-up phase = from 1 month after the third dose through the end of the study.

e. A telephone contact at 6 months after the last vaccination.

6.1.11 Immunogenicity Analyses

Datasets analyzed

Post-hoc statistical analyses performed within the framework of this submission were based only on data from Groups 1 and 2.

- Of the 999 subjects randomized in Group 1 (Trumenba®+Gardasil®):
  - 857 (85.8%) subjects were included in the 2-dose series evaluable immunogenicity population (per-protocol),
  - 814 (81.5%) subjects were included in the third dose evaluable immunogenicity population,
  - 901 (90.2%) and 861 (86.2%) subjects, were included in the 2-dose series mITT population and in the third dose mITT population, respectively.
- Of the 998 subjects randomized in Group 2 (Trumenba®+Saline):
  - 849 (85.1%) subjects were included in the 2-dose series evaluable immunogenicity population (per-protocol),
  - 812 (81.4%) subjects were included in the third dose evaluable immunogenicity population,
  - 909 (91.1%) and 812 (81.4%) subjects were included in the 2-dose series mITT population and in the third dose mITT population, respectively.

Analyses Related to Main Immunogenicity Objective

The main immunogenicity objective of this submission was to assess immune response to Trumenba® 1 month after the 2-dose series and the third dose using 5 key parameters that were defined in Section 6.0 of this review. Results of assessments performed are shown in Table 5.

Table 5: Results for Immune Responses Utilizing Group 2 Data and 5 Key Parameters

A. Results after the 2-dose series - based on the 2-dose series evaluable immunogenicity population

Variables	Strain/Variant	# of subjects*	Estimate of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	827	74.0	(70.9, 77.0)
hSBA Titer 4-fold rise	PMB2001 [A56]	758	92.7	(90.7, 94.5)
hSBA Titer 4-fold rise	PMB2948 [B24]	790	63.5	(60.1, 66.9)
hSBA Titer 4-fold rise	PMB2707 [B44]	807	48.8	(45.3, 52.3)
Composite hSBA response	**For 4 primary strains**	**757**	**52.6**	**(48.9, 56.2)**

B. Results after the third dose - based on the third dose evaluable immunogenicity population

Variables	Strain/Variant	# of subjects*	Estimate of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	788	86.4	(83.8, 88.7)
hSBA Titer 4-fold rise	PMB2001 [A56]	730	95.3	(93.6, 96.8)
hSBA Titer 4-fold rise	PMB2948 [B24]	774	84.8	(82.0, 87.2)
hSBA Titer 4-fold rise	PMB2707 [B44]	788	80.7	(77.8, 83.4)
Composite hSBA response	For 4 primary strains	763	83.9	(81.1, 86.4)

Source The reviewer's table based on the Response Document, April 2015, Tables 15 and 16

# of subjects - number of subjects with valid and determinate hSBA titers for the given strain at both the specified time points*

Note LLOQ = 1 16 for PMB80 [A22]; LLOQ =1 8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]

Note The 4-fold increase is defined in Section 6.0 of this review.

Table 5 demonstrates that the proportions of subjects from Group 2 achieving 4-fold increase in hSBA titer from baseline to one month after the 2-dose series were 74% for strains PMB80 (A22), 92.4% for PMB2001 (A56), 63.5% for PMB2948 (B24), and 48.8% for PMB2707 (B44), while 52.6% of subjects achieved the composite hSBA response (hSBA ≥ LLOQ for all 4 primary MnB test strains combined). As per Table 5, estimates of immune responses after the third dose are notably higher than after the 2-dose series, especially for family B strains and for the composite hSBA response.

Table 6 presents GMTs and percentages of subjects with hSBA ≥LLOQ after the 2-dose series estimated for the 2-dose series evaluable immunogenicity population for Group 2.

Table 6: Estimates of hSBA GMTs and Percentages of Subjects with hSBA ≥ LLOQ after 2-dose Series for Group 2 PP Population

Strain/Variant	Variables	# of Subjects	Estimate	95% CI
PMB80 [A22]	GMT	841	34.0	(32.0, 36.0)
PMB80 [A22]	% of subjects with hSBA ≥ LLOQ	841	86.2	(83.7, 88.5)
PMB2001 [A56]	GMT	833	77.4	(73.0, 82.0)
PMB2001 [A56]	% of subjects with hSBA ≥ LLOQ	833	98.6	(97.5, 99.3)
PMB2948 [B24]	GMT	809	16.4	(15.3, 17.7)
PMB2948 [B24]	% of subjects with hSBA ≥ LLOQ	**809**	**74.9**	**(71.8, 77.9)**
PMB2707 [B44]	GMT	813	12.2	(11.2, 13.3)
PMB2707 [B44]	% of subjects with hSBA ≥ LLOQ	**813**	**58.3**	**(54.8, 61.7)**

Source: The reviewer's table based on the applicant's Response Document, April 2015

Note LLOQ = 1 16 for PMB80 [A22]; LLOQ =1 8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44].

*Note Titers below the LLOQ were set to 0.5*LLOQ for analysis.*

Table 7: Estimates of hSBA GMTs after the Third Dose for the Third Dose Group 2 PP Population

Strain/Variant	Variables	# of Subjects	Estimate	95% CI
PMB80 [A22]	GMT	801	57.8	(54.4, 61.4)
PMB2001 [A56]	GMT	802	128.2	(120.6, 136.3)
PMB2948 [B24]	GMT	793	28.0	(26.2, 29.9)
PMB2707 [B44]	GMT	795	31.9	(29.3, 34.8)

Source: The reviewer's table based on the applicant's Response Document, April 2015

Note LLOQ = 1 16 for PMB80 [A22]; LLOQ =1 8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44].

*Note Titers below the LLOQ were set to 0.5*LLOQ for analysis.*

As shown in Tables 6 and 7, for Group 2, the hSBA GMTs at 1 month after the 2-dose series were 34, 77.4, 16.4, and 12.2, while 1 month after booster were 57.8, 128.2, 28.0, and 31.9, for strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], PMB2707 [B44], respectively. These results demonstrate that GMTs were notably higher after the third dose than after the 2-dose series. Please note that for family B strains PMB2948 [B24] and PMB2707 [B44], 25.1% and 41.7% of subjects, respectively, had titers below LLOQ after the 2-dose series. But, the corresponding numbers after the third dose were 7.4% and 14.3%.

Analyses based on 5 key parameters related to four primary MnB strains showed no substantial differences between Groups 1 and 2, but hSBA GMTs and proportions of subjects with titers greater than LLOQ for Group 2 (Trumenba + Saline) were higher than those for Group 1 (Trumenba + Gardasil).

6.1.12 Subgroup Analyses

Results for subgroup analyses can be found in the Statistical Review of STN 125549/0, Section 6.1.11.12.

6.1.13 Safety Analyses

The primary safety objective of this study was to evaluate the safety profile of Trumenba®. As per the study protocol, the profile was measured by the proportions of subjects reporting local reactions, systemic events, and adverse events (AEs). Complete safety evaluation for the 3-dose series of Trumenba® can be found in the statistical and clinical reviews of STN 125549/0, Section 6.1.13.

For the purpose of this statistical review, only serious adverse events (SAEs) were considered for the 3 study groups in each of the 4 study phases (periods of time) defined in Section 6.0 (Table 2). A total of 2483 subjects were included in the safety population (992 subjects from Group 1; 990 subjects from Group 2; 501 subjects from Group 3).

Based on the entire safety population (Clinical Study Report, B1971011, page 168), a total of 32 (1.3%) subjects reported SAEs: 12 (1.2%) subjects from Group 1, 16 (1.6%) subjects from Group 2, and 4 (0.8%) subjects from Group 3.

Numbers of SAEs observed in the 4 time periods are presented in Table 8.

Table 8: Summary of SAEs Reported for Each Analysis Time Period

	During 2-dose series vaccination phase	During 2-dose series follow-up phase	During the third dose phase	During the third dose follow-up phase
# of Subjects in Group 1	992	992	871	848
# of SAEs in Group 1 # (%) of subjects with at least one SAE	4 4 (0.4)	2 2 (0.2)	2 2 (0.2)	5 4 (0.5)
# of Subjects in Group 2	990	990	869	845
# of SAEs in Group 2 # (%) of subjects with at least one SAE	4 4 (0.4)	4 4 (0.4)	1 1 (0.1)	8 7 (0.8)
# of Subjects in Group 3	501	501	452	439
# of SAEs in Group 3 # (%) of subjects with at least one SAE	1 1 (0.2)	1 1 (0.2)	0 0.0	2 2 (0.5)

Source The reviewer's table based on the applicant's Response Document, May 2015

The total number of SAEs reported during the whole study period was 34 (32 subjects). Of the 30 SAEs reported in Groups 1 and 2, 9 subjects had psychiatric disorders. The SAEs included 2 autoimmune cases, one case of Sydenham's chorea in Group 1 (Trumenba® + Gardasil®), and one case of IgA nephropathy in Group 2 (Trumenba® + Saline). All SAEs were claimed by the investigator as clinically unrelated to the investigational vaccine.

