# NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

## Study information

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| **Title** | A Pregnancy Registry Study to Evaluate the Safety of PENBRAYA™ Meningococcal Vaccine Exposure During Pregnancy |
| **Protocol number** | C3511007 |
| **Protocol version identifier** | Version 1.0 |
| **Date** | 18 January 2024 |
| **EU Post Authorization Study (PAS) register number** | To be registered before the start of data collection |
| **Active substance** | *Neisseria meningitidis* groups A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid carrier protein and recombinant lipidated factor H binding protein variants from *Neisseria meningitidis* Group B, Subfamily A and Subfamily B |
| **Medicinal product** | PENBRAYA (PF-06886992; BB-IND 017319) |
| **Research question and objectives** | The research question is: What is the risk of maternal, neonatal, and infant safety outcomes among individuals exposed to PENBRAYA during pregnancy?<br><br>The specific objective is: To estimate the proportion of major congenital malformation (MCM), spontaneous abortion (SAB), elective termination, stillbirth, preterm birth, and small for gestational age (SGA) among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to last menstrual period (LMP) |
| **Country of study:** | United States |
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## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| ACOG | American College of Obstetricians and Gynecologists |
| AE | Adverse event |
| AEM | Adverse event monitoring |
| ART | Assisted reproductive technology |
| CBER | Center for Biologics Evaluation and Research |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| DCT | Data collection tool |
| DOC | Date of Conception |
| EC | Ethics Committee |
| EDC | Electronic data capture |
| EDD | Estimated date of delivery |
| EDP | Exposure during pregnancy |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| EU PAS | European Union electronic register of Post-Authorization Studies |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| GPP | Good Pharmacoepidemiology Practices |
| GVP | Good Pharmacovigilance Practice |
| HCP | Healthcare provider |
| HIV | Human immunodeficiency virus |
| INTERGROWTH | International Fetal and Newborn Growth Consortium for the 21st Century |
| IRB | Institutional Review Board |
| LMP | Last menstrual period |
| MACDP | Metropolitan Atlanta Congenital Defects Program |
| MCM | Major congenital malformation |
| NIS | Non-interventional study |
| PASS | Post-authorization safety study |
| PI | Prescribing information |
| PMC | post-marketing commitment |
| SAB | Spontaneous abortion |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SGA | Small for gestational age |
| TERIS | Teratogen Information System |
| US | United States |
| VRCC | Virtual registry coordinating center |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, Degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
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## 4. ABSTRACT

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

**Protocol Version:** 1.0 (18 January 2024)

**Authors:** Cherise Wong, PhD ScM; Kristin Veley, PharmD, MPH, PPD, part of Thermo Fisher Scientific

**Rationale and Background:**

PENBRAYA (*Neisseria meningitidis* Groups A, B, C, W, and Y Vaccine; MenABCWY) is a pentavalent meningococcal vaccine composed of 2 licensed meningococcal vaccines: Trumenba® (*N meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine [bivalent rLP2086, also referred to as MenB-fHbp]) and Nimenrix® (meningococcal polysaccharide groups A, C, W, and Y tetanus toxoid conjugate vaccine [MenACWY-TT]).

On 20 October 2023, the United States (US) Food and Drug Administration (FDA) approved PENBRAYA for the prevention of meningococcal disease caused by meningococcal groups A, B, C, W, and Y in adolescents and young adults 10 through 25 years of age. As part of the PENBRAYA pharmacovigilance plan and in fulfillment of a post-marketing commitment (PMC) requested by the Center for Biologics Evaluation and Research (CBER), this non-interventional study (NIS) is being conducted to evaluate the safety of PENBRAYA exposure during pregnancy in a real-world setting.

**Research Question and Objectives:**

The research question is: What is the risk of maternal, neonatal, or infant safety outcomes among individuals exposed to PENBRAYA during pregnancy?

The specific objective is:

To estimate the proportion of major congenital malformation (MCM), spontaneous abortion (SAB), elective termination, stillbirth, preterm birth, and small for gestational age (SGA) among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to last menstrual period (LMP).

**Study Design:**

A prospective, registry-based observational cohort study in the US. This study will be a new, product-based pregnancy registry.

**Setting and Study Population:**

Voluntary registry enrollment will begin after product approval and the study period will begin at the PENBRAYA approval date.

