



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: CAPT Mike Smith, PhD
Chair of the Review Committee
Office of Vaccines Research and Review
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Through: Kerry Welsh, MD, PhD
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Subject: Review of Pharmacovigilance Plan

Sponsor: Pfizer

Product: PENBRAYA (MenABCWY)

Application Type / Number BLA / STN 125770/0

Proposed Indication Active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by N meningitidis groups A, B, C, W, and Y.

Submission Date: October 21, 2022

Action Due Date: October 20, 2023

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA STN 125770/0 based on the safety profile of Penbraya. Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) and/or Postmarketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Penbraya, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

N meningitidis is an obligate human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening invasive meningococcal disease (septicemia, meningitis, or both). *N meningitidis* serogroups A, B, C, W, and Y are five of the six meningococcal serogroups that cause the majority of meningococcal disease globally. Disease incidence is highest in children younger than five years of age, adolescents and young adults (16-21 years), and older adults (65 years and over)^{1,2}. In the US, serogroups B, C, W, and Y are responsible for approximately 78% of disease across all ages³. In the US, serogroup B now exceeds all other serogroups in incidence, accounting for 68% of invasive meningococcal disease among individuals 11 to 23 years of age.

Current preventive vaccination strategies generally require immunizations for separate ACWY conjugate vaccines and serogroup B vaccines. In the US, MenACWY vaccination rates among adolescents 13 to 17 years of age are approximately 89.3% for ≥ 1 dose and 54.4% for ≥ 2 doses. MenB vaccination coverage among 17 year-olds, however, is approximately 28.4%⁴.

Anti-meningococcal antibodies protect against invasive meningococcal disease via complement mediated bactericidal activity. MenABCWY induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N meningitidis* groups A, C, W, and Y and to the fHbp subfamily A and B variants of *N meningitidis* group B.

3 PRODUCT INFORMATION

3.1 Product Description

Penbraya, the pentavalent (MenABCWY) combined vaccine, is a suspension for intramuscular injection. It is supplied as a sterile lyophilized MenACWY-TT vaccine component to be reconstituted with the sterile MenB-fHbp suspension vaccine component. The Men ACWY-TT vaccine component consists of *N meningitidis* groups A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid. The MenB-fHbp vaccine component is a sterile suspension composed of two recombinant lipidated fHbp variants from *N meningitidis* group B, one from fHbp subfamily A and one from fHbp subfamily B (A05 and B01, respectively).

Each 0.5 mL dose of MenABCWY contains 5 mcg of each conjugated polysaccharide of groups A, C, W, and Y (total of 20 mcg conjugates), 60 mcg of each group B fHbp variant (total of 120 mcg protein), 44 mcg tetanus toxoid, 0.78 mg L-histidine, 0.097 mg trometamol, 28 mg sucrose, 0.25 mg aluminum as AlPO₄, (b) (4) sodium chloride, and 0.018 mg PS80 at pH 6.0. There are no preservatives.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125770 in the USPI is: Indicated for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

The MenB-fHbp vaccine component is approved and marketed in the US as Trumenba since October 29, 2014. It is manufactured by Wyeth, a subsidiary of Pfizer, and is approved for active immunization of individuals from age 10 years to 25 years against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroup B.

The MenACWY-TT component is marketed outside of the US as Nimenrix (Meningococcal Groups A, C, W-135 and Y Conjugate Vaccine). Pfizer acquired Nimenrix from GlaxoSmithKline Biologicals (GSK) in 2015. In the EU, Nimenrix is indicated for active immunization of individuals from the age of 6 weeks and above against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

5 DESCRIPTION OF PENBRAYA CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed are from the Summary of Clinical Safety, as well as the individual study reports, submitted to STN 125770/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our focused review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125770/0 be approved. Please refer to the package insert for the final clinical safety data.

The studies contributing to the clinical study safety dataset are summarized in Table 1.