6.2 Trial #2: B1971012

Title of the study: *"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 Initiation Date: March 3, 2011 (the first subject visit)
Study Completion Date: September 18, 2012 (the last subject visit)
Final Serology Date: August 30, 2013

6.2.1 History of Study Protocol and Changes in the Conduct of the Study

The original study protocol was submitted to CBER on April 20, 2010, and was followed by four amendments and one document related to the administrative changes made to the final amendment. Revisions of the study design included modifications of the immunogenicity/safety endpoints and statistical evaluations.

It is important to note that the study conduct was interrupted. The study was restarted following implementation of a substantial protocol amendment, which extended the dosing visit time windows to allow subjects impacted by the delay to remain in the study. More information on changes in the conduct of the study can be found in Section 6.2.1 of the Statistical Review of STN 125549/0.

6.2.2 Objectives

The objective of study B1971012 was to assess the safety, tolerability, and immunogenicity of Trumenba® administered in healthy subjects aged ≥ 11 to < 19 years according to different dose schedules. The dose schedules were: (1) 0-, 1-, and 6-months, (2) 0-, 2-, and 6-months, (3) 0- and 6-months, (4) 0- and 2-months, and (5) 2- and 6-months.

Detailed information on objectives and endpoints considered in this study was provided in Section 6.2.2 of the Statistical Review of STN 125549/0.

6.2.3 Design Overview

Study B1971012 was a Phase 2, randomized, placebo-controlled, single-blind, multicenter trial carried out in the European Union. Subjects were randomly assigned to 5 groups in a 3:3:3:2:1 ratio (Group 1: Group 2: Group 3: Group 4: Group 5) to receive study vaccinations as per the study design presented in Table 9. It was planned that approximately 1716 subjects would be enrolled into this clinical trial. Subjects were stratified into 2 age groups: ≥ 11 to < 14 and ≥ 14 to < 19 years at the time of enrollment.

Table 9: Study B1971012 Design

Group #	Visit 1 Month 0	Visit 2 Month 1	Visit 3 Month 2	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 7	Visit 7 Month 12
Group 1	Trumenba	Trumenba	Saline		Trumenba		Phone contact
Group 2	Trumenba	Saline	Trumenba		Trumenba		Phone contact
Group 3	Trumenba	Saline	Saline		Trumenba		Phone contact
Group 4	Trumenba	Saline	Trumenba		Saline		Phone contact
Group 5	Saline	Saline	Trumenba		Trumenba		Phone contact
Blood draw (all groups)	20 mL		20 mL	20 mL		20 mL	

Source The applicant's table based on the study protocol, page 5

6.2.4 Population

At the time of enrollment (baseline), the study population consisted of 11-19 year-old females and males:

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and/or a legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Lucia Lee's clinical review of STN 125549/0.

6.2.5 Study Treatments or Agents Mandated by the Protocol

Vaccination plan per study group is presented in Table 9 of this review.

The investigational products:

- o Trumenba® (bivalent rLP2086) vaccine - a 0.5-mL dose formulated to contain 60 µg (120 µg total) of purified subfamily A and a purified subfamily B rLP2086 proteins, [redacted] polysorbate 80, and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0, and
- o Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose

were supplied by the applicant.

6.2.6 Sites and centers

Study B1971012 was undertaken by Wyeth, a Pfizer company, and conducted at 60 sites in the Czech Republic, Denmark, Finland, Germany, Poland, Spain, and Sweden.

6.2.7 Surveillance/Monitoring

Information on the study monitoring was provided in Section 6.2.7 of the Statistical Review of STN 125549/0.

6.2.8 Endpoints and Criteria Related to this Submission

Immunogenicity endpoints were:

- ✓ Titers at baseline and 1 month after the 2-dose series and the third dose vaccinations
- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the 2-dose series and after the third dose,
- ✓ Proportion of subjects achieving a composite hSBA response defined as hSBA titer ≥ LLOQ for all 4 primary strains combined,
- ✓ hSBA GMTs for each of the 4 primary strains 1 month after the 2-dose series and after the third dose,
- ✓ Proportion of subjects with hSBA titer ≥ LLOQ for each primary strain.

Safety endpoints/parameters

As stated in Section 6.0 of this review, percentages of subjects reporting at least one SAE and the numbers of episodes were summarized for each study group and for each of the 4 study phases (periods of time).

More information on immunogenicity and safety endpoints as well as parameters considered in the original study protocol can be found in Section 6.1.8 of the STN 125549/0 Statistical Review.

6.2.9 Statistical Considerations and Statistical Analysis Plan

Hypotheses

Information related to the original hypotheses can be found in the Statistical Review of STN 125549/0.

Statistical analysis

For the purpose of descriptive evaluations of immune responses to Trumenba® 1 month after the 2-dose series and after the third dose, the 5 key parameters defined in Section 6.0 of this review, GMTs, and the percentage of subjects with ≥ LLOQ for each of the four primary strains and the corresponding 95% CIs were estimated using relevant populations.

Safety data collected during the clinical study were evaluated utilizing frequencies of SAEs during the 2-dose series and the third dose periods.

6.2.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects were balanced across the five vaccination study groups. Males and females were equally represented in the study and across the vaccine groups. The majority of subjects were white (99%). The older age group (14 to < 19 years old) constituted 63.3% of subjects. The mean age (± SD) at the first vaccination was 14.4 (±2.20) years, while the age range was 11 to 18 years.

Disposition of subjects

A total of 1714 subjects were enrolled in this study and included in the safety analyses. A summary of the randomized subjects' disposition is presented in Table 10. Group 5 (schedule 2-, 6-months) is not considered for the 2-dose series immune response evaluation and therefore is not shown in Table 10.

Table 10: Disposition of All Subjects (Vaccine Groups as Randomized) Considered in this Review

Disposition of Subjects	**Group 1** Schedule 0,1,6-month n(%)	**Group 2** Schedule 0,2,6-month n(%)	**Group 3** Schedule 0,6-month n(%)	**Group 4**[a] Schedule 0,2-month 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 Statistical reviewer's table based on the Response Document Change in Dosing Regimen, Tables 8 and 9
Note Definition of four study phases (time periods) can be found in Section 6.0 of this review.
a. 2-Dose series vaccination phase = from Trumenba vaccination 1 to 1 month after Trumenba vaccination 2.
2-Dose series follow-up phase = from 1 month after Trumenba vaccination 2 to the end of the study

6.2.11 Immunogenicity Analyses

Note: *An unexpected serious adverse reaction (SUSAR) occurred during the B1791012 study course, and the study conduct was interrupted. Vaccinations were temporarily paused, which caused a delay in the vaccination visits of some subjects. Affected subjects were not able to meet their originally intended dosing schedule. Following the study pause, vaccination visit windows for originally intended administration were extended by 90 days and by 30 days for vaccinations at Month 6. Vaccination visit windows were*

extended to allow subjects impacted by the study pause to remain in the study. The protocol and statistical analysis plan (SAP) were modified to include sensitivity analyses designed to evaluate the impact of the vaccination delay on the observed immune responses.

Datasets Analyzed

Due to the study pause, for the purpose of the immunogenicity analyses, four immunogenicity populations were established and were used for performing primary and sensitivity immunogenicity analyses. Discussion and definitions of these populations can be found in the Statistical Review of STN 125549/0.

In this review, the per-schedule evaluable immunogenicity populations were considered as the primary immunogenicity populations for the statistical analyses for both the 2-dose series and the third dose immune responses. The per-schedule evaluable immunogenicity population (subsets of the evaluable immunogenicity population) consisted of subjects who received Trumenba® "as randomized and scheduled," taking into account the originally intended dosing schedule strict visit window criteria. Numbers of subjects included in different immunogenicity populations are summarized by group in Table 11.

Table 11: Immunogenicity Populations Considered for Analyses: Whole Study Duration

Populations	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	Group 4 n(%)
Randomized	427 (100)	430 (100)	427 (100)	286 (100)
mITT	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	***193 (45.2)***	***165 (38.4)***	***209 (48.9)***	***173 (60.5)***
Per-schedule immunogenicity population	202 (47.3)	170 (39.5)	249 (58.3)	182 (63.6)
Out-of-schedule subset population	233 (54.6)	265 (61.6)	217 (50.8)	113 (39.5)

Source: Reviewer's table based on the Clinical Study Report (original BLA 125549/0)

As per Table 11, only 45.2%, 38.4%, 48.9%, and 60.5% of randomized subjects were included in the per-schedule evaluable immunogenicity populations for Group 1, Group 2, Group 3, and Group 4, respectively.