The study population will include a single cohort of pregnant individuals in the US exposed to PRENBAYA during pregnancy.

Pregnant individuals will be enrolled in the registry over the first 6 years of the study. However, since registry enrollment will begin after product approval and protocol finalization, some participants may provide retrospective data if exposed prior to registry launch. All participants will be followed through the end of pregnancy, and all liveborn infants will be followed through 12 months of age. The total study duration will be approximately 8 years to allow for sufficient follow-up time for the last enrolled participant and liveborn infant.

**Variables**:

**Exposure**

The exposure of interest will be at least 1 dose of PENBRAYA.

**Outcomes**

The following maternal, neonatal, and infant safety outcomes will be assessed:

- MCM
- SAB
- Elective termination
- Stillbirth
- Preterm birth
- SGA

**Covariates**

Demographic and baseline characteristics for participants will include maternal age, maternal race/ethnicity, clinical characteristics, obstetric history, comorbidities, current and past therapies, as well as other vaccines administered during pregnancy or within 30 days prior to LMP.

**Data Sources**

Information on all study variables will be collected from enrolled pregnant individuals and the healthcare providers involved in their care or the care of their infants.

**Sample Size**

The registry will aim to enroll 50 individuals with PENBRAYA exposure during pregnancy or within 30 days prior to LMP. Due to the vaccination recommendations in place for PENBRAYA, as well as prior meningococcal NIS experience where enrollment following exposure was low, PENBRAYA exposure during pregnancy is expected to be limited. As such, the study will be limited in its ability to achieve its objective with adequate precision (ie, to estimate the risk of maternal, neonatal, and infant safety outcomes among individuals exposed to PENBRAYA during pregnancy).

Annual interim reports will provide information on PENBRAYA uptake and study accrual during the 6-year enrollment period.

**Data Analysis**

Demographic and baseline characteristics of study participants will be summarized with descriptive statistics. The proportion of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge. Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population (retrospectively enrolled or exposed to known teratogens or investigational medications during pregnancy). If sample size permits, subgroup and sensitivity analyses will be performed to examine the extent to which changes in certain methods or assumptions affect the results.

**Milestones**

Enrollment of individuals in the registry is expected to begin in April 2024, and data collection will continue through April 2032 (unless target enrollment is achieved earlier). Annual interim reports will be submitted to the FDA every April, from 2025 to 2032, and a final comprehensive study report will be submitted in April 2033. Each annual interim report will provide information on the registry design and results to date, including the number of enrolled participants, their characteristics, and their outcomes. The final comprehensive study report will present results from the full statistical analysis and provide an interpretive discussion of the results.

## 5. AMENDMENTS AND UPDATES

None.

## 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Final Protocol | 31 January 2024 |
| Registration in the EU PAS register | Prior to the start of data collection |
| Start of data collection[a] | 30 April 2024 |
| End of enrollment | 30 April 2030 |
| End of data collection (i.e., study completion) | 30 April 2032[b] |
| Interim study report 1 | 30 April 2025 |
| Interim study report 2 | 30 April 2026 |
| Interim study report 3 | 30 April 2027 |
| Interim study report 4 | 30 April 2028 |
| Interim study report 5 | 30 April 2029 |
| Interim study report 6 | 30 April 2030 |
| Interim study report 7 | 30 April 2031 |
| Interim study report 8 | 30 April 2032 |
| Final study report[c] | 30 April 2033 |

a. The planned date for the first visit of the first participant; actual date may differ, as registry launch is dependent upon FDA and institutional review board approval of the protocol.
b. The planned date for the last visit of the last participant, i.e., study completion date.
c. Final study report must be submitted within 12 months of the end of data collection.

## 7. RATIONALE AND BACKGROUND

On 20 October 2023, the United States (US) Food and Drug Administration (FDA) approved PENBRAYA™ (PENBRAYA US PI 2023) for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in adolescents and young adults 10 through 25 years of age.

Meningococcal disease is an infectious disease, with an estimated 1.2 million cases and 135,000 deaths per year, worldwide (Rouphael 2012). In the US, the average incidence of meningococcal infection is 0.53 cases per 100,000 persons per year, with infants <1 year having the highest incidence of 5.38 cases per 100,000 persons per year (Cohn 2010). The incidence of invasive meningococcal disease peaks in both infants and adolescents/young adults. Adolescents/young adults have higher carrier rates, which increases the risk of transmission and active infection in this population (Burman 2019).