Study identifier	Penbraya Vaccination Schedule	Comparator group	Number of participants exposed (N)	Study population	Safety Set
C3511001 (pivotal)	0, 6 months	Trumenba + ACWY-CRM vaccine (Menveo)	1763 Penbraya 649 comparator	Age 10 – 25 years Subanalyses for prior ACWY vaccine	Core safety set
B1971057 (stage 1)	0, 6 months	Trumenba + ACWY-CRM vaccine (Menveo)	543 Penbraya 1057 comparator	Age 10 – 25 years Subanalyses for prior ACWY vaccine	Core safety set
B1971057 (stage 2)	At least 4 years after primary series	Trumenba + ACWY-CRM vaccine (Menveo)	144 Penbraya 96 comparator	Age 10 – 25 years Subanalyses for prior ACWY vaccine	Safety of booster dose
C3511004	0, 12 months (group 1)	0, 36 months (group 2)	146 group 1 148 group 2	Age 11 years - \leq 15 years	Overall safety set

*adapted from Table 1, Summary of Clinical Safety STN 125770/0, Module 2.7.4

5.2 Adverse events

Local reactions included redness, swelling, and pain at the site of Penbraya administration. Systemic events included fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain, and joint pain. For studies C3511001 and B1971057, an e-diary was used to solicit adverse events in the first seven days after vaccine administration. An e-diary was not used in study C3511004; thus reported adverse events in this study were included in the unsolicited adverse events.

Additional unsolicited AEs, including serious adverse events (SAE), medically attended adverse events (MAE) and newly diagnosed chronic medical conditions (NDCMC) were collected in the first 30 days after each vaccination in all studies. In studies C3511001 and B1971057, SAEs, MAEs, and NDCMCs were reported until 6 months after the second study vaccination (Vaccination and Followup phases). In study C3511004, AEs, SAEs, MAEs, and NDCMCs were reported until 6 months after vaccination 1 (vaccination and followup phases).

The Core Safety Dataset includes data from Studies C3511001 and B1971057 Stage 1. The overall safety dataset includes, in addition, participants from the Extended Interval Study C3511004. Results of safety data from participants of study B1971057 Stage 2 is not integrated, but reported separately.

5.2.1 Clinical study C3511001 'A Phase 3, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of MenABCWY in Health Participants ≥ 10 to < 26 years of age'

Safety related Withdrawals: There were three participants in the Penbraya group and two participants in the Trumenba + MenACWY group who withdrew due to AEs. The sponsor did not consider three withdrawals in the Penbraya group related to receipt of the vaccine (suicide attempt, disruptive mood dysregulation disorder, and head injury in a motor vehicle accident). The two participants in the control group withdrew due to depression with suicidal ideation and a rash.

Most common AEs: Following primary vaccination series, local reactions occurred in 94.6 % of Penbraya recipients. The most common local reaction was pain at the injection site (94.2%), followed by erythema (32.8%) and swelling (34.0%). Systemic reactions occurred in 81.6% of Penbraya recipients. The most common systemic events were fatigue (63.9%) and headache (57.8%). Most local and systemic events were mild to moderate in severity and were reported in a similar percentage of ACWY-naïve and ACWY-experienced participants. There were no withdrawals due to reactogenicity. Similar percentages in the study and comparator groups experienced at least one AE, related AEs, and severe AEs. Related AEs were reported in a small proportion of participants (0.6% in both groups) and most were reactogenicity events.

SAEs: Within 30 days after any vaccination, similar proportions of participants in the two groups reported both SAEs (0.2% and 0% respectively) and MAEs (6.3% and 6.3% respectively). Throughout the study, including the followup phase, 11 participants (0.6%) in the Penbraya group and 4 participants (0.6%) in the control group develop SAEs. There was an imbalance of SAEs in the SOC Psychiatric disorders with four participants with six SAEs of SOC psychiatric disorders (depression, anxiety, suicide ideation/attempt, disruptive mood dysregulation) in the Penbraya group as opposed to 0 participants in the comparator group. None of the SAEs were considered related to vaccine by the sponsor.

One participant in the Penbraya group had an MAE, a mild swollen tongue after vaccine dose 2, which started on day 1 and lasted 7 days, and was considered related to Penbraya administration.

The proportion of participants with NDCMCs for individual System Organ Class (SOC) were generally similar except for psychiatric disorders (nine participants in the Penbraya group versus one participant in the control group) due to a higher number of attention deficit hyperactivity disorder in the Penbraya group (six participants) relative to the Trumenba + MenACWY group (one participant). These were not considered related to vaccine administration by the sponsor, because, in five of the participants who received Penbraya, the onset of ADHD-related symptoms started prior to study enrollment. The remaining participant in the Penbraya group and the participant in the control group had a history of a condition(s) prior to enrollment that commonly co-occur with ADHD (e.g. anxiety, depression, and substance use).

Deaths: There were no deaths reported during the study.