The immunogenicity statistical analyses related to the objective of this submission were performed on the per-schedule evaluable immunogenicity population data for Groups 1, 2, 3, and 4.

- Of the 427 subjects randomized in Group 1 (0, 1, 6-month schedule)
  - 197 (46.1%) subjects were included in the 2-dose series per-schedule evaluable immunogenicity population (per-protocol),
  - 193 (45.2%) subjects were included in the third dose per-schedule evaluable immunogenicity population,

- 395 (92.5%) and 383 (89.7%) subjects were included in the 2-dose series mITT population and in the third dose mITT population, respectively.

- Of the 430 subjects randomized in Group 2 (0, 2, 6-month schedule)
  - 246 (57.2%) subjects were included in the 2-dose series per-schedule evaluable immunogenicity population (per-protocol),
  - 165 (38.4%) subjects were included in the third dose per-schedule evaluable immunogenicity population,
  - 379 (88.1.1%) and 381 (88.6%) subjects were included in the 2-dose series mITT population and in the third dose mITT population, respectively.

- Of the 427 subjects randomized in Group 3 (0, 6-month schedule)
  - 209 (48.9%) subjects were included in the 2-dose series per-schedule evaluable immunogenicity population (per-protocol),
  - 426 (99.8%) subjects were included in the 2-dose series mITT population.

- Of the 286 subjects randomized in Group 4 (0, 2-month schedule)
  - 173 (60.4%) subjects were included in the 2-dose series per-schedule evaluable immunogenicity population (per-protocol),
  - 286 (100%) subjects were included in the 2-dose series mITT population.

Analyses Related to Main Immunogenicity Objective

The main immunogenicity objective of this submission was to assess immune response to Trumenba® 1 month after the 2-dose series and after the third dose, using 5 key parameters that were defined in Section 6.0 of this review. Results of assessments performed are tabulated in Table 12.

Table 12: Results for Immune Responses Utilizing Groups 1 and 2 Data and 5 Key Parameters

I. Results after the 2-dose series based on the 2-dose per-schedule evaluable immunogenicity population

Variables	Strain/Variant	Group 1 # of subjects*	Group 1 Estimates of parameters (%) and 95% CI	Group 2 # of subjects*	Group 2 Estimates of parameters (%) and 95% CI	Group 3 # of subjects*	Group 3 Estimates of parameters (%) and 95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	187	58.8 (51.4, 66.0)	240	72.5 (66.4, 78.0)	203	82.3 (76.3, 87.7)
hSBA Titer 4-fold rise	PMB2001 [A56]	181	87.8 (82.2, 92.2)	236	90.7 (86.2, 94.1)	202	90.1 (85.1, 93.9)
hSBA Titer 4-fold rise	PMB2948 [B24]	184	51.1 (43.6, 58.5)	236	54.2 (47.7, 60.7)	200	64.5 (57.4, 71.1)
hSBA Titer 4-fold rise	PMB2707 [B44]	185	48.1 (40.7, 55.6)	236	53.4 (46.8, 59.9)	197	66.0 (58.9, 72.6)
Composite hSBA response	For 4 primary strains	173	52.0 (44.3, 59.7)	229	52.0 (45.3, 58.6)	188	72.9 (65.9, 79.1)

II. Results after the third dose based on the third dose per-schedule evaluable immunogenicity population

Variables	Strain/Variant	Group 1 # of subjects*	Group 1 Estimates of parameters (%) and 95% CI	Group 2 # of subjects*	Group 2 Estimates of parameters (%) and 95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	183	77.6 (70.9, 83.4)	162	87.7 (81.6, 92.3)
hSBA Titer 4-fold rise	PMB2001 [A56]	182	91.2 (86.1, 94.9)	160	93.8 (88.8, 97.0)
hSBA Titer 4-fold rise	PMB2948 [B24]	185	74.1 (67.1, 80.2)	161	78.3 (71.1, 84.4)
hSBA Titer 4-fold rise	PMB2707 [B44]	188	80.9 (74.5, 86.2)	159	78.6 (71.4, 84.7)
Composite hSBA response	For 4 primary strains	178	80.3 (73.7, 85.9)	159	81.8 (74.9, 87.4)

Source: The reviewer's table based on the Response Documents, April 2015 and the Clinical Study Report Addendum (page 6)

# of subjects - number of subjects with valid and determinate hSBA titers for the given strain at both the specified time points*

Note: LLOQ = 1:16 for PMB80 [A22]; LLOQ =1:8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44].

Remarks:

As per Table 12, for Groups 1 and 2 (for which the second dose of Trumenba® was administered on a 1- or 2-month schedule) immune responses after the third dose (based on the third dose per-schedule evaluable immunogenicity population) are notably higher than after the 2-dose series, especially for family B strains. Additionally, Table 12 demonstrates that:

- *For Group 2 (0-, 2-, and 6- month schedule), the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series and after the third dose have tendency to be higher than for Group 1(0-, 1-, and 6-month schedule). The same property can be observed for the composite endpoint. These effects could be due to a different vaccination schedule.*
- *For Group 3 (0- and 6-month schedule), the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series and estimates of composite endpoint are:*
  - *Noticeably higher than for Group 1 and Group 2*
  - *Comparable with the immune responses to Trumenba® after the third dose in Group 1 and Group 2 for family A strains, but lower than for family B strains and estimates of composite endpoint.*

Results of immune responses utilizing 5 key parameters after the 2-dose series based on the 2-dose evaluable immunogenicity population are shown in Table 13 for Group 4.

Table 13: Results for the 5 Key Immunogenicity Objectives for the 2-Dose Per-Schedule Evaluable Immunogenicity Population for Group 4

Variables	Strain/Variant	# of Subjects	Estimate of Parameter (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	167	74.3	(66.9, 80.7)
hSBA Titer 4-fold rise	PMB2001 [A56]	163	93.3	(88.2, 96.6)
hSBA Titer 4-fold rise	PMB2948 [B24]	171	56.1	(48.4, 63.7)
hSBA Titer 4-fold rise	PMB2707 [B44]	166	57.2	(49.3, 64.9)
Composite hSBA response	For 4 primary strains	161	57.8	(49.7, 65.5)

Source: The reviewer's table based on the applicant's table, Response Document (April, 2015), page 6

Note: LLOQ = 1:16 for PMB80 [A22]; LLOQ =1:8 strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]

Tables 13 and 12.I demonstrate that the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series were similar for Groups 2 (0-, 2-, 6-month schedule) and 4 (0-, 2-month schedule).

6.2.12 Subgroup Analyses

Results for subgroup analyses can be found in the Statistical Review of STN 125549/0, Section 6.2.12.

6.2.13 Safety Analyses

As per the study protocol, the primary safety objective of this study was to evaluate the safety profile of Trumenba® measured by the proportions of subjects reporting local reactions, systemic events, and adverse events (AEs). Complete safety evaluation for the 3-dose series of Trumenba® can be found in the statistical of STN 125549/0, Section 6.2.13 and clinical reviews of STN 125549/0.

For the purpose of this statistical review, only serious adverse events (SAEs) were considered for three study groups in each 4 study phases (periods of time) defined in Section 6.0 (Table 2). A total of 1117 subjects were included in the analyses: 426 for Group 1, 414 for Group 2, and 277 for Group 4.

Numbers of SAEs in the 4 time periods are presented in Table 14 for Groups 1 and 2.

Table 14: Summary of SAEs reported for Each Analysis Time Period: Groups 1 and 2

	During 2-dose series vaccination phase	During 2-dose series follow-up phase	During booster phase	During booster follow-up phase
Group 1- # of Subjects in the specified phase	426	426	383	383
Group 1 - # of subjects with at least one SAE	3	5	0	4
Group 1 - % of subjects with at least one SAE (95%CI)	0.7 (0.1, 2 0)	1.2 (0.4, 2.7)	0.0 (0.0, 1 0)	1.0 (0.3, 2.7)
Group 1 - # of SAEs in analysis interval	3	6	0	4
Group 1 - % of subjects with at least one SAE related to vaccine	0.0 (0.0, 0 9)	0.0 (0.0, 0 9)	0.0 (0.0, 1 0)	0.0 (0.0, 1.0)
Group 2 - # of Subjects in the specified phase	414	414	382	382
Group 2 - # of subjects with at least one SAE	8	1	2	3
Group 2 - % of subjects with at least one SAE (95%CI)	1.9 (0.8, 3 8)	0.2 (0.0, 1 3)	0.5 (0.1, 1 9)	0.8 (0.2, 2.3)
Group 2 - # of SAEs in analysis interval	11	1	2	3
Group 2 - # of SAEs related to vaccine	5	0	0	0

Source The reviewer's table based on the applicant's Response Document, May 2015

Table 15 presents the number of subjects reporting at least one SAE during the whole study period, for the safety population and Groups 1, 2, and 4.