Risk factors for meningococcal infection include age (<5 years), immunodeficiency (complement pathways), asplenia, chronic disease, crowded living conditions, human immunodeficiency virus (HIV) infection, and smoking (Bosis 2015). Early symptoms of *Neisseria meningitidis* infection may include sudden onset fever, nausea, vomiting, headache, severe muscle weakness, rash, sore throat, and respiratory symptoms (Bosis 2015). Later symptoms may include neck stiffness, photophobia, altered mental status, hemorrhagic rash, and death (up to 50% in untreated patients; Nadel 2016).

The most common bacterial causative agent of invasive meningococcal disease is *Neisseria meningitidis.* Between 2003 and 2007, 13.9% of meningitis cases in the US were due to *Neisseria meningitidis* (Thigpen 2011). Since the mid-1990s, serogroups C and Y have been the most common causative agents of meningitis in the US.

PENBRAYA (*Neisseria meningitidis* Groups A, B, C, W, and Y Vaccine; MenABCWY) is a pentavalent meningococcal vaccine composed of 2 licensed meningococcal vaccines: Trumenba® (*N meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine [bivalent rLP2086, also referred to as MenB-fHbp]) and Nimenrix® (meningococcal polysaccharide groups A, C, W, and Y tetanus toxoid conjugate vaccine [MenACWY-TT]) (PENBRAYA US Package Insert 2023).

There have been no clinical studies of PENBRAYA in pregnant individuals, nor have there been developmental toxicity studies in animals (PENBRAYA US PI l 2023). Thus, there is a lack of information on the safety of PENBRAYA exposure during pregnancy. As part of the PENBRAYA pharmacovigilance plan and in fulfillment of a post-marketing commitment (PMC) requested by the Center for Biologics Evaluation and Research (CBER), this non-interventional study (NIS) is being conducted to evaluate the safety of PENBRAYA exposure during pregnancy in a real-world setting.

This NIS is designated as a post-authorization safety study (PASS) and is a PMC to the FDA.

## 8. RESEARCH QUESTION AND OBJECTIVES

**Research Question:** What is the risk of maternal, neonatal, or infant safety outcomes among individuals exposed to PENBRAYA during pregnancy?

**Research Objective:** To estimate the proportion of major congenital malformation (MCM), spontaneous abortion (SAB), elective termination, stillbirth, preterm birth, and small for gestational age (SGA) among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to last menstrual period (LMP).

## 9. RESEARCH METHODS

### 9.1. Study Design

This registry-based, prospective, observational cohort study will enroll and follow pregnant individuals 10 through 25 years of age in the US who are exposed to PENBRAYA during pregnancy. This study will be a new, product-based pregnancy registry. Participation in the registry is voluntary and participants can withdraw their consent to participate at any time.

Data will be collected from enrolled pregnant individuals and the healthcare providers (HCPs) involved in their care or the care of their infants. The study outcomes are MCM, SAB, elective termination, stillbirth, preterm birth, and SGA. The main measures of their occurrence are the proportion of each outcome in the study cohort.

This study design aligns with current FDA guidance for designing and implementing pregnancy exposure registries (FDA 2019). All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines in the US for the patient population and HCP specialty where this noninterventional study is being conducted. The schedule of office visits and treatment regimens will be determined by HCPs. Only data that are typically documented in participants' medical records in the course of medical care will be collected. No additional laboratory tests or HCP assessments will be required for this study.

