Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

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To:	Drusilla Burns Chair, Review Committee Office of Vaccine Research and Review
Through:	Wei Hua, MD, PhD, MS, MHS Chief, Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA Michael Nguyen, MD Deputy Director, Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
Subject:	Pharmacovigilance Plan Review
Applicant:	Wyeth Pharmaceuticals, Inc. (a subsidiary of Pfizer, Inc.)
Product:	Trumenba (*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein rLP2086 [subfamily A and B; E. coli] Vaccine)
Proposed Indication:	Active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years
Submission type:	Original BLA
BLA number/Submission Date:	STN 125549/0.0, Rolling Submission, starting May 8, 2014; Complete BLA submitted June 16, 2014
PVP Submission Date:	Original PVP (Version 1.0)-As part of Rolling Submission 4: June 16, 2014; Amendment 4 (125549/0.4)
Action Due Date:	February 14, 2015

Table of Contents

1 EXECUTIVE SUMMARY

Introduction

Neisseria meningitidis is a bacterium that can cause life-threatening invasive meningococcal disease (IMD), such as meningitis and bacteremia, with a case fatality rate as high as 15%.[1] Approximately one third of all IMD cases and one quarter of outbreaks in the US are caused by serogroup B.[2] Outbreaks tend to occur more frequently among adolescents and young adults.[3] The relatively higher incidence in these age groups is believed to be due to increased social mixing and exposure to new strains of *N. meningitidis* while in closed, crowded communities such as classrooms, dormitories, and military institutions.[4]

Outbreaks of meningitis B at Princeton and the University of California-Santa Barbara in 2013 prompted discussions with the Food and Drug Administration (FDA) about an accelerated approval pathway for licensure of Trumenba in December 2013. Breakthrough Therapy designation was granted on March 19, 2014, and Pfizer submitted the biologic licensing application (BLA) for Trumenba as a "rolling submission" on a Priority Review timeline beginning on May 8, 2014, with all BLA components submitted by June 16, 2014.

Product Description and Indication

Pfizer's vaccine candidate, Trumenba, is composed of 60 µg each of 2 lipidated Factor H binding protein (fHBP) variants (A05 from subfamily A and B01 from subfamily B), recombinantly expressed in *Escherichia coli*. Trumenba is indicated for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years. The vaccine is to be administered as 120µg bivalent rLP2086 in a 3-dose series at months 0, 2, and 6.

BLA Epidemiology Review

The nonclinical toxicology studies found no evidence of systemic toxicity and were deemed adequate by the sponsor to support the preclinical safety of the product and a pregnancy category B.

In the overall safety data (all 7 BLA studies), 4,576 subjects received ≥1 dose of bivalent rLP2086. The majority of this exposure (4,335 or 95%) was at the 120 µg dose level. Of the 4,576 subjects who received ≥1 dose of bivalent rLP2086, 97.6% were adolescents and 2.4% were adults. In all 7 BLA studies, 1,028 subjects received ≥1 dose of a control injection only (saline and/or other non-rLP2086 vaccine). In the 4 controlled core safety studies, 2,566 subjects received ≥1 dose of 120 µg bivalent rLP2086 either as a single agent or administered concomitantly with a licensed vaccine, and 2,272 subjects received 3 doses of 120 µg bivalent rLP2086 administered using a 0, 2, 6-month schedule. The majority of subjects who received ≥1 dose of bivalent rLP2086 were enrolled in the US studies (77.7%), with the remainder in Europe and Australia.

Clinical studies showed local reactions at the injection site and systemic generalized events, such as fever, chills, and malaise occurring more frequently among vaccinees, with systemic events tending to decrease with each subsequent dose. A higher proportion of subjects in the 120 µg bivalent rLP2086 group compared with the control group reported related AEs (6.63% vs 3.56%), severe AEs (4.40% vs 2.87%), immediate AEs (3.86% vs 2.28%), and AEs that led to discontinuation (1.17% vs 0.40%), yet rates in both groups were relatively low. Similar percentages of subjects in the 120 µg bivalent rLP2086 group and the control group reported SAEs during the vaccination phase (1.21% vs 0.89%) and throughout the study (1.71% vs 1.58%). There were no SAEs considered related to study vaccine for the 4 controlled core safety studies. One subject in the 120 µg bivalent rLP2086 group in Study B1971010 died during the study due to a road traffic accident (the subject was a passenger) and the death was considered unrelated to vaccination.

Although pregnancy was an exclusion criterion, 7 females were inadvertently vaccinated while pregnant. Only 1 of these had a known adverse outcome (spontaneous abortion) 84 days post-vaccination (gestational age unknown); however, it was deemed unrelated to vaccination.

Autoimmune (AI) and neuroinflammatory (NI) conditions were assessed and 14 cases (13 AI, 1 NI) were initially identified, all among 120 µg bivalent rLP2086 (Trumenba) vaccinees and none among control vaccinees. Further evaluation revealed only 2 AI cases that could have had a possible causal association with Trumenba, and after comparison of the disease rates in the study population with background rates in a same-age population, only 1 of these (idiopathic thrombocytopenia) seemed medically plausible, but was still not associated with an increased risk among Trumenba vaccinees. Among the 14 identified AI/NI cases, 8 had evidence they were pre-existing at the time of Trumenba vaccination and only 2 of these occurred in controlled studies. Evaluation of these cases for potential exacerbation or "unmasking" of latent or asymptomatic disease revealed no increased risk of this process and no medically plausible explanation for a common process among all 8 cases. The conclusion after this in-depth review was that AI/NI conditions were not a safety concern for Trumenba.

Risk Management Plan

Pfizer identified the following risks or missing information for Trumenba vaccinees 11-25 years of age and proposed the corresponding Action Plan for these items:

Important Identified Risks	**Planned Pharmacovigilance Actions**
None	–
Important Potential Risks	**Planned Pharmacovigilance Actions**
Anaphylactic reactions	• Labeling • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) • Ascertain incidence rate of anaphylactic reactions in rLP2086 vaccinees in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016
Important Missing Information	**Planned Pharmacovigilance Actions**
Vaccine effectiveness	• Collaborate with federal agencies to monitor epidemiology of invasive meningococcal disease in the US with respect to rLP2086/fHBP variants and characterization of new emerging variants, including susceptibility of any novel strains to killing by immune sera from Trumenba vaccinees
Vaccine failure	• Routine pharmacovigilance
Bactericidal response in subjects with terminal complement deficiency	• Routine Pharmacovigilance • Ascertain terminal complement deficiency status and bactericidal response of subjects in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.
Safety in pregnancy and lactation	• Observational pregnancy study using electronic health care data (Study B1971052) • Routine Pharmacovigilance • Monitor pregnancy and/or lactation status of female subjects and any SAEs among births to pregnant women exposed in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.

Epidemiology Reviewer Recommendations

Based on the review of the pre-licensure safety data and Pfizer's proposed pharmacovigilance plan, the Epidemiology reviewer agrees with the Risk Management Plan as proposed by Pfizer with the following actions for post-licensure safety surveillance activities of Trumenba:

- Routine pharmacovigilance to monitor AEs among vaccine recipients in accordance with 21 CFR 600.80
- Observational pregnancy study (Study B1971052) as a Post-marketing Commitment (PMC) in accordance with Section 901 of FDAAA 2007 Title IX
- Completion and review of additional ongoing studies, as agreed to with the Office of Vaccine Research and Review (OVRR), including the above noted planned study examining vaccine effectiveness and planned studies in the pediatric population <10 years of age, per the Pediatric Research Equity Act (PREA)

2 INTRODUCTION

2.1 Background

Neisseria meningitidis is a gram-negative diplococcus that is pathogenic only in humans. It colonizes the nasopharynx asymptomatically in anywhere from 10-25% of the adult population but occasionally causes more invasive disease.[5-7] Transmission with *N. meningitidis* is via contact with droplets from the upper respiratory tract of patients or asymptomatic carriers.[8] However, under certain circumstances that are not well understood, it is capable of invading the human host and causing life-threatening invasive meningococcal disease (IMD), such as meningitis, bacteremia, and bacteremic pneumonia.[1] These manifestations can be rapidly fatal within 24-48 hours or result in permanent significant clinical sequelae in those who survive, such as neurologic disability, limb amputation, and hearing loss.[3,9,10]

Predicting an individual person's risk of IMD is difficult. Most carriers of *N. meningitidis* remain well. Though infants have the highest risk of disease, carriage of *N. meningitidis* is infrequent in infants. Carriage rates increase through childhood to peak in late adolescence and decline in older adults.[5,6] The highest rates of carriage are observed in adolescents and young adults, often notable among individuals living in university and college dormitories and military barracks, making these groups important targets for implementation of a preventive vaccination strategy.[11-13]

2.2 Epidemiology of Meningococcal Disease

When classified according to the polysaccharide capsule surrounding the bacterium, only six capsular serogroups (A, B, C, W-135, X, and Y) are associated with IMD. The epidemiology of disease caused by these groups varies geographically, with group A causing large epidemics in Africa, in which the incidence can exceed 1,000 cases per 100,000 population, and groups B and C causing more sporadic disease predominantly in industrialized countries.[7,14] More recently, groups W-135 and X (in Africa) and group Y (in the United States, Canada, and other countries) have emerged as important disease-causing isolates. The World Health Organization estimates that there are 1.2 million cases of IMD worldwide and 135,000 related deaths annually.[7] In industrialized countries, disease rates range from 0.1 per 100,000 individuals during endemic periods to 5-15 or more cases per 100,000 individuals during prolonged epidemics.[1,15,16] While incidence is at an historic low in the US, the Centers for Disease Control and Prevention (CDC) estimates that 800 -1,200 cases of this potentially devastating disease occur annually.[3]

Historically, the incidence of IMD was characterized by periodic cycles. Since the 1990s, when the incidence in the USA peaked at >1 per 100,000 people, the incidence has declined annually.[9,14] In 1997, the incidence was reported as 1.1 cases per 100,000 people and has subsequently declined 86% to 0.15 cases per 100,000 people in 2012.[17,18] This marked decline in cases has occurred in all age groups and may be the result of population immunity to circulating strains, changes in behavioral risk factors or other unknown factors.[3,14] Furthermore, the overall annual incidence decline began prior to the introduction in 2005 of the meningococcal conjugate vaccine that target serogroups A, C, Y and W.[3] The incidence of serogroup B has also declined during this time period even though immunization is not conferred by the licensed vaccines.