Table 15: Summary of Subjects Reporting at Least 1 SAE during the Whole Study Period, Safety Population: Groups 1, 2, 3, and 4

	Group 1 Schedule 0,1,6	**Group 2** Schedule 0,2,6	**Group 3** Schedule 0, 6	**Group 4** Schedule 0,2
Number of subjects in study safety population	426	414	451	277
Number of subjects with at least one SAE	12	14	7	7
% of subjects with at least one SAE (95% CI)	2.8 (1.5, 4.9)	3.4 (1.9, 5.6)	1.6 (0.6, 3.2)	2.5 (1.0, 5.1)
Number of SAEs	13	17	10	8
# of SAEs related to vaccination	0	5	0	0

Source Statistical reviewer's table based on CSR B1971012, pages 185-186

The total number of subjects who reported at least one SAE during the whole study period was 43 (2.5% = 43/1712). Of the 51 SAEs reported in the study, 5 SAEs were considered by the applicant to be related to the study vaccination; these 5 events occurred in the 0-, 2-, 6-month schedule group. Additionally, 5 subjects were diagnosed with autoimmune conditions during the course of the study, but these cases were considered by the applicant as not related to the study vaccination.

Remarks

Regarding safety, it appears that there were no noticeable differences between the 3-dose and 2-dose schedule groups; however, the total number of subjects in Group 3 who reported at least one SAE was lower than in Groups 1 and 2.

6.3 Trial #3: B1971010

Title of the study: "*A Phase 2, randomized, placebo-controlled, single-blind trial to assess the safety, tolerability, and immunogenicity of Repevax® and Bivalent rLP2086 vaccine when administered concomitantly in healthy subjects aged ≥ 11 to <19 years*"

Study Initiation Date: March 18, 2011 (the first subject visit)
Study Completion Date: February 19, 2013 (the last subject visit)
Final Serology Date: August 30, 2013

6.3.1 History of Study Protocol

The final study protocol dated July 22, 2010, was modified by 4 amendments and one administrative change. Revisions of the study design included modifications of the inclusion/exclusion criteria, immunogenicity and safety endpoints, as well as planned statistical evaluations. More information on changes introduced into the study design can be found in Section 6.3.1 of the Statistical Review of STN 125549/0.

6.3.2 Objectives

The main immunogenicity objective of study B1971010 was to demonstrate that the immune responses induced by Repevax® given concomitantly with Trumenba® (Group 1) were non-inferior to the immune responses induced by Repevax® alone (Group 2), when responses were measured 1 month after Vaccination 1.

Additionally, some secondary and exploratory objectives were established and were related to the assessment of the safety, tolerability, and immunogenicity of Trumenba® administered as a 3-dose schedule in healthy subjects aged ≥ 11 to < 19 years.

Note: The 5th parameter (composite parameter) of the 5 key immunogenicity parameters (see Section 6.0 of this review) related to the immune responses to Trumenba® cannot be considered for this study because hSBA testing was not performed for all four primary MnB strains in all study subjects. Serum samples from approximately 50% of subjects were hSBA tested with respect to PMB80 [A22] and PMB2948 [B24] strains, and another 50% of serum samples were tested with respect to PMB2001 [A56] and PMB2707 [B44] strains.

Detailed information on objectives and endpoints considered in this study is provided in Section 6.3.2 of the Statistical Review of STN 125549/0.

6.3.3 Design Overview

Study B197010 was a Phase 2, randomized, placebo-controlled, single-blind, multicenter trial in which subjects of age ≥ 11 to < 19 years were randomly assigned in a 1:1 ratio to Group 1 and Group 2. It was planned that approximately 750 would be enrolled into this clinical trial at approximately 34 sites (on average, 22 subjects per site). A summary of the study design is presented in Table 16.

Table 16: Study B1971010 Design

Group #	Month 0 Visit 1	Month 1 Visit 2	Month 2 Visit 3	Month 3 Visit 4	Month 4 Visit 5	Month 5 Visit 6	Month 12 Visit 7
Group 1	Trumenba + Repevax Blood draw	Blood draw	Trumenba	Blood draw	Trumenba	Blood draw	Phone contact
Group 2	Saline + Repevax Blood draw	Blood draw	Saline	Blood draw	Saline	Blood draw	Phone contact

Source: Statistical reviewer's table based on the study protocol

Of the 753 enrolled subjects, 4 were not randomized because of a site error, and the remaining 749 were randomized and included in the ITT population. Of these 749 subjects, 373 subjects were in Group 1 (Trumenba® + Repevax®) and 376 subjects were in Group 2 (Saline + Repevax®).

6.3.4 Population

At the time of enrollment (baseline), the study population consisted of 11 to 19 year-old females and males:

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and/or the legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

6.3.5 Study Treatments or Agents Mandated by the Protocol

Vaccination plan per study group is presented in Table 16 of this review.

The investigational products were supplied by the applicant and they were:

- o Trumenba® (bivalent rLP2086) vaccine - a 0.5-mL dose formulated to contain 60 µg (120 µg total) of purified subfamily A and a purified subfamily B rLP2086 proteins, [redacted] polysorbate 80, and 0.25 mg of Al3+ as AlPO4 in 10 mM histidine buffered saline at pH 6.0,
- o Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose.
- o Repevax® (a diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine) – a low dose as per vaccine label.

6.3.6 Sites and Centers

Study B1971010 was conducted at 34 sites in Finland, Germany, and Poland.

6.3.7 Surveillance/Monitoring

According to the applicant, the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

6.3.8 Endpoints and Criteria for Study Success

In order to assess the immune responses to Trumenba® vaccine (Group 1) using hSBA, blood samples were drawn from each subject immediately before Vaccination 1, 28 to 42 days after the second dose, and 28 to 42 days after the third dose (Vaccination 3).

Study endpoints and parameters related to this submission

Immunogenicity endpoints were:

- ✓ Titers at baseline and 1 month after the 2-dose series and the third dose vaccinations

- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the 2-dose series and after the third dose.
- ✓ hSBA geometric mean titers (GMTs) for each of the 4 primary strains 1 month after the 2-dose series and after the third dose.
- ✓ Proportion of subjects with hSBA titer ≥ LLOQ for each primary strain.

Safety endpoints/parameters

As stated in Section 6.0 of this review, the percentages of subjects reporting at least one SAE and the numbers of episodes were summarized for each group in each of the 4 periods of time.

More information on other immunogenicity and safety endpoints and parameters considered in the original study protocol can be found in Section 6.3.8 of the Statistical Review of STN 125549/0.

6.3.9 Statistical Considerations and Statistical Analysis Plan

The primary hypotheses and statistical decision rules related to immunogenicity of Repevax® were not relevant to the objective of this sBLA and thus were not considered in this review.

Statistical analysis

For the purpose of evaluations of immune responses to Trumenba® 1 month after the 2-dose series and the third dose (called by the applicant a booster dose), 4 key parameters (4-fold increase) defined in Section 6.0 of this review, GMTs, and percent of subjects with titer ≥ LLOQ for each of four primary strains and the corresponding 95% CIs were estimated using corresponding populations.

Safety data collected during the clinical study for Group 1 were evaluated utilizing frequencies of events during the 2-dose series and the third dose in four phases of the study period.

6.3.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects, e.g., gender ratios, were balanced across the two vaccination study groups. Males constituted about 51% of the enrolled subjects. The majority of subjects were white (99%). The younger age group (11 to < 14 years old) constituted about 58% of the subjects. The median age at the first vaccination was 13 years, while the age range was 11 to 18 years.

Disposition of subjects

A summary of the randomized subjects' disposition is presented in Table 17.

Table 17: Disposition of Randomized Subjects

Disposition of Subjects	**Group 1 (**Trumenba + Repevax) n(%)	**Group 2 (**Saline + Repevax) 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 (2.7)	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 Statistical reviewer's table based on the Response Document, Change in Dosing Regimen, May, 2015, Table 1
Note Definition of four study phases (time periods) can be found in Section 6.0 of this review.

In Group 1, a total of 342 (91.7%) subjects completed the 2-dose series vaccination phase. The primary reasons for withdrawal from the 2-dose series vaccination phase were: subject no longer willing to participate in study (13 subjects, 3.5%) and protocol violation (8 subjects, 2.1%). Five (1.3%) subjects from Group 1 withdrew due to adverse events (AEs). In Group 1, 330 (88.5%) subjects completed the booster dose follow-up phase and thus completed the study.