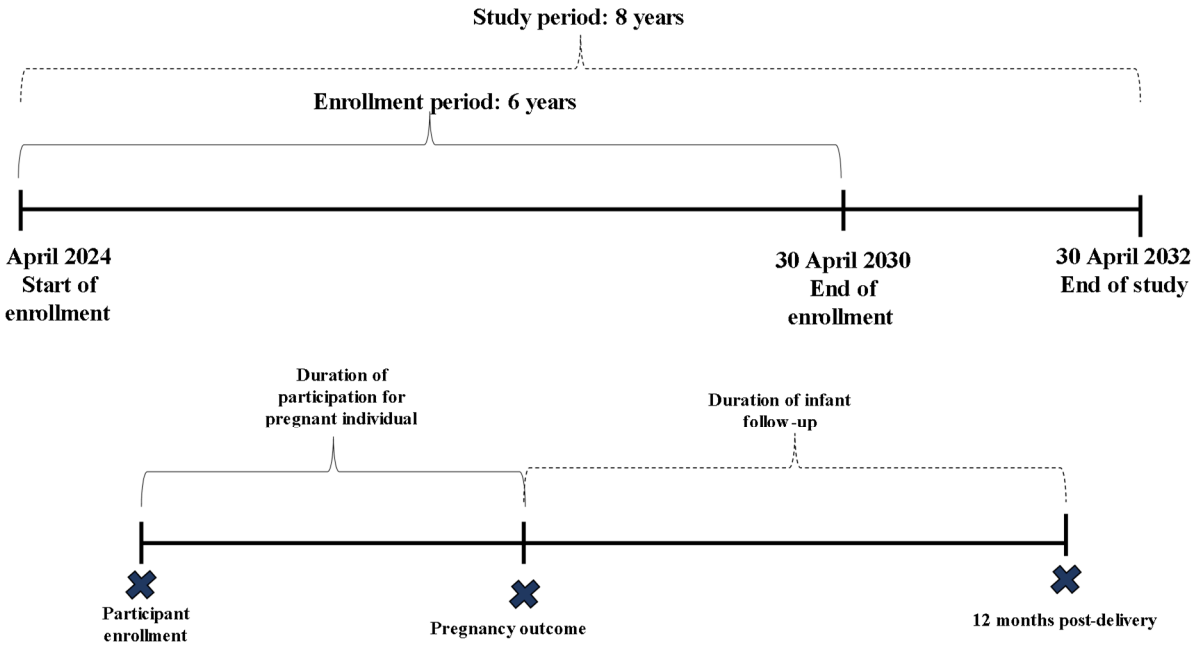
### 9.2. Setting

The study population will be derived from eligible individuals in the US enrolled in the pregnancy registry. The virtual registry coordinating center (VRCC) will coordinate enrollment and data collection (details provided in Section 9.4). Pregnant individuals will be identified in the US during the study period using an active, targeted, multi-pronged recruitment campaign, as described in Annex 3.

#### 9.2.1. Study Period

The registry will launch following FDA and institutional review board (IRB) approval of the protocol. Enrollment is targeted to begin in April 2024 and end in April 2030. Data collection will continue through April 2032. For each enrolled pregnant individual, participation will begin at enrollment and end at pregnancy outcome, and all liveborn infants will be followed through 12 months of age after pregnancy outcome. Figure 1 illustrates the total study duration as well as the duration of participation for pregnant individuals and their infants.

**Figure 1. Overview of Study Duration and Duration of Participant Follow-up**



### 9.2.2. Inclusion Criteria

Study participants who have consented to the study must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Currently or recently pregnant (recently pregnant defined as enrollment within 1 year of pregnancy outcome)
    - Only prospectively enrolled participants (i.e., individuals who are currently pregnant at enrollment) will be included in the main analysis population; retrospectively enrolled participants (i.e., individuals whose pregnancy outcomes have occurred) will be included in supplementary analyses (Section 9.7.5)
2. Participants 10 through 25 years of age at the time of enrollment*
3. Received at least one dose of PENBRAYA during pregnancy or within 30 days prior to LMP
4. Personally signed and dated informed consent document or, upon waiver of written consent by the relevant IRB/independent ethics committee, verbal consent, indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study
5. Authorization for the enrolled participants' HCP(s) to provide data to the registry
6. Contact information (for participant and HCPs)

    *The current age inclusion criterion is based on the US prescribing information (PI). If the Advisory Committee on Immunization Practices (ACIP) recommendation further expands the indicated age, criterion will be adjusted accordingly.

### 9.2.3. Exclusion Criteria

There are no exclusion criteria for this study. However, some participants included in the registry may be excluded from the main analysis population (details in Section 9.7).

## 9.3. Variables

### 9.3.1. Pregnancy Period

The registry will conform to the American College of Obstetricians and Gynecologists (ACOG) recommendations for determining the "best" estimated date of delivery (EDD); then, EDD will be used to calculate gestational age. Per ACOG, gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the LMP, first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to

determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (ACOG 2017).