Adverse events of special interest (AESIs): Three participants in the Penbraya group had AESIs. One participant had severe headache and this was considered related to the administration of Penbraya. One participant with severe status migrainosus and one participant with mild unconfirmed alopecia areata were considered to have adverse events unrelated to Penbraya administration.

Pregnancy: Though study participation required a negative pregnancy test prior to vaccination, throughout the duration of the study, there were seven pregnancies in the Penbraya group and two in the control group of female participants or female partners of male participants. Of five pregnancies in the Penbraya group with a known outcome, there were four live births, one of which was preterm. There was one participant with a fetal loss for which no additional information is available. Of the two pregnancies in the control group, one resulted in a full term infant and one resulted in a premature infant.

5.2.2 Clinical study B1971057 Stage 1 'A Phase 3, Randomized, Active-Controlled, Observer-Blinded Study to Assess the Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 (Trumenba) When Administered as a 2-Dose Regimen and a First-in-Human Study to Describe the Immunogenicity, Safety, and Tolerability of a Bivalent rLP2086-Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects

Safety related withdrawals: Three participants who received Penbraya were withdrawn during Stage 1 of this study due to an AE. None of these were assessed by the Sponsor to be related to the investigational product:

- 1) 16 year old male with a prior history of ADHD and depression and a family history of psychiatric disorders with severe aggression 10 days after dose 1
- 2) 18 year old female with a drug overdose suicide attempt 50 days after dose 1
- 3) 20 year old female who developed chronic urticaria 94 days after receiving dose 1 who withdrew four months after onset of urticaria.

Among the controls, the diagnoses were maculopapular rash, Crohn's disease, and ulcerative colitis. The diagnoses of Crohn's disease and ulcerative colitis were felt to be unrelated by the Sponsor while the rash was felt to be related.

Most common AEs: Following primary vaccination series, 94.3% of recipients of Penbraya experienced a local reaction. The most common local reaction was pain at the injection site (93.4%), with 26% of participants experiencing swelling and 24.5% experiencing erythema. After primary vaccination, 80.6% of recipients experienced a systemic reaction. The most common systemic events were fatigue (63.3%) and headache (59.4%). Most local and systemic events were mild to moderate in severity and were reported in a similar percentage of ACWY-naïve and ACWY-experienced participants.

SAEs: SAEs were reported by 1.1% and 0.8% of MenABCWY and Trumenba + MenACWY recipients respectively during the vaccination phase. There were 13 individuals reporting SAEs in the MenABCWY and 16 in the Trumenba + MenACWY group. Proportions of MAEs reported after MenABCWY and Trumenba + MenACWY were similar during the Stage 1 vaccination phase (26.2% and 26.7% respectively) and was similar between ACWY-naïve and ACWY-experienced participants. There were three reported NDCMCs in MenABCWY recipients (0.6%). The reported NDCMCs were mild polycystic ovarian syndrome, mild scoliosis, and a mild varicocele, which were reported at 140, 145, and 158 days after vaccination respectively. These were not felt to be related to vaccine administration by the sponsor.

Deaths:

One ACWY-naïve MenABCWY recipient died 109 days after vaccination 2 from a motor vehicle accident.

Adverse events of special interest (AESIs): There were no sponsor-confirmed autoimmune or neuroinflammatory conditions reported by MenABCWY recipients.

Pregnancy: Though study participation required a negative pregnancy test prior to vaccination, throughout the duration of the study, there were 11 pregnancies in the Penbraya group and 16 in the control group among female participants and female partners of male participants. Of six pregnancies in the Penbraya group with a known outcome, there were three full term live births and three spontaneous abortions. Of the 12 pregnancies in the control group with a known outcome, 10 resulted in full term infants, one resulted in a spontaneous abortion, and one resulted in an elective termination.

5.2.3 Clinical study C3511004 ‘A Phase 2b, Randomized, Observer-Blinded Trial to Describe the Safety, Tolerability, and Immunogenicity of MenABCWY Administered on 2 Different Dosing Schedules in Healthy Participants ≥11 to <15 Years of Age’

This study has interim results available from both doses of group 1 (0, 12 month dosing) and the first dose of group 2 (0, 36 month dosing).

Safety related withdrawals: Four participants, all from group 2, withdrew from the study, two after dose 1 and two after dose 2. All four reported suicidal ideation or intentional overdose.

Most common AEs: Because this study did not provide participants with an e-diary to report solicited adverse events, unsolicited adverse events were predominantly reactogenicity events.