The majority of meningococcal disease cases occurring in the US are caused by serogroups B, C and Y. From 2002 through 2011, each of these serogroups accounted for approximately one-third of the cases and the remaining few cases were attributable to serogroup W-135 and other cases in which the serogroup was not identified.[3] However, fluctuations in the annual distribution have been observed. In 2012, 40% of IMD cases were attributable to serogroup B, 17.5% to serogroup C, 33% to serogroup Y, and the remaining 9% to serogroup W-135 and other serogroups.[18]

The highest incidence of meningococcal disease in the US occurs in children <5 years of age. The overall incidence among children < 12 months of age from 2002-2011 was 4.3 cases per 100,000 persons, but

incidence declined after 1 year of age. Among adolescents and young adults 11-24 years of age, the incidence ranged from 0.4 to 0.5 cases per 100,000 persons.[3]

Approximately one third of all meningococcal disease cases and one quarter of outbreaks in the US are caused by serogroup B.[2] In the US, the current overall rate of endemic Meningitis B (MenB) disease is relatively low. The greatest burden of MenB disease in the US occurs in children <5 years of age (peak incidence in infants under 5 months of age), with another peak of disease occurring in adolescents and young adults. The average annual incidence of MenB disease in the US (2002-2011) was 0.1 and 0.2 per 100,000 for 11-18 year olds and 19-24 year olds, respectively.[3] The incidence among adults 25-64 years of age and ≥65 years of age was 0.2 cases and 0.5 cases per 100,000 persons, respectively.[3] Outbreaks tend to occur more frequently among adolescents and young adults.[3] The relatively higher incidence in adolescents and young adults is believed to be due to increased social mixing and exposure to new strains of *N. meningitidis* while in closed, crowded communities such as classrooms, dormitories, and military institutions, and because of the higher frequency of risk behaviors such as smoking.[4]

As compared to the relatively low national rate, hyperendemic or persistently high levels of MenB disease have been reported in a number of US states (e.g., Oregon).[19] Also of concern have been sporadic clusters such as those that occurred in 2009 among students attending the University of Pennsylvania.[20] MenB can cause protracted outbreaks, despite chemoprophylaxis and promotion of control measures, as was seen during the outbreak of MenB disease cases from January 2008 through November 2010 at a university in Ohio.[2] Thirteen (13) cases occurred during the 3-year outbreak, with 10 cases (1 fatal) determined to be caused by MenB. More recently, 8 students at Princeton University (March 2013 through November 2013) and 4 students at University of California-Santa Barbara (November 2013) developed MenB disease in local outbreaks. These specific outbreaks at universities in New Jersey and California prompted public health agencies, with approval of the universities, to utilize an investigational MenB vaccine under a treatment Investigational New Drug Application (IND) to address the health crisis.[21,22] This vaccine (Novartis' Bexsero®) had already been licensed for use earlier in 2013 in Europe, Australia, and Canada, where incidence of MenB disease is greater.[14] It is worth noting that no specific safety concerns have been identified for this vaccine thus far in these countries.

The case fatality ratios associated with IMD range from 11-15% for serogroups B, C and Y.[1] A children's hospital-based surveillance study observed the risk of death is 3 times higher among children ≥ 11 years of age, compared with children who were younger than 11 years.[10] Up to 20% of survivors experience long-term sequelae.[3,10] Between 1990 and 2002, 3,335 meningococcal deaths were reported in the US, leading to an average annual age-adjusted mortality rate of 0.10 per 100,000 population.[23]

2.3 Meningococcal Vaccines

Protection against meningococcal infection is mediated by antibody and/or complement recognition of bacterial cell surface constituents such as capsular polysaccharide or outer membrane proteins leading to activation of the classical and/or alternative complement pathways that ultimately result in bacterial destruction. The process of serum bactericidal killing can be mimicked in an in vitro serum bactericidal assay using human complement (hSBA). An hSBA titer is defined as the highest serum dilution that kills at least 50% of the target bacteria in the assay. The hSBA measures functional serum bactericidal (rather than bacterial binding) antibody levels. It is now well established that the bactericidal activity measured in the hSBA is an in vitro reflection of the mechanism of protection from meningococcal disease that occurs in vivo. An hSBA titer ≥1:4 indicates protection; however, an hSBA titer of <1:4 does not always indicate susceptibility to disease.[24]

The capsular polysaccharides of *N. meningitidis* are important virulence factors that inhibit host cell protection mechanisms. The discovery that serum bactericidal antibodies to meningococcal capsular polysaccharides protect against IMD was the basis for development of meningococcal vaccines targeting capsular polysaccharide structures for serogroups A, C, Y, and W-135.[25] In the 1970s and 1980s, monovalent and bivalent polysaccharide vaccines for prevention of serogroups A and C disease (Merck and Connaught, 1974 and 1978), and a quadrivalent polysaccharide vaccine (Menomune®, MPSV4) to protect against serogroups A,

C, Y, and W-135 disease (Connaught, 1981) were licensed. In 2005, a quadrivalent (serogroups A, C , Y and W-135) meningococcal conjugate vaccine (Menactra®, ACWY-D) was licensed in the US for individuals 9 months through 55 years of age, and in 2010, another quadrivalent meningococcal conjugate vaccine (Menveo®, MenACWY-CRM) was licensed in the US for use in adolescents and adults 11-55 years of age; in 2011, its indication was expanded to include children 2-10 years of age, and in 2013, expanded further to include children as young as 2 months of age. Both vaccines have been recommended by the Advisory Committee on Immunization Practices (ACIP) for vaccination of all adolescents 11-18 years of age and for individuals in the indicated age range at increased risk of IMD. The widespread implementation of the quadrivalent vaccines for serogroups A, C, Y and W-135 has resulted in a greater proportion of meningococcal disease in the US being caused by serogroup B strains.

2.4 Rationale for Development of Bivalent rLP2086 Vaccine

The high case fatality rate and permanent serious sequelae in survivors emphasizes MenB disease as a serious public health concern. In the absence of a broadly effective MenB vaccine in the US, prevention of MenB disease is severely hindered. Chemoprophylaxis, while highly effective for prevention of MenB disease among close contacts of individual patients, is not a sufficient or practical public health measure to prevent IMD for the general healthy US population or during large-scale disease outbreaks. Furthermore, antibiotic treatment of IMD has many important limitations, including difficulty ensuring simultaneous administration of drugs (to successfully eliminate carriage), drug side effects, and the potential for emergence of resistant organisms.[26] Broad-based vaccination of the 10-25 year old age group not only directly protects individuals with increased risk of disease, but may have the potential to decrease carriage and transmission of meningococci to unvaccinated individuals of all ages within the community.[27] While the ACIP recommends routine vaccination of all persons 11-18 years of age with a licensed quadrivalent A, C, Y, and W-135 polysaccharide-protein conjugate vaccine, these vaccines do not prevent meningococcal disease caused by serogroup B. Therefore, a licensed MenB vaccine for adolescents and young adults 10-25 years of age that provides broad protection against epidemiologically relevant disease-causing strains would fill an important unmet medical need in the US.

Although meningococcal disease caused by serogroups A, C, W-135, and Y can be prevented by the use of conjugate vaccines to generate bactericidal antibodies to the respective capsular polysaccharides, the serogroup B capsular polysaccharide is composed of polysialic acid repeating units that are similar to structures found on human neuronal cells. Antibodies generated against serogroup B capsular polysaccharide are cross-reactive with the polysialic acid moieties expressed on human neural cell adhesion molecules. As a result, serogroup B polysaccharides are poorly immunogenic due to self-tolerance mechanisms and, even if antibodies were generated, the possibility of antibody cross-reactivity raises safety concerns.[28]

To address the unmet need for MenB prevention, outer membrane vesicle (OMV) vaccines have been used to control epidemics caused by clonal outbreak strains.[29] However, due to wide variability of OMV antigens across strains, the OMV vaccine approach is not tenable for broad global disease prevention of MenB disease.[30] Accordingly, research efforts at Pfizer used a biochemical approach to identify surface-exposed protein antigens that could elicit bactericidal antibodies and confer protective immunity against a broad spectrum of MenB strains without the potential antibody cross-reactivity to human cells. As a result of this preclinical work, the novel surface-expressed lipoprotein 2086 (LP2086), or factor H binding protein (fHBP), was identified.[31] This protein is a virulence factor that plays a role in the interaction of *N. meningitidis* with the human host by recruiting the negative complement regulator, factor H, to the surface of the bacterium, thereby reducing complement-mediated bactericidal activity in vivo.[32] Factor H binding protein variants segregate into two immunologically distinct subfamilies, designated A and B,[31] and the immune response to each subfamily variant is not cross-protective. Therefore, to provide broad protection against MenB disease, Pfizer's vaccine candidate, bivalent rLP2086, is composed of 2 lipidated fHBP variants (A05 from subfamily A and B01 from subfamily B), recombinantly expressed in *Escherichia coli*. It prevents MenB disease by inducing broadly protective hSBA responses against epidemiologically diverse serogroup B strains. Strains used in the SBA for

early-phase clinical studies were selected from a pool of approximately 180 MenB isolates, which had been obtained from invasive disease isolates in the United States or Europe between 1970 and 2004.

2.5 Pertinent Regulatory History

The clinical development of bivalent rLP2086 began in 2006 with 3 early Phase 1 studies in subjects aged 18-36 months (99 subjects enrolled), 8-14 years (127 subjects enrolled), and 18-25 years (103 subjects enrolled). These studies were conducted using an initial formulation of bivalent rLP2086. Overall, bivalent rLP2086 was shown to be well-tolerated and immunogenic in Phase 1 trials in doses of the vaccine as high as 200 µg.

The IND was filed on September 19, 2008 and ultimately, the candidate vaccine was granted Fast Track Designation on October 23, 2009. Between April 2010 and June 2012, continued efforts were made to define and reach agreement on licensing criteria for the vaccine. Final agreement was reached in February 2013 regarding the endpoint for each study.

The MenB outbreaks at Princeton and UC-Santa Barbara were the impetus for discussions about an accelerated approval pathway for licensure of Trumenba in December 2013. Breakthrough therapy designation was granted on March 19, 2014, and Pfizer submitted the BLA for Trumenba as a "rolling submission" on a Priority Review timeline beginning on May 8, 2014, with all BLA components submitted by June 16, 2014. As of the date of this review, Trumenba has not been licensed in any countries outside the US.