Based on ACOG's recommendations, the registry will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, whether the ultrasound was performed at $<14^{0/7}$, $14^{0/7}$ to $21^{6/7}$, or $\geq 22^{0/7}$ gestational weeks will also be recorded. EDD data will be collected on each data collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate, based on the timing of the correction and the methods used to determine the corrected EDD, and follow-up with the HCP, if needed. Based on EDD, the following information will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational weeks, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
  - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester
  - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
  - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester
- Date of conception (DOC), defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If EDD is not reported by the HCP but LMP data are available, the registry will use first day of LMP to calculate EDD, gestational age, and DOC.

### 9.3.2. Exposure

Details on exposure to PENBRAYA will be collected from participants' HCPs at enrollment, at the end of the second trimester, and at pregnancy outcome (Annex 4, Table 8). Individuals will be considered exposed during pregnancy if they receive at least one vaccine dose anytime from 30 days prior to LMP to the end of pregnancy (live birth or fetal loss). The 30-day window corresponds to the time to achieve seroresponse in >90% of subjects vaccinated with PENBRAYA (PENBRAYA US PI 2023).

Exposure will be categorized by trimester (described in Section 9.3.1) and by the outcome-specific relevant etiologic period (Table 1 and Table 4).

Depending on the timing of PENBRAYA exposure during pregnancy, some PENBRAYA-exposed individuals will not contribute to the analyses of all outcomes, as each outcome is

associated with an outcome-specific relevant etiologic period (summarized in Table 4). For example, the relevant etiologic period for MCM is the first trimester, whereas the relevant etiologic period for SGA is the full pregnancy period. Hence, pregnant individuals who are exposed to PENBRAYA after the first trimester will not contribute to the analysis of MCM but will contribute to the analysis of SGA.

### 9.3.3. Outcomes

Table 1 presents definitions for the outcomes of interest: MCMs, SAB, elective termination, stillbirth, preterm birth, and SGA. For outcomes not reported by the HCP, additional information on outcome ascertainment is provided.

**Table 1. Outcome Definitions and Ascertainment**

| Outcome | Definition | Additional information on ascertainment |
|---|---|---|
| Major congenital malformation (MCM) | An abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (CDC 2020) | The registry defines and codes MCMs with criteria specified by the CDC MACDP (CDC 2021).<br>a) Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses (Holmes and Westgate 2011).<br>b) Adjudication process: A panel of 2 independent experts in clinical genetics and neonatology, blinded to exposure, will review all MCMs reported to the registry and classify them using the CDC's MACDP system. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Annex 3. These assessments will be recorded in the database. If there is a discrepancy, a third expert will independently review and code the case serving as tiebreaker. These reviews will occur soon after the MCM is reported. Additional reviews will occur if new information is received for the case, as well as the possible temporal association between exposure (to PENBRAYA) and the development of observed defects. Additionally, the Steering Committee will review all MCM cases reported to the registry and reach consensus on the coding of each case. The Sponsor will not be involved in any activities related to case review or adjudication. |
| Spontaneous abortion (SAB) | An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks | Section 9.3.1 provides information on the methods used to calculate gestational age. |
| Elective termination | A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to fetal abnormalities | None |

## Table 1. Outcome Definitions and Ascertainment

| Outcome | Definition | Additional information on ascertainment |
|---|---|---|
| Stillbirth | Involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (ACOG 2020b) | Section 9.3.1 provides information on the methods used to calculate gestational age. |
| Preterm birth | A live birth occurring at <37 gestational weeks | Section 9.3.1 provides information on the methods used to calculate gestational age. |
| Small for gestational age (SGA) | Birthweight <10 percentile for sex and gestational age using standard growth charts for full and preterm liveborn infants (Battaglia and Lubchenco 1967) | For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks (Villar 2014; Villar 2016). The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research. |

Abbreviations: ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; INTERGROWTH-21st = International Fetal and Newborn Growth Consortium for the 21st Century; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.