6.3.11 Immunogenicity Analyses

Datasets analyzed

The statistical analyses performed within the framework of this submission were based only on data from Group 1.

Of the 373 subjects randomized in Group 1 (Trumenba®+Repevax®):

- 315 (84.5%) subjects were included in the 2-dose series evaluable immunogenicity population (per-protocol),
- 307 (82.3%) subjects were included in the third dose evaluable immunogenicity population,
- 340 (91.2%) and 329 (88.2%) subjects were included in the 2-dose series mITT population and in the third dose mITT population, respectively.

Analyses Related to Main Immunogenicity Objective

The main immunogenicity objective of this submission was to assess immune response to Trumenba® 1 month after the 2-dose series and after the third dose as measured by the

percentage of subjects achieving ≥4-fold rise in hSBA titer. Detailed information on the endpoint and the relevant parameter can be found in Section 6.0 of this review. Results of assessment performed on the relevant evaluable immunogenicity population are shown in Table 18.

Table 18: Subjects achieving ≥ 4-Fold Rise in hSBA Titer After the 2-Dose Series and the Third Dose

A. Results after the 2-dose series based on the 2-dose series evaluable immunogenicity population

Variables	Strain/Variant	# of subjects*	Estimate of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	155	69.7	(62, 77)
hSBA Titer 4-fold rise	PMB2001 [A56]	135	86.7	(80, 92)
hSBA Titer 4-fold rise	PMB2948 [B24]	160	59.4	(51, 67)
hSBA Titer 4-fold rise	PMB2707 [B44]	144	50.7	(42, 59)

B. Results after the third dose based on the third dose evaluable immunogenicity population

Variables	Strain/Variant	# of subjects*	Estimate of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	153	87.6	(81, 92)
hSBA Titer 4-fold rise	PMB2001 [A56]	136	92.6	(87, 96)
hSBA Titer 4-fold rise	PMB2948 [B24]	156	80.8	(74, 87)
hSBA Titer 4-fold rise	PMB2707 [B44]	143	77.6	(70, 84)

Source The reviewer's table based on the Response Document, April 2015, Table 3

# of subjects - number of subjects with valid and determinate hSBA titers for a given strain at both the specified time points*

Note LLOQ = 1 16 for PMB80 [A22]; LLOQ =1 8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]

Note The 4-fold increase is defined in Section 6.0 of this review.

As per the applicant, the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series and after the third dose were similar for the relevant evaluable immunogenicity populations and mITT populations.

Remarks

As per Table 18, based on the Group 1 dataset, immune responses to Trumenba® after the third dose for the third dose per-schedule evaluable immunogenicity population are notably higher than after the 2-dose series.

6.3.12 Subgroup Analyses

Results for subgroup analysis can be found in the Statistical Review of STN 125549/0, section 6.3.12.

6.3.13 Safety Analyses

For the purpose of this statistical review, only serious adverse events (SAEs) were considered for Group 1 in each of the 4 study phases (periods of time) defined in Section 6.0 (Table 2). A total of 374 subjects were included in the safety population for Group 1.

Information on the complete study safety analysis can be found in the Statistical Review of STN 125549/0, section 6.3.13.

Distribution of SAEs by the 4 time periods is presented in Table 19.

Table 19: Summary of SAEs reported for Each Analysis Time Period: Group 1

	During 2-dose series vaccination phase	During 2-dose series follow-up phase	During the third dose phase	During the third follow-up phase
# of subjects in for the specified analysis interval	374	374	331	330
% of subjects with at least one SAE in analysis interval	5	5	2	1
% of subjects with at least one SAE (95% CI)	1.3 (0.4, 3.1)	1.3 (0.4, 3.1)	0.6 (0.1, 2.2)	0.3 (0.0, 1.7)
# of SAEs in analysis interval	5	5	2	3
% of subjects with at least one SAE related to vaccine	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.1)	0.0 (0.0, 1.1)

Source The reviewer's table based on the Response Document, May 2015, Table 3

In Group 1, 12 (3.2%) subjects reported 15 SAEs throughout the study course. All SAE cases were determined by the investigator to be not related to the investigational product. A death due to a traffic accident was reported in the study.

Four subjects from Group 1were diagnosed with autoimmune conditions. The conditions were not considered by the investigator to be related to vaccination, but 2 events (autoimmune thyroiditis and arthritis infective) led to withdrawals from the study. Two events of idiopathic thrombocytopenic purpura and arthritis infective were classified as SAEs.

7. Integrated Overview of Efficacy

7.1 Background

The objective of this sBLA review is to assess the applicant's request for the change in the vaccine administration. The proposed change in the Trumenba® schedule was specified in two steps:

1 First, the proposed schedule of Trumenba® was specified as follows: a two dose regimen given at least one month apart and an optional booster (a third dose) given four months later.
2 Next, the second proposed Trumenba® dosing regimen was specified as follows:

- ✓ Standard dosing: A series of 2 doses (0.5 mL each) administered at 0 and 6 months.
- ✓ Accelerated dosing: 2 doses (0.5 mL each) administered at least 1 month apart followed by the third dose given at least 4 months after the second dose.

The second proposal was needed because data submitted in the supplement did not support a schedule in which the third dose of Trumenba® is optional.

Two different Trumenba® regimens are recommended for two different populations: standard dosing for routine immunization and accelerated schedule for individuals at increased risk of disease.

Support of new administration of Trumenba® is to be based on a retrospective review of data generated by three clinical trials -- B1971011, B1971012, and B1971010. General information on these clinical studies is provided in Table 1 (see Section 5.3). It is important to note that these 3 clinical trials were designed to support administration of a 3-dose series on the 0-, 2-, and 6-month schedule and were previously submitted/utilized as the basis of the Biologics License Application (BLA) STN 125549/0.

The immunogenicity objective of the current submission is to assess immune response to Trumenba® 1 month after the 2-dose series and the third dose in the relevant populations using 5 key parameters or 4-fold titer increase defined in Section 6.0 of this review. The safety assessment of Trumenba® is to be based only on consideration of serious adverse events (SAEs) in each study for 4 phases/periods of time defined in Section 6.0 (Table 2).

7.2 Overview of Efficacy

The retrospective Trumenba® immunogenicity assessment of the regimen consisting of the 2-dose series followed by the third dose was based on data collected during the course of trials B1971011, B1971012, and B1971010, while assessment of the proposed additional so-called standard dosing regimen is based on a retrospective review of the immunogenicity data from only one group, Group 3 of the B1971012 study. The foremost immunogenicity information regarding the immune responses to Trumenba® was generated by exploratory analyses related to 5 key parameters. Please see Section 6.0 of this review for more details.

A total of 4947 subjects were vaccinated in three studies (B1971011, B1971012, and B1971010), of which 4052 subjects received at least 1 injection of Trumenba®. The remaining 895 subjects were in comparison groups and received saline with concomitant Repevax® (study B1971010) or Gardasil ® (study B1971011) vaccines. Of 4052 subjects who received at least 1 injection of Trumenba®, 2846 (70%) and 2291 (46%) subjects were included in the corresponding 2-dose series and the third dose evaluable immunogenicity populations, respectively, while 1706 and 1626 subjects were included

in the 2-dose series and the third dose evaluable immunogenicity populations, respectively, only for study B1971011 carried out in the US.

Finding of the evaluations of the immune responses to Trumenba® after the 2-dose series and the third dose based on the data generated by studies B1971011, B1971012, and B1971010, and the relevant statistical concerns are summarized below.

Clinical trial B1971011:

- An exploratory analysis performed on the PP evaluable populations for the 2-dose series and booster using estimates of key immunogenicity parameters demonstrated that:
  - After the 2-dose series and for Groups 1 and 2:
    - Proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series for family B strains were about 62% and 46% for PMB2948 [B24] and PMB2707 [B44] strains, respectively,
    - The composite hSBA response (hSBA ≥ LLOQ for all 4 primary MnB test strains combined) was about 51%.
  - After the third dose, proportions of subjects achieving 4-fold rise and the composite hSBA response were over 79% for both Groups 1 and 2.

  Immune responses observed after the third dose were notably higher than after the 2-dose series (please see Section 6.1.10 of this review).

- Immune responses to Trumenba®, as measured by GMTs and the proportions of subjects with titers ≥ LLOQ, were lower after the 2-doses series than after the third dose (please see Section 6.1.10 of this review).

  Table 20 presents percentages of subjects with hSBA ≥LLOQ after the 2-dose series and the third dose estimated for the post-third dose PP population based on pooled Groups 1 (Trumenba®+Gardasil ®) and 2 (Trumenba®+Saline) data.