2.6 Product Description

The vaccine candidate, bivalent rLP2086, consists of 2 purified recombinant lipidated factor H binding proteins (fHBPs), or rLP2086 antigens, one protein antigen from each of the fHBP subfamilies A and B, as identified from *Neisseria meningitidis* serogroup B strain M98250771 (variant A05, subfamily A) and strain CDC1573 (variant B01, subfamily B). The vaccine is a sterile liquid suspension composed of the rLP2086 proteins formulated at 120 µg/mL/subfamily in 10 mM histidine buffer, pH 6.0, (b)(4) sodium chloride with 0.5 mg/mL aluminum as aluminum phosphate (---(b)(4)-------) and Polysorbate 80 added ----------(b)(4)----------. It is available in 0.5 mL single-dose pre-filled syringes with dosage strength of 60 µg of subfamily A and 60 µg of subfamily B rLP2086 (120 µg total protein) per 0.5 mL dose and is administered via intramuscular injection.

2.7 Indications and Dosage

Trumenba is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10-25 years of age. The vaccine is to be administered as 120µg bivalent rLP2086 in a 3-dose series at months 0, 2, and 6.

2.8 Objectives/Scope of the Review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed in the US, and to evaluate the pharmacovigilance plan (PVP) submitted by Pfizer for the Trumenba BLA.

3 MATERIALS REVIEWED

Submit Date	Source	Document Type	Document(s) Reviewed
05/08/2014 05/12/2014 06/16/2014	Pfizer	BLA	125549/0.0, 0.1, 0.4; Module 1.2, Cover Letters: (Original) MnB BLA Rolling Submissions 1, 2 & 4
05/29/2014	Pfizer	BLA	125549/0.2; Module 2.3.P.2, Pharmaceutical Development
06/16/2014	Pfizer	BLA	125549/0.4; Module 1.14.1, Labeling: Draft Labeling
06/16/2014	Pfizer	BLA	125549/0.4; Module 1.16, Risk Management Plan: Pharmacovigilance Plan, Version 1.0, dated 06/09/2014
06/16/2014	Pfizer	BLA	125549/0.4; Module 2.2, Introduction
05/08/2014	Pfizer	BLA	125549/0.0; Module 2.4, Non-clinical Overview
06/16/2014	Pfizer	BLA	125549/0.4; Module 2.5, Clinical Overview

Submit Date	Source	Document Type	Document(s) Reviewed
05/08/2014	Pfizer	BLA	125549/0.0; Module 2.6, Non-clinical Written and Tabulated Summaries •Subsection 2.6.1: Introduction •Subsection 2.6.6: Toxicology Written Summary
06/16/2014	Pfizer	BLA	125549/0.4; Module 2.7, Clinical Summary •Subsection 2.7.3: Summary of Clinical Efficacy •Subsection 2.7.4: Summary of Clinical Safety •Subsection 2.7.6: Synopses of Individual Studies
05/08/2014	Pfizer	BLA	125549/0.0; Module 4.2.3, Non-clinical Study Reports; Toxicology •Subsection 4.2.3.2: Report 60511 / WAY-263069 (rLP2086) and AlPO4 (CL136352): 5-Cycle (1 dose/2 week cycle) Intramuscular Toxicity Study in Rabbits (Protocol 05_0388) •Subsection 4.2.3.2: Report 51777 / WAY-263069 (rLP2086) and AlPO4 (CL136352): 5-Cycle (1 dose/2 week cycle) Intramuscular Toxicity Study in Rabbits (Protocol 05_0388)-Antibody Report •Subsection 4.2.3.2: Report 74041 / rLP2086 and AlPO4 (CL136352): Repeat 5-Cycle (1 dose/2 week cycle) Intramuscular Toxicity Study in Rabbits (Protocol 07_1434)
05/08/2014	Pfizer	BLA	125549/0.0; Module 4.2.3, Non-clinical Study Reports; Toxicology •Subsection 4.2.3.5.1: Report 63113 / WAY-263069 (rLP2086) and AlPO4 (CL136352): A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits (Wyeth Protocol 05_2860) •Subsection 4.2.3.5.1: Report 75947 / Meningococcal B Vaccine (rLP2086): A Combined Intramuscular Fertility and Developmental Toxicity Study in Female Rabbits (Protocol 08_3574)
06/16/2014	Pfizer	BLA	125549/0.4; Module 5.2, Tabular Listing of All Clinical Studies
05/12/2014	Pfizer	BLA	125549/0.1; Module 5.3.5, Reports of Efficacy and Safety Studies (Synopses, Study Report Bodies, Discontinued Patients, Adverse Event Listings, and Case Report Forms) •Subsection 5.3.5.1: Study Reports of Controlled Clinical Studies ➢ Study B1971004: Final Report: A Phase 1, Randomized, Open-Label, Parallel-Group, Active- and Placebo-Controlled Study to Assess the Safety And Tolerability of 60, 120, and 200 mcg Meningococcal Group B rLP2086 Vaccine in Healthy Adult Subjects (Protocol 6108A1-1004-US, CSR-80305) ➢ Study B1971005: Stage 1 Interim Report: A Randomized, Single-Blind, Placebo-Controlled, Phase 2 Trial of the Safety, Immunogenicity, and Tolerability of Meningococcal Serogroup B (MnB) rLP2086 Vaccine at Doses of 60mcg, 120 mcg, and 200 mcg in Healthy Adolescents Aged 11 to 18 Years ➢ Study B1971010: Final Report: 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 •Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies ➢ Study B1971003: An Open-Label Safety and Blood Collection Study In MnB rLP2086 Vaccinated Healthy Adult Volunteers For Immunological Assay Development ➢ Study B1971012: Final Report: 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

Submit Date	Source	Document Type	Document(s) Reviewed
06/16/2014	Pfizer	BLA	125549/0.4; Module 5.3.5, Reports of Efficacy and Safety Studies (Synopses, Study Report Bodies, Discontinued Patients, Adverse Event Listings, and Case Report Forms) •Subsection 5.3.5.1: Study Reports of Controlled Clinical Studies ➢ Study B1971011: Final Report: 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 Years •Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies ➢ Study B1971042: Final Report: A Single-Arm, Open-label Study to Describe the Safety, Tolerability, and Immunogenicity of Bivalent rLP2086 Vaccine in Laboratory Workers ≥18 to ≤65 Years of Age •Subsection 5.3.5.3: Reports of Analyses of Data from >1 Study ➢ Integrated Summary of Safety
06/25/2014	Pfizer	BLA	125549/0.6; Module 5.3.5, Reports of Efficacy and Safety Studies •Subsection 5.3.5.3: FDA-DMC Responses ➢ Appendix 1: 2 Alopecia Cases ➢ Appendix 4: MS DMC document ➢ Appendix 5: Alopecia-Hypothyroidism DMC document ➢ Minutes-1May2014-Modlin-AdHocMeeting ➢ Minutes-20May2014-DMC Meeting
06/25/2014	Pfizer	BLA	125549/0.7; Module 1.9.4, Proposed Pediatric Study Request and Amendments
08/14/2014	Pfizer	BLA	125549/0.11; Module 1.11.3, Efficacy Information Amendment •Response to 07Aug2014 IR Re: Summaries of Clinical Safety and Financial Disclosures
08/15/2014	Pfizer	BLA	125549/0.12; Module 5.3.5, Reports of Efficacy and Safety Studies •Subsection 5.3.5.2: Multi-Year Pregnancy Study Concept Proposal (IR response deemed satisfactory by Epi/PVP Reviewer)
08/15/2014	Pfizer	BLA	125549/0.13; Module 1.11.3, Efficacy Information Amendment •Assessment of Background Rates for Other AI Disease (IR response deemed satisfactory by Epi/PVP Reviewer)
09/09/2014	Pfizer	BLA	125549/0.20; Module 1.11.3, Efficacy Information Amendment •Response to 29Aug2014 IR on Epidemiology/PVP-Clinical Issues, dated 09/08/2014 (IR response deemed satisfactory by Epi/PVP Reviewer)
throughout	FDA	OVRR Clinical Reviewer	Collaborative meetings & discussion regarding safety issues; draft clinical review summary, distributed prior to Mid-cycle meeting (09/29/2014)
throughout	FDA	OBE Statistical Reviewer (Safety)	Collaborative meetings & discussion of analytic approaches to evaluating specific safety issues in BLA; calculation of lower bound of 95% CI of risk ratios for AI/NI diseases among study population (09/30/2014)
throughout	Other	References	Medical literature review *(see detailed listing at end of report)*

4 PHARMACOVIGILANCE PLAN REVIEW

4.1 Non-clinical Safety Findings

The toxicity assessment conducted for bivalent rLP2086 consisted of 2 repeat-dose and 2 fertility and developmental toxicity studies in rabbits. The initial studies were conducted with the initial vaccine formulation; whereas, the repeat studies used the final clinical vaccine formulation.

In both single-dose and repeat-dose toxicity evaluations, doses up to 400 µg were well tolerated; however, there was slight injection site irritation (edema and/or erythema) in the vehicle control and/or vaccine groups, and increases in mean body temperature, fibrinogen, and total globulins in the vaccine groups, which were

reversible prior to the next dose and were not considered adverse as they are an anticipated response after administration of rLP2086.

The reproductive and developmental toxicity of bivalent rLP2086 vaccine was evaluated in female rabbits in two fertility and developmental toxicity studies. The dose used in these toxicity studies (200 µg) was equivalent to the highest evaluated dose in clinical studies on a per dose basis. In both studies, bivalent rLP2086 was administered IM at a dose of 200 µg to F_0 does prior to mating (17 and 4 days before mating) and on Gestation Days (GDs) 10 and 24. The vaccine did not affect mating, fertility, or embryo/fetal viability, growth and/or development of F_1 fetuses and pups. There were no effects of bivalent rLP2086 on the external, palatal, visceral, or skeletal morphology of F_1 offspring. Findings in does were limited to non-adverse injection site irritation, which consisted of slight, transient edema and/or erythema, in the vehicle and vaccine groups.

The nonclinical toxicology studies found no evidence of systemic toxicity and were deemed adequate by the sponsor to support the preclinical safety of the product and a pregnancy category B.