SAEs: One patient reported orbital cellulitis within six months after dose 1; this was not considered attributable to vaccine by the sponsor. No other SAEs were reported. No

participants had newly diagnosed chronic medical conditions (NDCMC) that were attributed to the vaccine.

Deaths: No deaths occurred in either group in this study.

Adverse events of special interest (AESIs): One event of restless leg syndrome was considered an event of confirmed neuroinflammatory origin in a participant in Group 2 with an onset of 140 days after Vaccination 1. This event was classified as mild in severity, related to vaccine, with an outcome of resolved.

Pregnancy: There were no pregnancies reported in this study.

Reviewer comment: The adverse events seen in the clinical trials safety dataset are primarily those related to reactogenicity and are expected. While there was imbalance in psychiatric disorders, the individual case narratives were reviewed and it appears that neither the withdrawals nor the serious adverse events are related to vaccine administration.

5.2.4 Pooled Data across studies (Study C3511001 and B1971057)

Pregnancy: Pregnancy data in both studies includes female study participants and male study participants with pregnant partners. In the group that received Penbraya, out of 18 pregnancies, 11 had a known outcome; fetal loss occurred in four pregnancies (three spontaneous abortion and one fetal loss with cause unknown) and live births occurred in seven pregnancies (one premature, six full term). Among the control group, among the 14 out of 18 pregnancies for which outcome is known, fetal loss occurred in two pregnancies (one spontaneous abortion and one elective termination) and live births occurred in 12 pregnancies (one premature, 11 full term). Among pregnancies where an approximate date of conception could be calculated, only one pregnancy in the Penbraya group and four in the control group had vaccination in the 30 days prior to the estimated date of conception (proximate to vaccination). The pregnancy in the Penbraya group and the three in the control group with known pregnancy outcome all had live births with full term infants. All fetal losses occurred in female participants who received vaccine between 2 months and 3.5 years prior.

Reviewer comment: In the clinical trials for Penbraya, there were 36 pregnancies. After exclusion of male participants, unknown or distal timing of exposure, elective termination, and unknown outcome, only four pregnancies were available for assessment of safety.

6 SUMMARY OF FOREIGN POSTMARKETING EXPERIENCE

Penbraya is not approved in any country to date. However, Trumenba, one component of Penbraya, was approved in the United States on October 29, 2014 and is also approved in 31 foreign countries. Nimenrix, the second component of Penbraya, is not approved in the US but has been approved and administered in approximately 53 other countries. The postmarketing experience provided by the Sponsor therefore

summarizes the worldwide reports of adverse events following administration of the component parts of Penbraya (Trumenba and Nimenrix).

6.1 Sponsor's Analysis

6.1.1 Trumenba Postmarketing Experience

The Sponsor has estimated that approximately (b) (4) have been distributed worldwide from launch until October 28, 2022.

Cumulatively, as of October 28, 2022, a total of 4246 total postmarketing cases were received and reviewed. The majority of cases (2903, 68.4%) were from the US. Of all the reports, 3765 (88.7%) were non-serious, 481 (11.3%) were serious, and one case was fatal. Medical confirmation was obtained in 81.2% of cases. Gender was female in 38%, male in 32.6%, and not reported in 29.3%. Of the total, 2210 (50%) were in the age range of 10-25 years, and 1475 (34.7%) did not have an age provided.

The fatality lacked any detailed information on vaccination dates, timing of death, cause of death, concomitant drugs, or patient history to allow for any meaningful assessment.

The most frequently PTs (in $\geq 2\%$ of reports) in the postmarketing reports are listed in Table 2 below.

Table 2: Trumenba most frequently reported PTs

PTs	Total (n)	Percentage of Total Cases (N=4246)
Pyrexia	960	22.60
Headache	633	14.90
Vaccination site pain	490	11.54
Product administration error	410	9.65
Product storage error	392	9.23
Inappropriate schedule of product administration	380	8.95
Pain	306	7.21
Chills	295	6.95
Product administered to patient of inappropriate age	274	6.45
Incomplete course of vaccination	269	6.33
Vaccination site erythema	253	5.96
Nausea	244	5.75
Fatigue	235	5.53
Vomiting	233	5.49
Pain in extremity	198	4.66
Expired product administered	192	4.52
Vaccination site swelling	181	4.26
Erythema	156	3.67

Dizziness	152	3.58
Malaise	140	3.30
Wrong product administered	133	3.13
Myalgia	128	3.01
Asthenia	107	2.52
Off label use	106	2.50
Syncope	101	2.38
Swelling	89	2.10
Rash	88	2.07

Adapted from Table 3, page 11, Response to Information Request dated December 27, 2022, STN 125770/0.5, Module 1.11.3

The Sponsor concluded that there was no new safety information or trends identified through this cumulative review.