  Table 20: Estimates of Percentages of Subjects with hSBA ≥ LLOQ after the 2-dose Series and the Third Dose for Pooled Groups 1 and 2 Data: Post-Third Dose PP Population

Strain/Variant	Sampling Time Point	# of Subjects	Estimate	95% CI
PMB80 [A22]	1 Month after 2-dose series	1595	84.4	(82.5, 86.1)
PMB80 [A22]	1 Month after third dose	1604	95.1	(94.0, 96.1)
PMB2001 [A56]	1 Month after 2-dose series	1585	98.0	(97.2, 98.6)
PMB2001 [A56]	1 Month after third dose	1598	99.1	(98.5, 99.5)
PMB2948 [B24]	1 Month after 2-dose series	1540	72.4	(70.1, 74.6)
PMB2948 [B24]	1 Month after third dose	1591	91.5	(90.0, 92.9)
PMB2707 [B44]	1 Month after 2-dose series	1559	55.8	(53.3, 58.3)
PMB2707 [B44]	1 Month after third dose	1594	84.2	(82.3, 85.9)

Source: Table based on Response Document, page 37

- For strains PMB2948 [B24] and PMB2707 [B44], about 25% and 42% of subjects, respectively, had titers below LLOQ after the 2-doses series.

- About 85% and 81% of the subjects were included in the evaluation of the immune responses after the 2-dose series and booster, respectively.

- About 12% of subjects withdrew from the study during the 2-dose series phase. Reasons for withdrawal are not clear.

Clinical trial B1971012:

- The main purpose of Phase 2 trial B1971012 was to enhance knowledge about the safety, tolerability, and immune responses to Trumenba® when the vaccine is administered in a healthy adolescent population under different administration schedules. While the primary objectives of this study were to assess the 3-dose schedules, the applicant presented also data related to the 4 primary strains titers measured after the first and the second doses.

- An unexpected serious adverse reaction (SUSAR) occurred during the B1791012 study course, and the study conduct was interrupted. Injections of vaccine were temporarily paused, which caused delays in the vaccination visits for some subjects. Therefore, vaccination visit windows were extended to allow subjects impacted by the study pause to remain in the study. The protocol and SAP were modified to introduce definitions of new immunogenicity populations and additional sensitivity analyses were designed to evaluate the impact of the vaccination delay on the observed immune responses.
- The immunogenicity statistical analyses related to the objective of this submission were performed on the per-schedule evaluable immunogenicity population stemming from Groups 1, 2, 3, and 4. This population consisted of subjects who received Trumenba® "as randomized and scheduled," taking into account the originally intended dosing schedule and strict visit window criteria, and constituted only about 40% of the total study population.
- Regarding the 2-dose series (two doses at least 1 month apart) and the optional third dose, when using datasets for Groups 1, 2, and 4, and the per-schedule evaluable immunogenicity populations for the 2-dose series and the third dose, the statistical analyses estimating 5 key immunogenicity parameters yielded the following results:
    - After the 2-dose series and for three Groups 1, 2, and 4:
        - For PMB2948 [B24] and PMB2707 [B44] family B strains, proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after the 2-dose series were below 54.3% for Groups 1 and 2, and about 57% for Group 4.
        - The composite hSBA responses (hSBA $\geq$ LLOQ for all 4 primary MnB test strains combined) were 52% for Groups 1 and 2, and 57.8% for Group 4.

- After the third dose, proportions of subjects achieving 4-fold rise and the composite hSBA response were over 74% and 80%, respectively, for both Groups 1 and 2.
- At five months after 2-dose series, for Group 4 (0, 2 months regimen), immune response to Trumenba® measured by numbers of subjects with hSBA titers ≥ 1:4 and ≥ LLOQ are presented in Table 21.

Table 21: Numbers (%) of Subjects with hSBA titer ≥ LLOQ Five Months after the 2-Dose Series: 2-Dose Per-Schedule Evaluable Immunogenicity Population (Group 4)

Strain/Variant	Number of Subjects	# (%) of subjects with titers ≥ 1:4 (95% CI)	# (%) of subjects with titers ≥ LLOQ (95% CI)
PMB80 [A22]	167	95 (56.9) (49,64)	91 (54.5) (47, 62)
PMB2001 [A56]	161	126 (78.3) (71, 84)	121 (75.3) (68,82)
PMB2948 [B24]	164	65 (39.5) (32, 48)	60 (36.6) (29, 45)
PMB2707 [B44]	162	**42 (25.9) (17,31)**	**38 (23.5) (14,27)**

Source Statistical reviewer's table based on CSR B1971012, Table 14.32
Note LLOQ = 1 16 for PMB80 [A22]; 1 8 for PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44]

Based on Table 21, five months after dose 2, the percentages of subjects with hSBA titers **below** LLOQ were 45%, 25%, 63%, and 76% for four primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], respectively.

- Regarding the standard dosing regimen, it appears that immune responses to Trumenba® after the 2-dose series on the 0- and 6- month schedule (Group 3) are comparable with the immune responses after the third dose in Group 1 (0-, 1-, and 6-month schedule) and Group 2 (0-, 2-, and 6-month schedule) for family A strains, but slightly lower for family B strains. Also, the estimate of the composite endpoint appears to be lower. Results of assessments of the immune responses to Trumenba® after the third dose (based on the third dose per-schedule evaluable immunogenicity population for Groups 1 and 2 and after the 2-dose series (Group 3) are shown in Table 22.

Table 22: Results for the 5 Key Immunogenicity Parameters after the Third Dose (Groups 1 and 2) and the 2-Dose Series (Group 3) Based on the Relevant Evaluable Immunogenicity Populations

Variables	Strain/Variant	Group 1 # of subjects*	Group 1 Estimates of parameters (%) and 95% CI	Group 2 # of subjects*	Group 2 Estimates of parameters (%) and 95% CI	Group 3 # of subjects*	Group 3 Estimates of parameters (%) and 95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	183	77.6 (70.9, 83.4)	162	87.7 (81.6, 92.3)	203	82.3 (76.3, 87.7)
hSBA Titer 4-fold rise	PMB2001 [A56]	182	91.2 (86.1, 94.9)	160	93.8 (88.8, 97.0)	202	90.1 (85.1, 93.9)
hSBA Titer 4-fold rise	PMB2948 [B24]	185	74.1 (67.1, 80.2)	161	78.3 (71.1, 84.4)	200	64.5 (57.4, 71.1)
hSBA Titer 4-fold rise	PMB2707 [B44]	188	80.9 (74.5, 86.2)	159	78.6 (71.4, 84.7)	197	66.0 (58.9, 72.6)
Composite hSBA response	For 4 primary strains	178	80.3 (73.7, 85.9)	159	81.8 (74.9, 87.4)	188	72.9 (65.9, 79.1)

Source The reviewer's table based on the Response Document, April 2015, and Clinical Study Report Addendum (page 6)
# of subjects - number of subjects with valid and determinate hSBA titers for a given strain at both specified time points*
Note LLOQ = 1 16 for PMB80 [A22]; LLOQ =1 8 for strains PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]
Note The 4-fold increase is defined in Section 6.0 of this review.

Immune responses to Trumenba® measured by the percentage of subjects with hSBA titers ≥ LLOQ at different time points during the study course are presented in Table 23.

Table 23: Percentage of Subjects with hSBA Titer ≥ LLOQ for Per-schedule Evaluable Immunogenicity Population (N= 183-209)

Strain	Before Dose 1	2 mths after Dose 1	**3 mths after Dose 1**	1 mth after Dose 2
PMB80 [A22]	22.1. (16.6, 28.4)	55.8 (48.6, 62.8)	**44.7 (37.6, 51.9)**	93.8 (89.5, 96.6)
PMB2001 [A56]	18.7 (13.6, 24.8)	59.9 (52.6, 66.9)	**51.4 (43.9, 58.8)**	98.1 (95.1, 99.5)
PMB2948 [B24]	12.9 (8.7, 18.2)	52.2 (45.1, 59.3)	**37.8 (30.9, 44.9)**	80.0 (73.8, 85.3)
PMB2707 [B44]	4.3 (2.0, 8.1)	21.9 (16.4, 28.4)	**13.3 (8.9, 18.8)**	75.8 (69.2, 81.6)

Source Statistical reviewer's table based on CSR B1971012, Table 14.32
Note LLOQ = 1 16 for PMB80 [A22]; 1 8 for PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44]

As per Table 23, three months after Dose 1 and three months before Dose 2, the percentages of subjects with hSBA titers ≥ LLOQ were 45%, 51%, 38%, and 13% for four primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], respectively. Therefore, it appears that persistence of antibodies before the second dose was low.

- The applicant showed that immune responses to Trumenba® for some immunogenicity populations (e.g., evaluable immunogenicity population, mITT) used for analyses were similar to responses estimated utilizing the 2-dose series and the third dose per-schedule immunogenicity populations.