### 9.3.4. Covariates

The following variables will be collected (or derived from collected data, as summarized in Section 9.4):

- Geographic region
- Calendar year at conception
- Maternal age at conception
- Maternal race
- Marital status
- Maternal ethnicity
- Maternal insurance status (commercial insurance, Medicaid insurance, or uninsured)
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment
- Method of conception
- Number of fetuses
- Fetal/infant sex
- Concurrent maternal medical conditions, including thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, inflammatory diseases, depression and other psychiatric disorders, hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, preterm labor, placental abruption, and incompetent cervix
- Prenatal testing (current pregnancy)
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA)
- Previous fetus/infant with congenital malformations (major and minor)
    - Family history of congenital malformations (major and minor)

- Maternal exposure to other drugs or biological products, including prescription and nonprescription drugs, dietary supplements, and vaccines, during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure

### 9.4. Data Sources

This will be a new, product-based pregnancy registry conducted by PPD (part of Thermo Fisher Scientific).

All data will be collected via data collection forms. Table 2 provides a summary of the data collection process, including the forms that will be used to collect the data, the timing for the completion of each form, the potential reporters or sources of data, and the types of data that will be collected. Annex 4 provides additional information on details of what is collected at enrollment, follow-up, at pediatric follow-up, and attempts to obtain follow-up information.

#### 9.4.1. Enrollment

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and participants. Recruitment will include pregnant individuals who received PENBRAYA, and their HCPs (see Annex 3 for details). This approach involves direct-to-HCP outreach as well as online and print advertising directed to HCPs and patients. Recruitment and retention strategy details (e.g., online advertising, website, HCP brochures) are described in Annex 3.

The VRCC will coordinate enrollment and data collection. Pregnant individuals who are interested in participating in the study will answer a set of screening eligibility questions via a web-based application or by calling the VRCCs. If eligible, the individual will be asked to provide informed consent (see Section 10.2 for details), their primary contact information, alternate contact information, contact information for HCPs who are/will be involved in their care or the care of their infant, and medical releases to allow these HCPs to provide data to the registry.

#### 9.4.2. Data Reporter

Information on all study variables will be collected from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants. As described in Table 1, it is anticipated that most obstetric data will be collected from the participant's obstetric HCP (e.g., obstetrician, family practitioner, general practitioner who provides care during pregnancy) and that most infant data will be collected from the infant's pediatric HCP (e.g., pediatrician, family practitioner, general practitioner who provides pediatric care). After enrollment, the registry may also request data from other HCPs involved in the participant's or infant's care (e.g., prescriber, specialist) or from additional HCPs who were not identified at enrollment (e.g., if a participant does not know who their pediatric HCP will be at the time

of enrollment or switches HCPs after enrollment) after appropriate medical releases are obtained from the participant.

Reporters will use electronic forms or paper data collection forms that can be submitted via e-mail/fax, or via phone interview. HCP reporters will be instructed to transcribe data from the participant's or infant's medical records into the data collection forms.