4.2 Clinical Safety Database

The safety analyses supporting the Risk Management Plan are comprised of data from 7 completed Phase 1 and 2 clinical studies; 4 in adolescents (Studies B1971005, B1971010, B1971011, and B1971012) and 3 in adults (Studies B1971003, B1971004, and B1971042). Overall, a total of 5,604 subjects were vaccinated: 4,576 subjects received ≥1 dose of bivalent rLP2086 (4,335 received the 120 µg dose) and 1,028 subjects received saline or other vaccines. All studies in the BLA used the final formulation of bivalent rLP2086.

The core safety data for this BLA submission are comprised of 4 randomized, controlled core safety studies (B1971004, B1971005, B1971010, B1971011) conducted with 120 µg of the final formulation using the proposed 0, 2, 6-month vaccination schedule. For the core safety data, a total of 2,566 subjects received ≥1 dose of 120 µg bivalent rLP2086 and 1,012 subjects were randomized to a control group. In randomized controlled studies conducted in the US, 1,994 subjects received ≥1 dose of bivalent rLP2086 at the 120 µg dose level using a 0, 2, 6-month vaccination schedule.

All other safety data are considered supportive and include data from 3 additional, non-controlled studies (i.e., without a control group) that used the 120 µg dose of the final formulation, as well as data from subjects who received 60 µg or 200 µg dose levels of the final formulation during their participation in 2 of the randomized controlled studies (B1971004 & B1971005).

4.3 Clinical Trial Exposure

In the 4 controlled core safety studies, 2,566 subjects received ≥1 dose of 120 µg bivalent rLP2086 either as a single agent or administered concomitantly with a licensed vaccine, and 2,272 subjects received 3 doses of 120 µg bivalent rLP2086 administered using a 0, 2, 6-month schedule. The majority of subjects who received ≥1 dose of bivalent rLP2086 were enrolled in the US studies (77.7%). Of the 1,012 subjects who received ≥1 dose of the control (saline) either as a single agent or administered concomitantly with a licensed vaccine, approximately half were enrolled in the US studies (50.7%).

In the overall safety data (all 7 BLA studies), 4,576 subjects received ≥1 dose of bivalent rLP2086, 4,284 subjects received 2 doses of bivalent rLP2086 and 3,320 subjects received 3 doses of bivalent rLP2086. The majority of this exposure was at the 120 µg dose level. Of the 4,576 subjects who received ≥1 dose of bivalent rLP2086, 2.4% were adults and 97.6% were adolescents. In all 7 BLA studies, 1,028 subjects received ≥1 dose of a control injection only (saline and/or other non-rLP2086 vaccine).

4.4 Sponsor Analysis (Safety Studies)

Table 1 describes pertinent information, including key safety findings, for all 7 studies included in this BLA. The 4 controlled core safety studies are denoted with an asterisk (*).

Table 1. 7 BLA Safety Studies for rLP2086

Study #; Region	Study Objectives	Study Design; Population Parameters	# of Subjects	(Safety Analyses) # Subjects/Exposure	Key Safety Findings
B1971003 Australia	Safety & Immunogenicity	Phase 2, Single-group, uncontrolled, open-label study; Age (years): ≥18 to ≤40	60	▪ 120µg rLP2086 (0,1,6-month): 60/60 (100%)	▪ No deaths **Related SAEs** ▪ 120µg rLP2086: 22 yo F, became pregnant Day 55 post-dose 2, w/d, delivered healthy boy; **Related NDCMCs** ▪ None **AI/NI cases** ▪ 120µg rLP2086: 38 yo F w/ psoriasis flare[1] 1 pt w/ celiac disease (exacerbation of gluten intolerance)[1]
B1971004* US	Safety & Immunogenicity	Phase 1, single-center, randomized, open-label, active- and placebo-controlled , parallel-group study; Age (years): ≥18 to ≤40	48	▪ 60µg rLP2086 (0,2,6-month): 12/48 (25%) ▪ 120µg rLP2086 (0,2,6-month): 12/48 (25%) ▪ 200µg rLP2086 (0,2,6-month): 12/48 (25%) ▪ Tdap (0-month) + Saline (0,2,6-month): 12/48 (25%)	▪ No deaths **Related SAEs** ▪ None **Related NDCMCs** ▪ None **AI/NI cases** ▪ None
B1971005* EU, Australia	Safety & Immunogenicity	Phase 2, randomized, single-blind, placebo-controlled study; Age (years): ≥11 to ≤18	536	▪ 60µg rLP2086 (0,2,6-month): 22/536 (4%) ▪ 120µg rLP2086 (0,2,6-month): 198/536 (37%) ▪ 200µg rLP2086 (0,2,6-month): 195/536 (36%) ▪ Saline (0,2,6-month): 121/536 (23%)	▪ No deaths **Related SAEs** ▪ 60µg rLP2086: None ▪ 120µg rLP2086: None ▪ 200µg rLP2086: 13 yo M w/ anaphylaxis post-dose 3 ▪ Saline: None **Related NDCMCs** ▪ 60µg rLP2086:None ▪ 120µg rLP2086: None ▪ 200µg rLP2086: 1 pt w/ migraine ▪ Saline: None **AI/NI cases** ▪ None
B1971010* EU	Safety & Immunogenicity; Concomitant with Repevax	Phase 2, randomized, placebo-controlled, single-blind study; Age (years): ≥11 to <19	752	▪ Grp1: 120µg rLP2086 (0,2,6-month) + Repevax (0-month): 374/752 (50%) ▪ Grp2: Saline (0,2,6-month) + Repevax (0-month): 378/752 (50%)	▪ 1 death: passenger in road traffic accident (not related) **Related SAEs** ▪ None **Related NDCMCs** ▪ None **AI/NI cases** ▪ 120µg rLP2086 + Repevax: 12 yo F w/ AI thyroiditis[1] 11 yo F w/ ITP 17 yo F w/ celiac disease[1] 11 yo M w/ post-infectious arthritis ▪ Saline + Repevax: None
B1971011* US	Safety & Immunogenicity; Concomitant with Gardasil	Phase 2, randomized, active-controlled, observer-blinded study; Age (years): ≥11 to <18	2483	▪ Grp1: 120µg rLP2086 (0,2,6-month) + Gardasil (0,2,6-month): 992/2483 (40%) ▪ Grp2: 120µg rLP2086 (0,2,6-month) + Saline (0,2,6-month): 990/2483 (40%) ▪ Grp3: Saline (0,2,6-month) + Gardasil (0,2,6-month): 501/2483 (20%)	▪ No deaths **Related SAEs** ▪ None **Related NDCMCs** ▪ None **AI/NI cases** ▪ Grp1: 11 yo F w/ Sydenham's chorea ▪ Grp2: 17 yo M w/ IgA nephropathy 16 yo M w/ Bell's palsy ▪ Grp3: None

Study #; Region	Study Objectives	Study Design; Population Parameters	# of Subjects	(Safety Analyses) # Subjects/Exposure	Key Safety Findings
B1971012 EU	Safety & Immunogenicity; 2-dose / 3-dose schedules	Phase 2, randomized, placebo-controlled, single-blind study; Age (years): ≥11 to <19	1712	▪ Grp1: 120µg rLP2086 (0,1,6-month): 426/1712 (25%) ▪ Grp2: 120µg rLP2086 (0,2,6-month): 414/1712 (24%) ▪ Grp3: 120µg rLP2086 (0,6-month): 451/1712 (26%) ▪ Grp4: 120µg rLP2086 (0,2-month): 277/1712 (16%) ▪ Grp5: 120µg rLP2086 (0,4-month): 128/1712 (8%) ▪ Grp 5: randomized, but only received 1 dose saline: 16/1712 (1%)	▪ No deaths **Related SAEs** ▪ Grp1: None ▪ Grp2: 15 yo F w/ vertigo, chills, HA 11 yo F w/ fever, vomiting ▪ Grp3: None ▪ Grp4: None ▪ Grp5: None **Related NDCMCs** ▪ None **AI/NI cases** ▪ Grp1: 16 yo F w/ Crohn's disease ▪ Grp2: 18 yo F w/ rheumatoid arthritis[1] ▪ Grp3: 15 yo M w/ hyperthyroidism[1] ▪ Grp4: 18 yo F w/ hypothyroidism[1] 16 yo F w/ hypothyroidism[1] ▪ Grp5: None
B1971042 US	Safety & Immunogenicity in Pfizer Lab workers	Phase 3, single-group, uncontrolled, open-label study; Age (years): >18 to <65	13	▪ 120µg rLP2086 (0,2,6-month): 13/13 (100%)	▪ No deaths **Related SAEs** ▪ None **Related NDCMCs** ▪ 120µg rLP2086: 56 yo M w/ gouty arthritis, deemed possibly related to vaccine **AI/NI cases** ▪ None

Abbreviations: AE=Adverse Event; AI=Autoimmune; EU=European Union; F=Female; F/U=Follow-up; Grp=Group; HA=Headache; ITP=Idiopathic Thrombocytopenia; M=Male; NDCMCs=Newly Diagnosed Chronic Medical Conditions; NI=Neuroinflammatory ; pt=patient; SAEs=Serious Adverse Events; USA=United States; w/d=withdrew; yo=years old

* Controlled Studies (data for 60µg & 120µg doses of rLP2086 in studies B1071004 & B1971005 are part of the supportive study data)

[1] Exacerbation of pre-existing autoimmune disease (never-diagnosed but baseline labs consistent with disease OR previously diagnosed but asymptomatic/latent)

4.4.1 Adverse Reactions and Adverse Events

The data presented from the clinical safety studies of this BLA support the following conclusions when 120 µg of bivalent rLP2086 (Trumenba) was administered using a 0, 2, 6-month schedule in the 4 randomized controlled core safety studies:

- Local reactions were reported in a higher proportion of subjects receiving Trumenba when compared to saline control. Pain at the injection site was the most common local reaction reported across all 4 studies but few subjects withdrew from any of the studies due to pain at the injection site.
- Most local reactions were mild or moderate in severity.
- Few subjects experienced local reactions with potentiation (worsening with each successive dose) after vaccination with Trumenba.
- Overall, the rate of withdrawal due to local reactions was low across all core safety studies (11 subjects of 2,566), whether subjects received Trumenba alone or concomitantly with another licensed vaccine (Repevax® or Gardasil®), suggesting that Trumenba administered alone or concomitantly was well tolerated by recipients.
- The incidences of systemic events were generally higher among Trumenba vaccinees when compared to the control group. The frequency of fever ≥38.0°C was generally low (<9%) across studies.
- Systemic events among Trumenba vaccinees were usually mild or moderate in intensity after each vaccination and generally resolved within 1 to 4 days after vaccination. Fatigue and headache were the most frequently reported systemic events among Trumenba vaccinees.
- A low percentage of subjects across groups experienced any systemic events with potentiation.
- In general, the incidence of reported systemic events tended to decrease with each subsequent dose.
- Concomitant administration of Trumenba and Repevax resulted in a higher proportion of subjects (12.1%) with fever than for subjects receiving Repevax alone (5.3%). Fever >40.0°C was not reported

for either group. The incidence of other systemic events was generally slightly higher for subjects receiving both Trumenba and Repevax than for subjects receiving Repevax alone.