In conclusion:

- Outcomes for the immune responses to Trumenba®, as measured by 5 key immunogenicity parameters, were notably higher after the third dose than after the

2-dose series. Therefore, that a 3-dose regimen provide benefit over a 2-dose regimen (given at 0, 1 month or 0, 2 months) cannot be ruled out (please see Tables 12 and 20 in this review).

- According to Table 22, immune responses to Trumenba® given as 3 doses at 0, 1, 6 months or 0, 2, 6 months are not substantially higher than those elicited by a 2-dose 0, 6 months schedule, i.e., when vaccines are given farther apart in time.
- According to Table 23, it appears that 3 months after the first dose (Group 3 - 0, 6 months schedule), the percentage of subjects with hSBA Titer ≥ LLOQ were below 52% for all 4 primary strains, in particular only 13.3% for PMB2707 [B44] strain .

Clinical trial B1971010:

- Study B1971010 generated limited data on immune responses to Trumenba®. Results yielded by this study on immune responses after the 2-dose series and the third dose should be interpreted taking into account the following considerations:
  - Immune responses to vaccination with Trumenba® were not tested and evaluated in the same subjects for all four primary MnB strains. Fifty percent of the subjects were tested for hSBA titers against PMB80 [A22], and PMB2948 [B24] strains, while the remaining 50% of the subjects were tested for titers against PMB2001 [A56] and PMB2707 [B44] strains.
  - The first dose of Trumenba® was given concomitantly with Repevax® vaccine.
  - Evaluation of the immunogenicity objective of this submission has *a post-hoc* character.

- Statistical analyses estimating 4 immunogenicity parameters (4-fold increases in hSBA titers) performed for Group 1 evaluable immunogenicity populations yielded the following results:
  - After the 2-dose series, proportions of subjects achieving 4-fold increase in hSBA titers from baseline to 1 month after the 2-dose series were 69.7%, 86.7%, 59.4%, and 50.7% for PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44] strains, respectively,
  - After the third dose, proportions of subjects achieving 4-fold rise were over 88% and 78% for subfamily A and B strains, respectively.

  These findings suggest that immune responses measured by 4-fold increase parameters demonstrated notably higher outcomes after the third dose than after the 2-dose series (additionally, please see Table 17 of this review).

With respect to all studies:

Immune responses to Trumenba® measured by the hSBA titers were comparable across the studies. The applicant stated (Clinical Overview, page 27) that "administration of Trumenba® as a 2-dose series in adolescents resulted in a high proportion of subjects with hSBA titers greater than the level considered the protective correlate." However,

according to Table 24, about 50% of subjects achieved a composite hSBA response (defined as hSBA titer ≥ LLOQ for all 4 primary strains combined) at one month after the 2-dose series.

Table 24: Proportions of Subjects Achieving Composite hSBA Response after the 2-Dose Series – Study Evaluable Population

Study	Group	# of subjects*	Estimate of endpoint (%)	95% CI
B1971011	Group 1	752	50.1	(46.5, 53.8)
B1971011	Group 2	757	52.6	(48.9, 56.2)
B1971012	Group 1	173	52.0	(44.3, 59.7)
B1971012	Group 2	229	52.0	(45.3, 58.6)
B1971012	Group 4	161	57.8	(49.7, 65.5)

Source: The statistical reviewer's table based on data from studies B1971011 and B1971012.

Additionally, based on Table 21, persistence of antibodies appears to be low five months after dose 2.

It is important to note that proportions of subjects achieving 4-fold increase in hSBA titer after the 2-dose series were only about 48% for the subfamily B strains , but were notably higher after the third dose (about 80%) and systematically lower than for the subfamily A strains (Tables 5, 10, and 18 in this review).

Table 25, prepared for PMB2707 [B44] strains, presents percentages of subjects achieving hSBA titer 4-fold increase from baseline to 1 month after the 2-dose series and after the third dose estimated utilizing PP-populations and studies B19711010, B1971011, and B19712.

Table 25: Proportions of Subjects Achieving hSBA Titer 4-fold Rise after 2-Dose Series and Third Dose for PMB2707 [B44] Strain – PP Populations

Study	Group	Sampling Time point	# of subjects	Estimate of endpoint (%)	95% CI
B1971011	Trumenba + Saline	1 Month after 2-dose series	807	48.8	(45.3, 52.3)
B1971011	Trumenba + Saline	1 Month after third dose	788	80.7	(77.8, 83.4)
B1971012	Trumenba (0-, 1-, and 6- mths)	1 Month after 2-dose series	185	48.1	(40.7, 55.6)
B1971012	Trumenba (0-, 1-, and 6- mths)	1 Month after third dose	188	80.9	(74.5, 86.2)
B1971012	Trumenba (0-, 1-, and 6- mths)	1 Month after 2-dose series	236	53.4	(46.8, 59.9)
B1971012	Trumenba (0-, 1-, and 6- mths)	1 Month after third dose	159	78.6	(71.4, 84.7)
B1971010	Trumenba + Repevax	1 Month after 2-dose series	144	50.7	(42.2, 59.1)
B1971010	Trumenba + Repevax	1 Month after third dose	143	77.6	(69.9, 84.2)

Source: The statistical reviewer's table based on data from studies B1971011, B1971012, and B1971010.

7.3 Efficacy Conclusions

Data submitted in this sBLA and generated by three clinical trials, B1971011, B1971012, and B1971010, designed to evaluate Trumenba® administration as a 3-dose series in individuals 10 through 19 years of age, provided some information on the

immunogenicity of Trumenba® administered in individuals 10 through 25 years of age as:

- Standard dosing: A series of 2 doses administered at 0 and 6 months, and
- Accelerated dosing: 2 doses administered at least 1 month apart, followed by the third dose at least 4 months after the second dose.

As per the applicant, the standard dosing would be recommended for routine immunization, while the accelerated schedule would be recommended for individuals at increased risk of disease.

Data were analyzed utilizing four or five key immunogenicity parameters. Evaluations of the new proposed dosing regimens (the 2-dose series and possibly the third dose) utilized:

- *Post-hoc* statistical analyses, which could introduce bias into the results
- Since tests for only 4 primary MnB strains were conducted, the breath of protection against MnB meningococcal disease conferred by Trumenba® was not established

In summary, data generated by the three studies included in this submission:

1. Do not provide adequate support (see Tables 5, 12, 18, 21, and 24 in this review) for changing the Trumenba® dosing regimen from a 3-dose series to a 2-dose series, given at least 1 month apart and potentially followed by the third dose administered any time after at least 4 months.
2. Do provide some justification for the applicant's proposal to change Trumenba® administration to standard and accelerated dosing regimens. Please see Tables 5, 12, 18, and 22 (Sections 6 and 7) of this review.

8. Integrated Overview of Safety

8.1 Safety Design, Data, and Subject Disposition

As per the protocols of studies B1971011, B1971012, and B1971010, the primary safety objectives of these studies were to evaluate the safety profile of Trumenba® as measured by the proportions of subjects reporting local reactions, systemic events, and adverse events (AEs). An integrated overview of safety data from 7 studies and the complete safety evaluation for the 3- dose series of Trumenba® can be found in the statistical and clinical reviews of STN 125549/0, Section 6.

For the purpose of this statistical review, only serious adverse events (SAEs) were considered for 4 study phases (periods of time) defined in Section 6.0 (Table 2). Information about SAEs is presented for each of three studies in Section 6 of this review. Please note that in the "Response Document, Change in Dosing Regimen" document (dated May 2015), after performing analyses on pooled SAE data:

- For 4 controlled studies (B1971011, -1010, -1005, and -1004)
- For all subjects from 7 studies (B1971011, -1010, -1012, -1005, -1004, -1003, and -1042),

the applicant provided safety information for subjects aged 11 to 25 years and for each of 4 safety analysis periods.

General information on Phase 2 studies used for safety evaluations was presented in Table 1 in this review.

Some results of safety analyses performed on 7 studies pooled data are also presented in this review for each of 4 safety analysis periods. As per the applicant, about 4509 subjects aged 11 to 25 years received at least 1 dose of Trumenba® final formulation at any dose level and for any schedule in the 7 studies. Detailed information on these 7 studies (e.g., on study designs), their demographic characteristics, and disposition of subjects included in the pooled safety data can be found in Section 8 of the STN 125549/0 Statistical Review.

8.2 Safety Results

Table 26 provides a summary, created based on the pooled data for 3 Phase II studies: B1971011 (Groups 2 and 3), B1971012 (Groups 1 and 2), and B1971010 (Groups 1 and 2), of reported SAEs.