Reviewer comment: The USPI for Trumenba includes all the above clinical PTs in section 6.1 Clinical Trials Experience with the exception of nausea, syncope, and rash. Hypersensitivity reactions, including anaphylactic reactions, and syncope are included in section 6.2 Postmarketing Experience.

6.1.2 Nimenrix Postmarketing Experience

The Sponsor has estimated that approximately (b) (4) doses have been distributed worldwide from launch until April 19, 2022. Nimenrix is not approved for use in the US.

Cumulatively, as of April 19, 2022, a total of 6406 total postmarketing cases were received and reviewed. The cases were from the Netherlands, Italy, UK, and 53 other countries. Three reports were from the US involving patients who received the vaccine in countries where Nimenrix is approved. Of all the reports, 4810 (75.1%) were non-serious, 1596 (24.9%) were serious, and six cases were fatal. Medical confirmation was obtained in 62.3% of cases. Gender was female in 44.0%, male in 44.9%, and not reported in 11.1%. Of the total, 2356 (36.8%) were in the age range of 10-25 years, and 693 (10.8%) did not have an age provided.

None of the six fatalities occurred in the age range of 10-25 years. Four fatalities occurred in infants. Review of the fatalities by the sponsor suggested alternate causes of death in four of the six reports. One report, in a 49 year old male, described an acute polyneuropathy developing six days after vaccination and resulting in death. Metronidazole was listed as a concomitant medication but no reason for its use was reported. Another report, in a 12 month old female, listed an unknown cause of death three days post-vaccination. Though gastroenteritis was listed, there was no GE reflux, vomiting, diarrhea, appetite changes, or stool changes described in the 2 weeks prior to reporting.

The most frequently PTs (in $\geq 2\%$ of reports) in the postmarketing reports are listed in Table 3 below.

Table 3: Nimenrix most frequently reported PTs

PTs	Total (n)	Percentage of Total Cases (N=6406)
Pyrexia	2187	34.14
Headache	867	13.53
Vaccination site pain	467	7.29
Nausea	424	6.62
Vomiting	386	6.03
Fatigue	366	5.71
Vaccination site erythema	328	5.12
Vaccination site swelling	325	5.07
Rash	304	4.75
Malaise	297	4.64
Dizziness	294	4.59
Decreased appetite	245	3.82
Pain in extremity	232	3.62
Myalgia	227	3.54
Incorrect dose administered	199	3.11
Diarrhea	197	3.08
Vaccination site inflammation	197	3.08
Somnolence	190	2.97
Urticaria	184	2.87
Erythema	183	2.86
Crying	182	2.84
Product preparation error	176	2.75
Vaccination site warmth	175	2.73
Syncope	167	2.61
Chills	156	2.44
Expired product administered	152	2.37
Rash macular	150	2.34
Listless	142	2.22
Pain	142	2.22
Hyperpyrexia	137	2.14
Product administered to patient of inappropriate age	132	2.06
Inappropriate schedule of product administration	131	2.04
Asthenia	128	2.00

Adapted from Table 7, page 17, Response to Information Request dated December 27, 2022, STN 125770/0.5, Module 1.11.3

Reviewer comment: Adverse events appear to be related to local and systemic reactogenicity. No fatalities occurred within the proposed age range indication for this product in the US.

6.2 FDA Analysis

6.2.1 VAERS Reports for Trumenba (component of PENBRAYA)

A query in Business Objects was conducted on December 23, 2022 for all VAERS reports of Trumenba. The query resulted in 3,411 VAERS events with data entry completed from any date, as of 12/23/22. Among these reports, 3,281 (96.2%) were domestic. Among all 3,411 events, 442 (13%) were reported as serious and two (0.1%) involved a fatality, one of which occurred in an 86 year old patient. Among all events with available recovery data (N = 3,411), 1,595 (46.8%) were reported as recovered at the time of the VAERS submission. Among the total serious events (N = 442), 212 (48%) were reported as recovered at the time of the VAERS submission. Among events with available vaccination to symptom onset interval data (N = 2,430), the median reported onset interval was 0 days. Among events with available age data (N = 2,529), the median age was 17 years respectively. Among events with available sex data (N = 3,054), 1,840 (53.9%) were female. Among all 3,411 events, 1,376 (40.3%) reported at least one concomitant vaccine. The top ten most frequently associated symptom MedDRA preferred terms (PTs) are as follows: pyrexia, headache, pain, nausea, chills, injection site pain, dizziness, injection site erythema, pain in extremity, and fatigue.