- Unsolicited adverse events (AEs) reported were generally illnesses/conditions common or expected in the age population (adolescent or adult) of a given study.
- The proportion of subjects in the Trumenba group and the control group reporting AEs within 30 days after each vaccination and during the vaccination phase were similar. The AE incidence rates were similar in the Trumenba group (160.3 per 100 subject-years) and the control group (156.9 per 100 subject-years).
- A higher proportion of subjects in the Trumenba group compared with the control group reported related AEs (6.63% vs 3.56%), severe AEs (4.40% vs 2.87%), immediate (occurring within 30 minutes of vaccination) AEs (3.86% vs 2.28%), and AEs that led to discontinuation (1.17% vs 0.40%); this higher incidence in the Trumenba group is accounted for by the higher incidence of AEs reflecting reactogenicity.
- The serious adverse event (SAE) incidence rates throughout the study were similar in the Trumenba group (2.2 per 100 subject years) and the control group (2.1 per 100 subject-years). None of the SAEs in the 4 controlled core safety studies were considered related to Trumenba (bivalent rLP2086 at the 120µg dose).
- One death occurred, which was considered unrelated to Trumenba (the subject died while a passenger in a car involved in a road traffic accident).
- The percentage of subjects reporting newly diagnosed chronic medical conditions (NDCMCs) was low (<1%) and similar when comparing subjects in the Trumenba group with the control group.
- Where Trumenba was administered with another vaccine (Repevax or Gardasil), there was no difference in the incidence of AEs reported in the group that received Trumenba concomitantly with another vaccine when compared with the group receiving Trumenba alone.
- The favorable tolerability profile of Trumenba was supported by observation of the low number of subjects (1.17%) who reported AEs resulting in withdrawal from study vaccination and in the proportion of subjects completing the vaccination phase between subjects in the Trumenba group compared to the control subjects pooled together for the integrated analysis.

When additional AE data from the remaining supportive safety studies without control groups and/or where Trumenba was administered on other schedules were included, the conclusions are in agreement with the conclusions from the core safety studies.

Additional issues noted in the overall safety data for all 7 BLA studies are as follows:

- 3 SAEs were considered related to study vaccine
  - B1971012 (120µg): 11 yr old white male with fever, chills, vomiting, and sudden onset severe headache 1 hour after receiving Dose 1; subject withdrawn from study
  - B1971012 (120µg): 15 yr old white female with chills, vertigo, and headache 70 minutes after receiving Dose 2; symptoms resolved within 3 days; subject withdrawn from study
  - B1971005 (200µg): 13 yr old white male with sudden onset headache, blotchy rash/flushing, nausea, chills, and vomiting 50 minutes after receiving Dose 3; seen in ER and ~4 hours later developed hypotension (BP 97/48), for which he received 1 dose epinephrine + Zyrtec; BP remained low, but no additional epi/antihistamines given; event diagnosed as anaphylactic reaction; mast cell tryptase levels normal before & after event (test sensitivity ~60-65% with cutoff of <7.0 µg/L); subject completed study, as SAE occurred after Dose 3
- Only 2 NDCMCs were considered related or possibly related to bivalent rLP2086 (B1971005: 200 µg-migraine; B1971012: 120 µg-gouty arthritis).
- The percentage of subjects reporting autoimmune (AI) or neuroinflammatory (NI) conditions was low (7 of the 2,566 subjects in the 4 controlled clinical trials, conducted in adolescents 11-18 years of age, that comprise the core safety studies), but these conditions were only noted for subjects who received Trumenba. When the 3 open-label, non-controlled, supportive studies conducted in individuals 11-65 years of age were included, a total of 14 cases of AI/NI conditions were reported.

- Of the 7 cases of AI/NI conditions reported in the 4 core safety studies:
  - 2 had evidence that the condition was preexisting prior to enrollment
  - 3 had a documented non-vaccine cause of the condition
  - 1 was highly likely pre-existing due to the timing of the vaccination and the known pathophysiology of the disease
  - Only 1 was considered to have a possible vaccine etiology
- Of the 7 cases of AI/NI conditions in the supportive (open-label) studies:
  - 6 had diagnostic evidence that the condition was pre-existing prior to the first vaccination.
  - Only 1 was considered to have a possible vaccine etiology

4.4.2 Autoimmune / Neuroinflammatory Conditions

Initially, the imbalance in case counts between Trumenba vaccinees and control vaccinees prompted further scrutiny by the CBER review team. This resulted in additional information and evaluation from Pfizer, including reports provided by Pfizer to the External Data Monitoring Committee (DMC) regarding the AI and NI cases identified in the 7 BLA studies, as well as in additional ongoing studies not included in the BLA. Data regarding cases in the ongoing studies was incomplete at the time of CBER review, and thus evaluation of AI/NI cases in this review include only those identified in the 7 BLA studies.

However, based on its own review of the completed and ongoing studies, the DMC requested Pfizer perform an evaluation of the preliminary data for cases of alopecia and hypothyroidism, as well as a literature review of expected background rates for multiple sclerosis (MS). These reports were forwarded to the CBER review team. The notable findings are as follows:

- Only 2 of 11 cases of alopecia were labeled "alopecia areata" (a possible AI disease), corresponding to an incidence rate of 13.9 per 100,000 person-years, which was similar to an observed background rate from the literature of 15.3-17.0 per 100,000 person-years.
- Only 3 of 8 cases of hypothyroidism were identified to have a confirmed AI etiology, corresponding to an incidence rate of 20.9 per 100,000 person-years, which was similar to observed background rates from the literature of 35 and 9 per 100,000 person-years (for females and males, respectively).
- 2 of the 4 reported MS cases had pre-existing symptoms of disease. The program-wide incidence rate for the remaining 2 cases (one of which could not be confirmed) is: 13.3 (95% confidence interval (CI): 1.6-48.1) per 100,000 person-years, which has a confidence interval that includes the background rates seen in the literature of 3.8-9.2 per 100,000 person-years and 5.1-11.6 per 100,000 person-years in Finland.

Table 2 lists each of the 14 AI/NI cases reported in the 7 BLA studies. Of these, 13 were designated autoimmune conditions, and 1 (Bell's Palsy) was designated a neuroinflammatory condition.

When a case is designated "Pre-existing", the subject had either of the following 2 circumstances:

- A previously diagnosed AI disease that was asymptomatic at study onset but became symptomatic during the study (1-psoriasis, 1-rheumatoid arthritis, 2-celiac disease)
- A yet undiagnosed AI disease that became symptomatic during the study and baseline (pre-vaccination) labs were consistent with early disease (1-hyperthyroidism, 3-hypothyroidism, including 1 autoimmune thyroiditis)

When a case is listed as having a "Possible Vaccine Etiology", the subject's condition occurred for the first time following study vaccination (Trumenba or Control-Saline/Repevax/Gardasil) and he/she did not have any known non-vaccine cause for the disease. Known non-vaccine causes for 3 of the cases (1-postinfectious arthritis, 1-Sydenham's chorea, 1-Bell's palsy) are listed in the table. Additionally, 1 case with IgA nephropathy occurred 1 day post-dose 1. Given this timing, the insidious nature of the disease pathophysiology, and the time required for autoantibody development, a causal association with vaccine was unlikely.

Table 2. Autoimmune / Neuroinflammatory Cases in the 7 BLA Studies

Study	Age (yrs)	Race	Sex	Condition	Pre-existing?	Possible Vaccine Etiology?	Reason not related	Concomitant Vaccination (if any)	Episode # (if >1)	# Days from rLP2086 Dose 1	# Days from rLP2086 Dose 2	# Days from rLP2086 Dose 3	Final study status
B1971003	38	W	F	Psoriasis	Y	N	-	-	1 2	21 190	- ?	- 14	completed
B1971003	?	?	?	Celiac disease (exacerbation of gluten intolerance)	Y	N	-	-	-	48	-	-	completed
B1971010	12	W	F	Autoimmune thyroiditis	Y	N	-	Repevax	-	184	140	-	withdrew
B1971010	11	W	F	Acute idiopathic thrombocytopenia	N	Y		Repevax	-	300	150	30	completed
B1971010	17	W	F	Celiac disease	Y	N	-	Repevax	-	28	-	-	completed
B1971010	11	W	M	Acute post-infectious arthritis	N	N	Strep infection preceding onset	Repevax	-	9	-	-	withdrew
B1971011	11	W	F	Sydenham's chorea	N	N	Strep infection preceding onset	Gardasil	-	55	13	-	completed
B1971011	17	B	M	IgA Nephropathy	N	N	Time from vaccination too short	-	-	1	-	-	withdrew
B1971011	16	W	M	Bell's palsy (w/ Lyme disease)	N	N	Lyme disease preceding onset	-	-	79	32	-	completed
B1971012	16	W	F	Crohn's disease	N	Y		-	-	123	95	-	withdrew
B1971012	18	W	F	Rheumatoid arthritis	Y	N	-	-	1 2	47 90	- 27	-	withdrew
B1971012	15	W	M	Basedow's (Grave's) disease (hyperthyroidism)	Y	N	-	-	-	53	25	-	withdrew
B1971012	18	W	F	Hypothyroidism	Y	N	-	-	-	280	224	-	completed
B1971012	16	W	F	Hypothyroidism	Y	N	-	-	-	35	-	-	withdrew

Abbreviations: F=Female; M=Male; N=No; Y=Yes

The AI/NI cases presented in the 7 BLA studies can be categorized as follows, according to whether the injection received (Trumenba vs. Control-Saline/Repevax/Gardasil) was a possible etiology.