Table 26: Summary of SAEs Reported for Each Analysis Time Period

	During 2-dose series vaccination phase	During 2-dose series follow-up phase	During booster phase	During booster follow-up phase
Trumenba*- # of Subjects in the specified phase	2204	2204	1965	1940
Trumenba* - # of subjects with at least one SAE	20	15	5	15
Trumenba* - % of subjects with at least one SAE	**0.91**	**0.68**	**0.25**	**0.77**
Trumenba* - # of SAEs in the analysis interval	23	16	5	19
Trumenba* - # of SAEs related to vaccine	**5**	0.0	0.0	0.0
Control** - # of Subjects in the specified phase	879	879	803	788
Control** - # of subjects with at least one SAE	4	2	2	8
Control** - % of subjects with at least one SAE	**0.46**	**0.23**	**0.25**	**1.0**
Control** - # of SAEs in the analysis interval	4	2	2	8
Control** - # of SAEs related to vaccine	0	0	0	0

Source The reviewer's table based on the applicant's Response Document, May 2015
Trumenba = pooled safety data of B1971011 (Group 2 - Saline and Trumenba at month 0, 2, 6), B1971012 (Groups 1 and 2- Trumenba three doses), and B1971010 (Group 1- Repevax at month 0, and Saline at month 2, 6 and Trumenba at month 0, 2, 6)*
*Control** = pooled safety data of B1971011 (Group 3- Gardasil and Saline at month 0, 2, and 6), and B1971010 (Group 2 - Repevax at month 0, and Saline at month 2, 6)*

As per Table 26:

- The percentage of Trumenba® vaccinees experiencing at least one SAE varied from 0.25% to 0.9% for the 4 time periods
- During the 2-dose series vaccination phase, the overall proportion of subjects with SAEs among Trumenba® vaccinees was 0.91% (20/2204) as compared to 0.46% (4/879) among the control subjects. The difference assessed in terms of the relative risk was RR=1.99, 95% CI: (0.68, 5.82).

- During the 2-dose series follow-up phase, the overall proportion of subjects with SAEs among Trumenba® vaccinees was 0.68% (15/2204) as compared to 0.23% (4/879) among the control subjects. The difference assessed in terms of the relative risk was RR=2.99, 95% CI: (0.69, 13.1).

A summary of SAEs reported in the 7 clinical trials included in submission STN 125549/0 for 4 safety pooled data phases is presented in Table 27.

Table 27: Subjects Reporting at Least 1 SAE for Each Analysis Interval – Pooled 7 Studies

	During 2-dose series vaccination phase	During 2-dose series follow-up phase	During third dose phase	During third dose follow-up phase	During courses of the study
Trumenba*- # of Subjects in the specified phase	4282	4282	3055	3004	4282
Trumenba* - # of subjects with at least one SAE	33	28	8	21	88
Trumenba* - % of subjects with at least one SAE	**0.77**	**0.65**	**0.26**	**0.70**	**2.06**

Source Table based on the "Response Document" dated May 2015, page 48.

Fifty nine (1.38%) of 4282 subjects aged 11 to 25 years who received Trumenba® reported at least 1 SAE during the 2-dose series vaccination and 2-dose series follow-up phases. Of the 3004 subjects in the Trumenba® group, 21 (0.70%) subjects reported at least 1 SAE during the third dose follow-up phase. During both the third dose phase and the third dose follow-up phase, 29 (0.95%) of 3055 subjects aged 11 to 25 years receiving Trumenba® reported at least 1 SAE.

Based on Tables 26 and 27, there were no marked differences in SAE rates between the 3 core safety studies (B1971011, -1010, -1012) and all 7 (pooled) studies.

Autoimmune Adverse Events

In studies B1971010, B1971012, and B1971011, the applicant reported 11 vaccinated subjects with autoimmune conditions. A list of the autoimmune cases is provided below in Table 26.

Table 28: List of Autoimmune Conditions

Study	Adverse Event Verbatim Term	Vaccine Administered	Last Dose	Days Since Last Dose
B1971010	HASHIMOTO'S THYROIDITIS	Trumenba+Repevax: Trumenba	Dose 2	141
B1971010	Idiopathic Thrombocytopenic Purpura	Trumenba+Repevax: Trumenba Trumenba	Dose 3	31
B1971010	WORSENING OF COELIAC DISEASE	Trumenba+Repevax	Dose 1	
B1971010	POST INFECTIOUS ARTHRITIS	Trumenba+Repevax	Dose 1	10
B1971011	SYDENHAM'S CHOREA	Trumenba + Gardasil Trumenba + Gardasil	Dose 2	18
B1971011	IGA NEPHROPATHY	Trumenba + Saline	Dose 1	2
B1971012	HYPOTHYROIDISM	Trumenba: Saline Trumenba: Saline	Dose 2/FU	
B1971012	RHEUMATOIDARTHRITIS	Trumenba: Saline: Trumenba	Dose 2	119
B1971012	GRAVES-BASEDOWDISEASE	Trumenba: Saline	Dose 1	84
B1971012	CROHNS DISEASE	Trumenba: Trumenba: Saline	Dose 2	96
B1971012	SUBCLINICAL HYPOTHYROIDISM	Trumenba	Dose 1	

Source: Table based on the Integrated Summary of Safety

Ten of these eleven subjects with autoimmune conditions were diagnosed during the 2-dose series vaccination and follow-up phases. But all 11 autoimmune conditions were considered by the investigator to be not related to vaccination.

8.3 Safety Conclusions

For the data submitted from three Phase II clinical trials, the targeted comparisons were not always straightforward due to different control regimens. Nevertheless, the analyses led to the following conclusions:

(1) There was no substantive difference in safety between subjects receiving Trumenba® vaccine and subjects considered as controls.

(2) The SAE frequency for the pooled data for the 3 studies B1971011, -1010, -1012 is consistent with the SAE frequency for the 7 studies B1971011, -1010, -1012, -1005, -1004, -1003, and -1042 for 4 time periods defined in Section 6 of this review.

9. Additional Statistical Issues

None.

10. Conclusions

Immunogenicity conclusion

The applicant's objective in this efficacy supplement was to support a request for a change in the Trumenba® administration. Descriptive analyses were utilized for evaluation of following three different Trumenba® regimens proposed by the applicant:

- Two doses administered 1 month apart and optionally followed by the third dose (the third dose is called "booster" by the applicant) at least 4 months after the second dose,
- Two doses administered at 0 and 6 months (so-called standard dosing).
- 2 doses administered at least 1 month apart, followed by the third dose given at least 4 months after the second dose (so-called accelerated dosing).

Data submitted in this submission:

1. Do not provide adequate support for changing the Trumenba® dosing regimen from a 3-dose series to a 2-dose series, given at least 1 month apart and potentially followed by the third dose administered any time after at least 4 months.
2. Do provide some justification for the applicant's proposal to change Trumenba® administration to the standard dosing recommended for routine immunization and the accelerated dosing recommended for individuals at increased risk of disease. Please see Tables 5, 12, 18, and 22 (Sections 6 and 7) of this review.

Moreover, there are several statistical issues (see Sections 6 and 7) that could influence results of the statistical analysis and introduce bias. It is worth noting the following issues:

(1) Retrospective specification of the objective to support Trumenba® dosing regimen change in the population of 10 to 25 year-olds
(2) Retrospective nature of the review of the data generated by the three studies
(3) Data generated by three submitted trials covering only the population aged 10 to 19 years
(4) *Post-hoc*, previously unplanned, analyses performed
(5) Over 10% of dropouts during the 2- dose series phase (see Sections 6 and 7)
(6) Evaluation of immune responses to vaccine based only on tests for 4 primary MnB strains. Therefore, data generated by the submitted studies do not provide the information on the breath of protection against MnB meningococcal disease.

<u>The statistical reviewer defers to the medical reviewer to assess the clinical importance of these statistical findings</u>.

Safety conclusion

The safety evaluations utilizing only SAE data for Trumenba® vaccinees indicated that the overall rates of SAEs estimated on the pooled data from the 3 studies B1971011, -1010, -1012 for four safety phases were consistent with the rates of SAEs observed in the seven studies.

Based on the available data submitted in this sBLA, a safety imbalance between the Trumenba® vaccinees and controls was not established.

Eleven (11) Trumenba® vaccinees with autoimmune conditions were reported in the three Phase 2 studies. Ten of these eleven subjects were diagnosed with autoimmune

conditions during the 2-dose series vaccination and followed-up phases. All 11 autoimmune conditions were considered by the investigator as not related to study vaccination. However, in study B1971012, two subjects in Group 2 reported 5 SAEs considered to be related to Trumenba® administration.

In summary: It appears that the statistical analyses taking into account only SAEs observed in the three studies do not indicate existence of serious safety problems related to the proposed modified regimen of Trumenba® administration.

The statistical reviewer defers to the clinical reviewer on the final assessment of the importance of the safety findings reported in this review.