Reviewer comment: The most frequently associated symptom PTs are consistent with local and systemic reactogenicity and are labeled.

Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the product.

6.2.2 Data mining

Data mining* for Trumenba (the component of Penbraya already approved in the US) was conducted using the Empirica 8.0 'VAERS Signals Weekly US All' run on 12/23/2022 with data lock point 12/16/2022. The results are presented in Table 4.

Table 4: Empirica Data Mining for Trumenba component

Event	US EB05 20221216	US Serious EB05 20221216	US Teen EB05 20221216	US Adult1 EB05 20221216	US Female EB05 20221216	US Male EB05 20221216
Chills	3.52	1.171	3.755	2.468	3.086	3.512
Fatigue	1.817	0.75	1.716	1.292	1.435	2.014

Headache	2.362	0.974	2.149	1.682	1.946	2.439
Influenza like illness	2.192	0.832	1.931	0.858	1.114	2.132
Myalgia	2.401	1.076	2.578	1.679	1.708	2.786
Pain	1.959	0.972	2.219	1.062	1.765	1.725
Pyrexia	2.506	1.409	2.384	1.362	2.099	2.332
Wrong product administered	1.352	0.819	1.32	0.417	1.265	1.274

Reviewer comment: PTs that have an EB05 \geq 2 in the ages of teen (age 9 to 18.9 years) and adult 1 (age 19 to 44.9 years) covering the approved ages for Trumenba in the US primarily represent reactogenicity and known local and systemic effects of Trumenba.

**Data mining is subject to a number of limitations including the limits of spontaneous surveillance systems described in the section above. There may be confounding by indication or false alerts from concomitant product administration. In addition, a signal may be reflected in multiple PTs that individually do not reach alert threshold.*

7 SPONSOR'S PHARMACOVIGILANCE PLAN

Table 5. Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Identified	None	Not applicable
Potential	None	Not applicable
Missing	Exposure during pregnancy and lactation	<ul style="list-style-type: none"> Summary and analysis of all reports of exposure during pregnancy and lactation in the post-marketing dataset in each periodic safety report for both interval and cumulative data. Pregnancy registry study

Adapted from Table 2 and 3, US Risk Management Pharmacovigilance Plan Version 1.2 STN 125770/0.21, Module 1.16

7.1 Safety-related Post-marketing Study

The Sponsor proposes the following pregnancy registry study as a Postmarketing Commitment (PMC).

Title: A Pregnancy Registry Study to Evaluate the Safety of PENBRAYA Meningococcal Vaccine Exposure During Pregnancy

Study Objective:

To assess spontaneous abortion, stillbirth, preterm birth, small for gestational age, and major congenital malformation among pregnant individuals exposed to

PENBRAYA any time during pregnancy or within 30 days prior to last menstrual period (LMP).

Study Design:

Non-intervention prospective cohort pregnancy registry in the US. Enrolled participants will be followed through the end of pregnancy and all liveborn infants will be followed through 6 months of age.

Study Participants:

Pregnant individuals who receive at least one dose of PENBRAYA any time during pregnancy or within 30 days prior to LMP.

Study Duration:

Enrollment will occur for six years with sufficient time (up to two years) after enrollment to account for the followup to be complete for the last enrolled participant.

Safety Outcomes:

- Spontaneous abortion
- Stillbirth
- Preterm birth
- Small for gestational age
- Major congenital malformation

Covariates:

- Maternal age and race/ethnicity,
- Clinical characteristics
- Obstetric history
- Comorbidities
- Current and past therapies,
- Other vaccines administered during pregnancy and within 30 days prior to LMP.

Data Sources:

- Participant self-report
- Health care provider report (including infant health care providers)

Data Analysis

Descriptive statistics on all eligible participants. Estimated registry enrollment is 50 pregnant individuals. Spontaneous abortion and stillbirth outcomes will be assessed as a percentage of all pregnancies. Preterm birth and small for gestational age outcomes will be assessed as a percentage of all singleton live births. Major congenital malformation outcome will be assessed as a percentage of live births among pregnancies with exposure in the first trimester.