Table 3. Autoimmune / Neuroinflammatory Case Distribution - All 7 BLA Studies

	rLP2086 (N=4,576)	Control (N=1,028)
TOTAL CASES	**14**	**0**
• Other non-injection etiology	3	0
• New case, injection etiology unlikely	1	0
• Possible injection etiology	2	0
• Pre-existing condition	8	0

Table 4. Autoimmune / Neuroinflammatory Case Distribution - 4 Controlled BLA Studies

	rLP2086 (N=2,566)	Control (N=1,012)
TOTAL CASES	**7**	**0**
• Other non-injection etiology	3	0
• New case, injection etiology unlikely	1	0
• Possible injection etiology	1	0
• Pre-existing condition	2	0

The case distribution noted in Tables 3 and 4 above, cross-referenced with Table 2, reveals only 2 AI cases (1-idiopathic thrombocytopenia (ITP), 1-Crohn's disease) in all 7 BLA studies in which Trumenba was a possible etiology; only 1 of these (ITP) occurred in one of the 4 controlled core safety studies.

4.4.3 Special Populations

4.4.3.1 Use in Pregnancy and Lactation

All 7 clinical studies required a negative pregnancy test for female subjects entering the studies and excluded women who were pregnant or breast feeding. Both maternal and paternal exposure during pregnancy (exposure in utero, EIU) were considered reportable. Follow-up was conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome.

Seven (7) female subjects in Studies B1971003, B1971005, B1971010, B1971011 and B1971012 became pregnant while receiving the 120 µg dose of bivalent rLP2086 (Trumenba).

- 1 case of spontaneous abortion in Study B1971012 with an onset 84 days post-vaccination (gestational age unknown) was reported as serious, but was deemed unrelated to vaccine.
- 6 non-serious cases
  - 3 pregnancies resulting in normal births for subjects who received Trumenba + Gardasil (1 case) and Trumenba alone (2 cases)
  - 2 elective terminations
  - 1 unknown pregnancy outcome in which the subject received Trumenba + saline
- There were no relevant cases reported in any of the other clinical studies.

There were 3 non-serious cases of exposure via semen reported for Study B1971003, where subjects received the 120µg dose of bivalent rLP2086 (Trumenba). All three cases resulted in full-term healthy infants.

4.4.3.2 Pediatrics

Safety and efficacy of Trumenba in children <10 years of age have not been established. The initial formulation was studied in 2 clinical trials involving children < 11 years of age, but those data are not included in this BLA since subjects received the initial formulation and not the final vaccine formulation.

4.4.3.3 Geriatrics

Safety and efficacy of Trumenba in adults >65 years of age have not been established.

4.5 Safety Concerns Within the Pharmacovigilance Plan (PVP)

4.5.1 Important Identified Risks

- None

4.5.2 Important Potential Risks

- Anaphylactic reactions
  - Anaphylactic reaction was reported for 1 subject in Study B1971005 in the 200 µg bivalent rLP2086 group (0.48% of 207 subjects)
  - This SAE occurred in a subject in the 11-14 year age group (representing 0.02% of the 4576 subjects participating to the 7 pooled studies; of the 4,576 subjects, 2,649 were in the age group between 11 and 14 years, thus this single case of anaphylaxis represents 0.04% of the subjects in this range of age).
  - This case represents an incidence of 22.8 cases (95% CI: 0.5767-126.9) per 100,000 subject-years of observation. (Note the lack of precision of the estimate represented by the wide confidence interval, given that this was only 1 case.)
  - Limited epidemiologic data is available that quantifies the incidence of anaphylaxis in the general population. Using data from a health maintenance organization in Washington State, Bohlke et al observed an incidence of 10.5 cases (95% CI: 8.1-13.3) per 100,000 person-years in children and adolescents under 18 years of age.[33]
  - Product information warning health care providers of possible anaphylactic reactions in patients with known hypersensitivity to the vaccine can help prevent them.

4.5.3 Important Missing Information

- Vaccine effectiveness
  - Measuring effectiveness against MenB disease will require surveillance of MenB disease throughout the US, as well as assessment of vaccination coverage among cases of MenB disease.
- Vaccine failure
  - Vaccination failure for Trumenba is defined as the development of invasive meningococcal disease caused by meningococcal serogroup B occurring after the subject's last dose in the recommended 3-dose series.
- Bactericidal response in subjects with terminal complement deficiency
  - Persons with component deficiencies in the final common complement pathway are more susceptible to *N. meningitidis* infection than complement-satisfactory persons. In addition, complement component-deficient populations frequently experience frequent meningococcal disease since their immune response to natural infection may be less complete than that of complement non-deficient persons. Antibody responses to Trumenba have not been evaluated in subjects with terminal complement deficiency.
- Safety in pregnancy and lactation
  - There is limited safety data on exposure during pregnancy obtained from the clinical program (pregnant females were excluded), and considering Trumenba will be used among women with childbearing potential.

4.6 Action Plan for Safety Issues

Table 5. Action Plan for Safety Issues Proposed by Pfizer

Important Identified Risks	Planned Pharmacovigilance Actions	Rationale for Proposed Actions
None	–	–
Important Potential Risks	**Planned Pharmacovigilance Actions**	
Anaphylactic reactions	• Labeling (Sections 4.4 & 4.8 of USPI)	• Labeling communicates the potential risk to health care providers.
Anaphylactic reactions	• Routine Pharmacovigilance (Adverse event reporting in accordance with 21 CFR 600.80)	• Routine pharmacovigilance measures will aid in the documentation and analysis of the event.
Anaphylactic reactions	• Ascertain incidence rate of anaphylactic reactions in rLP2086 vaccinees in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016	• Evaluation of the potential risk in ongoing phase 2 and 3 clinical studies will assist in further analysis and characterization of the event.
Important Missing Information	**Planned Pharmacovigilance Actions**	**Rationale for Proposed Actions**
Vaccine effectiveness	• Collaborate with federal agencies to monitor epidemiology of invasive meningococcal disease in the US with respect to rLP2086/fHBP variants and characterization of new emerging variants, including susceptibility of any novel strains to killing by immune sera from Trumenba vaccinees	• To evaluate population-level effectiveness after introduction of Trumenba
Vaccine failure	• Routine Pharmacovigilance. AE reporting for vaccination lack of effect (vaccine failure) reports following vaccination with Trumenba. Pfizer employs a systematic procedure to collect relevant information for lack of effect spontaneous reports that are made directly to them and attempts to obtain follow-up information when a report of this type is from a primary reporter with a known identity. Spontaneous and related AE reports of lack of effect will be closely followed for several factors including the frequency of occurrence, timing of the event in relation to immunization, serogroup of *N. meningitidis* strain causing infection, medications, and pre-existing medical conditions.	• As with other vaccines, it is expected that Trumenba may not protect 100% of the individuals receiving it.
Bactericidal response in subjects with terminal complement deficiency	• Routine Pharmacovigilance	• To obtain safety information following exposure to Trumenba among subjects with terminal complement deficiency
Bactericidal response in subjects with terminal complement deficiency	• Ascertain terminal complement deficiency status and bactericidal response of subjects in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.	• To obtain safety information following exposure to Trumenba among subjects with terminal complement deficiency
Safety in pregnancy and lactation	• Observational pregnancy study using electronic health care data (Study B1971052)	• Given limited safety data on exposure during pregnancy obtained from the clinical program, and the possibility that Trumenba will be used among women with childbearing potential, the proposed pregnancy study will provide safety data on Trumenba exposure during pregnancy in a real world setting after approval.
Safety in pregnancy and lactation	• Routine Pharmacovigilance	• To monitor pregnancy and birth outcomes in the post-approval period
Safety in pregnancy and lactation	• Monitor pregnancy and/or lactation status of female subjects and any SAEs among births to pregnant women exposed in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.	• To estimate the incidence of pregnancy outcomes (e.g., live birth, spontaneous abortion) in women exposed and not exposed to Trumenba during pregnancy and to estimate the incidence of birth outcomes (e.g., major congenital abnormalities) in infants exposed and not exposed to Trumenba in utero.
Data on younger children (<11 years of age)	• Pediatric Study Plan ➢ Study B1971017 ➢ Study B1971035	• To monitor the safety of Trumenba among children <11 years of age (required by PREA)

4.6.1 Ongoing or Planned Studies As Part of Action Plan for Safety Issues

4.6.1.1 Ongoing Studies

The following ongoing or planned studies will be completed as part of the Action Plan for Trumenba. Studies B1971009, B1971014, B1971015, and B1971016 have been developed under the IND for the product.

4.6.1.2 Pediatric Study Plan

Studies B1971017 and B1971035 are part of the Pediatric Study Plan as required by the Pediatric Research Equity Act (PREA) and are reviewed and discussed in greater detail in the Clinical Review memo.

Table 6. Ongoing or Planned Studies As Part of Action Plan for Safety Issues

Study #	Study Objectives	Study Design; Population Parameters	# of Planned Subjects	(Safety Analyses) # Subjects/Exposure	Estimated / Actual Study Start; Estimated / Actual Completion
B1971009	Safety & Immunogenicity	Phase 3, randomized, active-controlled, observer-blinded study; Age (years): ≥10 to <19	3600	▪ Grp1: 120µg rLP2086 (0,2,6-month), Lot 1 ▪ Grp2: 120µg rLP2086 (0,2,6-month), Lot 2 ▪ Grp3: 120µg rLP2086 (0,2,6-month), Lot 3 ▪ Grp4: HAV (0,6-month) + Saline (2-month)	April 18, 2013 Q4 2015
B1971014	Safety & Immunogenicity	Phase 3, randomized, active-controlled, observer-blinded study; Age (years): ≥10 to <26	5700	▪ Grp1: 120µg rLP2086 (0,2,6-month) ▪ Grp2: HAV (0,6-month) + Saline (2-month)	November 7, 2012 Q4 2015
B1971015	Safety & Immunogenicity	Phase 2, randomized, controlled, observer-blinded study; Age (years): ≥10 to <13	2625	▪ Grp1: 120µg rLP2086 (0,2,6-month) + MCV4/Tdap (0-month) ▪ Grp2: Saline (0,2,6-month) + MCV4/Tdap (0-month) ▪ Grp3: 120µg rLP2086 (0,2,6-month) + Saline (0-month)	September 28, 2011 LSLV: May 8, 2014
B1971016	Safety & Immunogenicity	Phase 3, randomized, placebo-controlled, observer-blinded study; Age (years): ≥18 to <26	3300	▪ Grp1: 120µg rLP2086 (0,2,6-month) ▪ Grp2: Saline (0,2,6-month)	May 3, 2013 Q4 2015
B1971017 (per PREA)	Safety & Immunogenicity	Phase 2, randomized, active-controlled, observer-blinded study; Age: ≥24 months to <10 years	400		September 2014
B1971033	Immunogenicity	Follow-up study Age (years): ≥11 to <19	Up to 800		September 7, 2012
B1971035 (per PREA)	Safety & Immunogenicity	Phase 2, randomized, active-controlled, observer-blinded study Age: ≥12 months to <18 months OR ≥18 to <24 months	Up to 396		May 2014

4.6.1.3 Observational Pregnancy Study

Pfizer voluntarily proposes an observational pregnancy study using electronic health care data to assess pregnancy outcomes and birth outcomes following exposure to vaccination with Trumenba prior to and during pregnancy. Pfizer has applied for the FDA-assigned labeling pregnancy Category B designation. Animal fertility and developmental toxicity studies with bivalent rLP2086 did not show a risk to embryo-fetal development or pre- or post-natal development and there have been no clinical trials conducted in pregnant women.

- Rationale: Given limited safety data on exposure during pregnancy obtained from the clinical program (Section 4.4.3.1) and considering Trumenba will be used among women with childbearing potential, this study will provide safety data on Trumenba exposure during pregnancy in a real world setting after approval.
- Objectives:
  - To estimate the incidence and risk ratio of adverse pregnancy outcomes (e.g., live birth, spontaneous abortion and stillbirth) in women exposed and not exposed to Trumenba prior to or during pregnancy

    - To estimate the incidence and risk ratio of adverse birth outcomes (e.g., major congenital abnormalities) among infants exposed and not exposed to Trumenba in utero
- Study Design: A population-based prospective cohort study using electronic health care data in the US
    - Exposure Status:
        - Exposed cohort: Women exposed to Trumenba prior to or during pregnancy & infants exposed to Trumenba in utero
        - Unexposed cohort: 2 groups
            - Women and infants exposed to other vaccines during the same time period as exposure to Trumenba
            - Women and infants not exposed to any vaccine during the same time period as exposure to Trumenba
    - Study Outcomes:
        - Live birth
        - Spontaneous abortion
        - Stillbirth
        - Major congenital abnormalities
    - Study Covariates:
        - Sociodemographics
        - Maternal comorbidities
        - Maternal prenatal behaviors
        - Concomitant medication / vaccination
        - Pregnancy history
        - Health care utilization
- Data Source(s): Electronic health care data (electronic medical record or insurance claims data) with an established pregnancy and birth outcome identification algorithm as demonstrated by the ----------(b)(4)---------- program, and others.
- Inclusion Criteria:
    - Continuous enrollment for 180 days prior to estimated start of pregnancy
    - Evidence of pregnancy during the study period
    - Must remain in the managed care organization for the entire duration of the pregnancy
- Data Collection Period: Initiation will begin after licensure of Trumenba and an ACIP recommendation for routine use has been provided
- Study Size: Sample size calculations to follow, based on estimates of exposed pregnancy episodes expected using vaccination rates per pregnancy for comparably-indicated vaccines (from VSD data)
- Data Analysis:
    - Incidence and risk ratios for pregnancy outcomes
    - Prevalence and prevalence ratios for birth outcomes
    - Stratified analyses by covariates
    - Detailed Statistical Analysis Plan (SAP) to follow
- Limitations:
    - Though data files are standardized on an annual basis, the algorithm is dependent on local coding practices and the availability of data including linkage to birth certificates.
    - Women may receive vaccination outside of the health care delivery system; thus, vaccine exposures could be misclassified, potentially introducing bias due to misclassification and reducing the observed counts of women and infants exposed to Trumenba.
    - Gestational age data are not always available in the EMR or claims data, potentially resulting in misclassification of birth outcomes or exposures.
    - Women who seek medical care from the system may not be representative of the entire US population, decreasing generalizability.
- Strengths:

- The database provides more comprehensive and more clinically meaningful information by capturing larger numbers of pregnant women receiving Trumenba, as well as all ascertaining more pertinent information, such as exposures, outcomes, and covariates.
- Compared to the traditional pregnancy registry design, the system can eliminate selection bias, as all exposure during pregnancy would be captured in the database.
- An appropriate comparison group can be identified in the same source population.
- Ascertainment of important study outcomes like spontaneous abortion will be improved, enhancing study validity and interpretability.

It should be noted that the number of people exposed to Trumenba will depend on whether the vaccine is recommended by ACIP and implemented within the national immunization program. Pfizer has submitted a concept proposal thus far and has proposed to submit a draft protocol for this multi-year pregnancy study to the FDA within 3 months following Trumenba accelerated approval.

5 OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

5.1 Biostatistics Review

The biostatistics review concluded that no safety imbalance was identified between Trumenba vaccinees and control vaccinees. Analyses related to the safety issue of autoimmune and neuroinflammatory conditions evaluated the relative risk ratios of the binomial proportions of cases in Trumenba vaccinees compared with subjects who received only control injections. Given that there were no cases of AI/NI disease among subjects receiving control injections only (which would result in a risk ratio of infinity), analysis focused on the lower bound of the 95% CI. If this value was appreciably less than 1.0, then the risk ratio could be presumed to represent no excess AI/NI risk among Trumenba vaccinees. [See Section 6.2 for further details on the assessment of AI/NI disease risk.]

5.2 Clinical Review

The clinical review related to efficacy issues is as follows:
The immunogenicity data using hSBA testing support use of Trumenba as a 3-dose series, with substantially higher titers measured after 3 doses than after 2 doses.

Concomitant vaccination (Gardasil): The non-inferiority criterion for human papillomavirus 18 (HPV-18) was not met. However, the seroconversion rate in both groups receiving Gardasil in Study B1971011 was >99% for each respective HPV type. In the last 10 years, there have been no breakthrough infections due to HPV-18.

The clinical review related to safety issues is as follows:
Data from the reproductive and developmental toxicity studies, in addition to the limited data regarding Trumenba exposure in pregnant females, support the designation of Pregnancy Category B.

Two SAEs resulted in a temporary pause in enrollment/vaccination of studies in the Trumenba program:

- 120 µg (final formulation): A 15 year-old female developed vertigo, severe chills and headache ~1 hour after the 2nd dose. No neurological abnormalities were noted on physical exam, and clinical laboratory results were within normal limits. Chills resolved the next day, vertigo resolved after 2 days, and headache resolved after 6 days. The subject had no previous history of vertigo or syncope. After the first Trumenba dose, she experienced moderate headache, fever, and severe injection site pain/swelling/redness.
- 200ug: A 13-year-old male experienced signs and symptoms consistent with an anaphylactic reaction. He developed acute onset of severe headache, vomiting and generalized flushed appearance ~50 minutes after the 3rd dose.

Among the 4,576 subjects who received bivalent rLP2086 vaccine at any dose, 13 autoimmune conditions and 1 neuroinflammatory condition were reported, compared with 0 (zero) among the 1,028 subjects who

received only control injection(s) (i.e., saline or other non-rLP2086 vaccine). Even at the maximum number of cases identified, there was no conclusive evidence of excess risk of AI or NI conditions among the overall population of bivalent rLP2086 vaccinees (total of 14 cases in 7 studies) compared to control group participants (lower bound of the 95% CI of the relative risk ratio = 0.92). [See Section 6.2 for further details on the assessment of AI/NI disease risk.]

Clinical laboratory evaluations showed increases in fibrinogen levels after each of the 3 doses and were dose-dependent, but transient (peaked at Day 3-4 and resolved by Day 14). Transient increases in fibrinogen levels have been observed with OMV vaccines.

The proposed plans for monitoring potential safety issues were deemed adequate by the clinical reviewer.

6 INTEGRATED RISK ASSESSMENT

6.1 Adverse Reactions and Adverse Events

The data presented in Section 4.4.1 demonstrate that although Trumenba is more reactogenic with regard to both localized and systemic reactions, it is still well-tolerated by the majority of recipients.

Incidence rates of AEs occurring within 30 days of vaccination were similar between Trumenba vaccinees and control vaccinees. Also, while a higher proportion of Trumenba vaccinees compared with control vaccinees reported related AEs, severe AEs, immediate AEs, and AEs that led to discontinuation, the proportions were still rather low, again suggesting an acceptable risk profile. Similar percentages of Trumenba vaccinees and the control vaccinees reported SAEs during the vaccination phase and throughout the study. There were no SAEs or deaths considered related to Trumenba for the 4 controlled core safety studies and the only death was deemed unrelated to vaccine. These data are consistent with a product that is acceptably safe and tolerable.

6.2 Autoimmune / Neuroinflammatory Conditions

In all 7 BLA studies, of 5,604 vaccinees, 4,576 received ≥1 dose bivalent rLP2086 (4,335 received the 120 µg dose) and 1,028 received only control injections/vaccines (i.e., saline, Repevax, and/or Gardasil). Initial assessment identified a total of 14 AI/NI cases (13 AI, 1 NI), all occurring among 120µg bivalent rLP2086 (Trumenba) vaccinees; no AI/NI cases occurred among control vaccinees. A detailed summary of each AI/NI case, including additional clinical and diagnostic information, is included in the Clinical Review memo.