The sponsor proposes the following milestones:

- Final protocol submission: 01/31/2024

- Study completion date: 04/30/2032
- Final study report (FSR) submission: 04/30/2033

Reviewer comment: The protocol synopsis and agreement to perform the study as a PMC were submitted to STN125770/0.21. Revised milestones were detailed in a response to an Information request submitted to STN 125770/0.27 on August 4, 2023. The proposed pregnancy registry will contribute data regarding the safety of exposure to PENBRAYA during pregnancy. Given the age range of the proposed indication, this study regarding the safety of Penbraya during pregnancy will provide important missing information. The proposed study is acceptable.

8 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

8.1 Important Identified Risks

None identified

8.2 Important Potential Risks

None identified

8.3 Important Missing Information

Exposure during pregnancy and lactation is listed in the latest pharmacovigilance plan. Current risk minimization measures include Sections 8.1 and 8.2 in the USPI which refer to the lack of data regarding safety of this vaccine during pregnancy and lactation. The sponsor agreed to include a summary and analysis of safety in pregnancy in periodic safety reports. A pregnancy registry study will also be performed as a PMC.

Reviewer comment: Reports of exposure during pregnancy and lactation in the post-marketing dataset in each periodic safety report and the data contributed from the pregnancy registry PMC will provide this important missing information.

9 DPV ASSESSMENT

To date, clinical studies of Penbraya and postmarketing passive reporting for the components of Penbraya (Trumenba and Nimenrix) have not demonstrated safety concerns other than labeled events of local and systemic reactogenicity. Given the age range of the proposed indication, lack of data regarding the safety of Penbraya during pregnancy is important missing information that will be addressed by enhanced pharmacovigilance (summary and analysis of safety in pregnancy in periodic safety reports) and a pregnancy PMC registry.

10 DPV RECOMMENDATIONS

Should Penbraya be approved for the new indication of active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y, the updated PVP, version 1.2 dated June 16, 2023, is adequate to monitor postmarketing safety for Penbraya with routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS). A safety-related postmarketing commitment (PMC) study is planned to examine the safety of this product in pregnancy. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

REFERENCES

1. Harrison LH et al The Global Meningococcal Initiative: recommendations for reducing the global burden of meningococcal disease. *Vaccine* 2011; 29(18):3363-71
2. Cohn AC, et al *MMWR Recomm Rep* 2013; 62(2):1-28
3. [Meningococcal Disease Surveillance | CDC](#) enhanced meningococcal disease surveillance reports 2019 final surveillance report. (accessed on December 2, 2022)
4. Pingali C, Yankey D, Elam-Evans LD, Markowitz LE, Williams CL, Fredua B, McNamara LA, Stokley S, Singleton JA. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2021 Sep 3;70(35):1183-1190. doi: 10.15585/mmwr.mm7035a1. PMID: 34473682; PMCID: PMC8422873.

APPENDIX
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	STN	Document(s) Reviewed
10/21/2022	Sponsor	125770/0	1.16.1 Pharmacovigilance Plan version 1.0
10/21/2022	Sponsor	125770/0	2.7.4 Summary of Clinical Safety
10/21/2022	Sponsor	125770/0	5.3.5.1 Study Reports C3511001, B1971057, C3511004
10/21/2022	Sponsor	125770/0	5.3.5.3 Integrated Summary of Safety
1/27/2023	Sponsor	125770/0.5	1.11.3 Response to IR of December 27, 2022 Postmarketing Experience for Trumenba and Nimenrix
5/25/2023	Sponsor	125770/0.17	1.11.3 Response to IR May 10, 2023 regarding Pregnancy Study as Post-marketing Commitment
5/25/2023	Sponsor	125770/0.17	1.16 Pharmacovigilance Plan version 1.1
6/20/2023	Sponsor	125770/0.21	1.16 Pharmacovigilance Plan version 1.2
6/20/2023	Sponsor	125770/0.21	5.3.5.1 Protocol Synopsis, A Pregnancy Registry Study to Evaluate the Safety of PENBRAYA Meningococcal Vaccine Exposure During Pregnancy
8/4/2023	Sponsor	125770/0.27	1.11.3 Response to IR August 1, 2023