Table 7 breaks down the 14 AI/NI cases into the following categories:

- 8 were pre-existing
  - 1-psoriasis, 1-rheumatoid arthritis, 1-hyperthyroidism, 2-celiac disease, 3-hypothyroidism (including 1-autoimmune thyroiditis)
- 3 (including the 1 NI case of Bell's palsy) had other, non-vaccine etiologies
  - 1-postinfectious arthritis (caused by group A strep), 1-Sydenham's chorea (caused by group A strep), 1-Bell's palsy (caused by Lyme disease)
- 1 was a new case, but vaccine etiology was unlikely (onset 1 day post-dose 1)
  - 1-IgA nephropathy
- 2 were considered to have a possible vaccine etiology
  - 1-Crohn's disease, 1-idiopathic thrombocytopenia

Table 7. AI/NI Case Distribution and Rates in Study Population[1] vs. Background Rates[2]

	All 7 BLA Studies	All 7 BLA Studies	4 Controlled Core Safety Studies (Subset of 7 BLA Studies)	4 Controlled Core Safety Studies (Subset of 7 BLA Studies)		
	rLP2086 (N=4,576)	Control (N=1,028)	rLP2086 (N=2,566)	Control (N=1,012)	Study Population Rate[1] per 100,000 PY (95% CI)	Background Rate[2] per 100,000 PY (95% CI)
TOTAL CASES	**14**	**0**	**7**	**0**	–	–
• Other non-injection etiology	**3**	**0**	**3**	**0**	–	–
• New case, injection etiology unlikely	**1**	**0**	**1**	**0**	–	–
• Possible injection etiology	**2**	**0**	**1**	**0**	–	–
» Idiopathic thrombocytopenia	1	0	1	0	22.71 (3.20-161.18)	5.96 (5.46-6.49)
» Crohn's disease	1	0	0	0	22.71 (3.20-161.18)	31.48 (30.34-32.65)
• Pre-existing condition	**8**	**0**	**2**	**0**	–	–
» Psoriasis	1	0	0	0	22.71 (3.20-161.18)	84.53 (83.22-85.86)
» Rheumatoid arthritis	1	0	0	0	22.71 (3.20-161.18)	13.47 (12.70-14.26)
» Hyperthyroidism (Basedow's disease)	1	0	0	0	22.71 (3.20-161.18)	13.22 (12.46-14.01)
» Celiac disease	2	0	1	0	45.42 (11.36-181.55)	15.10 (14.31-15.92)
» Hypothyroidism	3	0	1	0	68.13 (21.98-211.16)	161.79 (159.09-164.53)
- Autoimmune thyroiditis (1 of 3 w/ hypothyroidism)	(1)	(0)	(0)	(0)	22.71 (3.20-161.18)	30.22 (29.10-31.37)

Abbreviations: AI=autoimmune; BLA= biologic licensing application; CI=confidence interval; NI=neuroinflammatory; PY=person-years

[1] Calculated using person-time-at-risk contributed by all rLP2086 vaccinees in all 7 BLA studies, starting at first rLP2086 dose and ending at study completion or censoring AI/NI cases at symptom onset

[2] Calculated from source population of commercially insured persons in same age range as study population

Once categorized in this manner, it is apparent that only 2 AI cases identified in the course of the 7 BLA clinical studies could have had a potential causal association with Trumenba: 1 case with Crohn's disease, another with idiopathic thrombocytopenia (ITP). The subject with ITP also received Repevax concomitantly with Trumenba, providing another possible etiology for the disease. Using the cumulative person-years-at-risk contributed by all Trumenba vaccinees throughout the study period (and censoring AI cases at symptom onset), the estimated incidence rate of both Crohn's disease and ITP in the study population of all Trumenba vaccinees (based on a single case of each) was determined to be 22.71 (95% CI: 3.20-161.18) cases per 100,000 person-years (see Table 7). The background rates for these conditions were calculated by Pfizer using same-age population data from the ----------(b)(4)----------). The estimated background rate of Crohn's disease is 31.48 (95% CI: 30.34-32.65) cases per 100,000 person-years and the estimated background rate of ITP is 5.96 cases (95% CI: 5.46-6.49) per 100,000 person-years. It is important to note that the incidence rates of Crohn's disease and ITP in the study population were based on a single case, resulting in imprecise estimates with correspondingly wide confidence intervals. For each outcome, the 95% confidence interval (CI) of the estimated incidence rate includes the 95% CI of the background rate. Therefore, based on the currently available data, there is no sufficient evidence suggesting an increased risk of Crohn's disease or ITP following Trumenba.

Only 7 of the 14 AI cases occurred among the 4 controlled core safety studies (B1971004, B1971005, B1971010, B1971011), and only 1 of those had a possible Trumenba etiology (the ITP case).

An additional statistical analysis was performed to determine if there was an imbalance in the risk of new AI cases with possible vaccine etiology between Trumenba vaccinees and controls. Because no cases were observed in the control arm, the analysis yields a relative risk estimate of infinity (=2/0 for all 7 BLA studies; =1/0 for the 4 core safety studies). However, one can evaluate for an imbalance (i.e., excess risk) of new AI/NI cases among Trumenba vaccinees versus control vaccinees by calculating the lower bound of the 95% CI for the risk estimate. If it is appreciably <1.0, the evidence does not support a risk imbalance between the two groups. The 95% CI lower bound of the risk estimate was 0.08 for all 7 BLA studies and 0.03 for the 4 core safety studies. Both are substantially <1.0; therefore, there is no evidence suggesting an excess risk of new AI disease among Trumenba vaccinees.

Pre-existing or asymptomatic AI disease whose conditions were possibly exacerbated or "unmasked" with Trumenba was also a concern for this review. Performing similar evaluations of these AI cases to those made when assessing for possible causation, we found that 8 AI cases of the 14 AI/NI cases might have been exacerbated or "unmasked" after Trumenba vaccination. For each of these 8 cases, the estimated incidence rate was either lower than the background rate (psoriasis, hypothyroidism) or the corresponding 95% CI includes the 95% CI of the background rate (rheumatoid arthritis, hyperthyroidism, celiac disease) (see Table 7); therefore, there is no sufficient evidence suggesting an elevated risk of exacerbation or "unmasking" of asymptomatic AI disease occurring among Trumenba vaccinees.

Only 2 of the 8 pre-existing AI cases occurred among the 4 controlled core safety studies and could represent an exacerbation or "unmasking" of asymptomatic disease due to Trumenba vaccination (1-celiac disease flare and 1-new onset autoimmune thyroiditis with evidence of pre-vaccination antithyroid antibodies). The symptoms of autoimmune thyroiditis occurred 184 days (~6 months) post-dose 1, indicative of a weak temporal association and low likelihood that it was "unmasked" by Trumenba vaccination.

The statistical analysis comparing the risk of AI case exacerbations among Trumenba vaccinees with control vaccinees yields a relative risk estimate of infinity (=8/0 for all 7 BLA studies; =2/0 for the 4 core safety studies). However, the lower bound of the 95% CI for this risk estimate was 0.50 for all 7 BLA studies and 0.14 for the 4 core safety studies. Both are substantially <1.0; therefore, there is no evidence suggesting an excess risk of asymptomatic AI case exacerbations between the Trumenba and control groups.

Additionally, there is no single plausible disease mechanism that could explain exacerbation of all 8 pre-existing AI cases. It is more likely that these cases represent sporadic occurrences of different AI diseases at rates comparable to those typically seen in this age population.

Even without categorization of the AI/NI cases as above, and assuming a maximum number of 14 AI/NI cases either caused or exacerbated by Trumenba vaccination with no cases among control vaccinees, the 95% CI lower bound of the relative risk was 0.92 (<1.0). Therefore, there is no evidence suggesting an excess risk of new or exacerbated AI/NI conditions among Trumenba vaccinees.

In conclusion, based on the currently available data, there is no sufficient evidence to suggest that autoimmune and neuroinflammatory conditions (both new onset cases or exacerbation of pre-existing cases) are occurring more frequently among Trumenba vaccinees when compared with control vaccinees or the background population.

6.3 Use in Pregnancy and Lactation

[Please see Section 5.2 regarding the clinical reviewer's assessment of the use of Trumenba in pregnancy.]

The proposed observational pregnancy study aims to gather additional information regarding the safety of Trumenba during pregnancy in both mothers and infants. The concept protocol submitted by Pfizer outlines a general methodology for obtaining this information. Further information will be needed to finalize a specific study design, as well as specific exposure parameters and outcomes that will effectively monitor safety issues in this population. Nonetheless, the general concept and structure of the study appears appropriate. Use of an electronic health database does not carry many of the limitations of traditional pregnancy registries and appears to be a more comprehensive means of gathering safety information.

6.4 Risk Assessment Conclusions

Review and evaluation of adverse reactions, autoimmune conditions, and use in pregnancy currently suggests no excess risk for serious AEs or other specific medical conditions. However, although no substantial safety concerns were identified during the 7 clinical studies in this BLA, the safety database currently consists of only 4,576 bivalent rLP2086 vaccinees (4,335 at the 120 µg dose in Trumenba) and this may not constitute a large enough population to identify less common adverse outcomes. The 4 ongoing studies (B1971009, B1971014, B1971015, and B1971016) will contribute an additional 15,000 subjects to the safety database, with approximately 10,000 receiving Trumenba. Data from these studies will be reviewed and additional risk assessments will be performed to determine if additional monitoring for specific reactions or conditions beyond routine pharmacovigilance is needed.

Additionally, an ACIP recommendation for routine immunization will result in greater numbers exposed to the vaccine who will then be monitored for AEs or other specified outcomes. For instance, implementation and utility of the proposed observational pregnancy study will depend, in part, on the numbers that can be enrolled. Without an ACIP recommendation for routine use, such a study will require a longer period of time to fully investigate adverse pregnancy and birth outcomes. The Division of Epidemiology within the Office of Biostatistics and Epidemiology (OBE/DE) will also consider use of the Mini-Sentinel system to conduct postmarketing safety studies of Trumenba if it is recommended for routine use. Additional safety concerns identified in the remaining ongoing clinical studies or specific outcomes identified during post-licensure routine pharmacovigilance can be monitored more closely in such studies.

7 RECOMMENDATIONS

Based on the review of the pre-licensure safety data and Pfizer's proposed pharmacovigilance plan, OBE/DE agrees with the Risk Management Plan as proposed by Pfizer with the following actions for post-licensure safety surveillance activities of Trumenba:

- Routine pharmacovigilance to monitor AEs among vaccine recipients: Adverse event reporting in accordance with 21 CFR 600.80
- Observational Pregnancy Study: The sponsor proposed a post-marketing cohort study using electronic health care data to evaluate pregnancy and birth outcomes following exposure to Trumenba during pregnancy. Initiation will begin after licensure of Trumenba and once an ACIP recommendation for routine use has been made. This study will be conducted as a Postmarketing Commitment (PMC) under Section 901 of FDAAA 2007 Title IX.
- Completion and review of additional ongoing studies, as agreed to with the Office of Vaccine Research and Review (OVRR), including the above noted planned study examining vaccine effectiveness and planned studies in the pediatric population <10 years of age, per PREA

The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS).

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