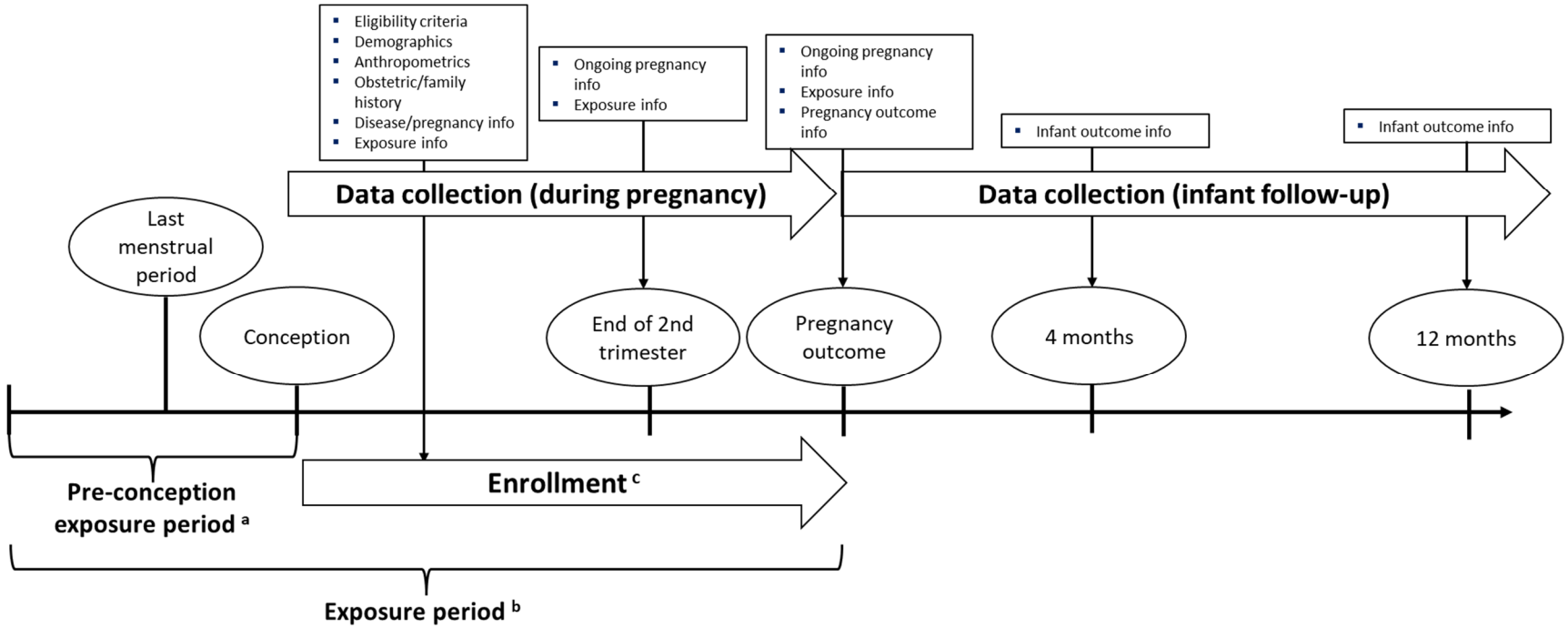
### 9.4.3. Data Collection Schedule

All participants will be followed through the end of pregnancy and all liveborn infants will be followed through 12 months of age (Figure 1 in Section 9.2.1). Information will be collected at enrollment, at the end of the second trimester (approximately 26 gestational weeks), and at the end of pregnancy (live birth or fetal loss). For liveborn infants, follow-up will be conducted up to 12 months of age to ensure that there are no updates to the data collected at birth. Infant data will be collected at 4 and 12 months of age. The second assessment is scheduled for the end of the second trimester because it is after important diagnostic tests like the 20-week anatomy scan.

### 9.4.4. Data collection details

Figure 2 and Table 2 provide a summary of the data collection forms and schedule. Additional details are provided in Annex 4, including a summary of information collected at each timepoint (e.g., at enrollment, at end of second trimester).

**Figure 2. Data Collection Schedule**




[a] Preconception exposure period is defined as 30 days (time period equivalent to time to seroresponse in >90% of subjects) prior to last menstrual period
[b] If a participant is exposed to the product during this time period, she will be considered exposed during pregnancy
[c] Participants may be retrospectively enrolled into the registry up to one year after pregnancy outcome but will not be included in main analysis

**Table 2. Summary of Data Collection Forms**

| Data collection form | Reporters | Timing of completion | Data collected |
|---|---|---|---|
| ***Registration Form for Participants*** | Participant | Enrollment | • Registration information, including eligibility criteria<br>• Maternal demographic characteristics<br>• Maternal pre-pregnancy anthropometrics |
| ***Registration Form for HCPs*** | Obstetric HCP and prescribing HCP, if needed | Enrollment | • Registration information, including eligibility criteria<br>• Maternal obstetrical history<br>• Family history of congenital malformations<br>• Baseline pregnancy information |
| ***Pregnancy Information Form*** | Obstetric HCP and prescribing HCP, if needed | Enrollment, end of second trimester*, and EDD/pregnancy outcome* | • Ongoing pregnancy information<br>• Maternal exposures during pregnancy |
| ***Pregnancy Outcome Form*** | Obstetric HCP and pediatric HCP, if needed | EDD/pregnancy outcome | • Pregnancy outcome information |
| ***Infant Outcomes Form*** | Pediatric HCP | 4 and 12 months after delivery | • Infant outcome information |
| ***Targeted Follow-up Form*** | Obstetric, pediatric, or other HCP | Any time after pregnancy outcome | • Targeted follow-up information |

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider.

* Obtain updated information since the previous contact.

## 9.5. Study Size

### 9.5.1. Assessment of study feasibility

Per ACIP recommendations, serogroup ACWY meningococcal vaccines are recommended for all adolescents with the first dose recommended at age 11 and the second dose recommended at age 16 years (Mbaeyi 2020). Additionally, serogroup B meningococcal vaccines are recommended for individuals 10 years of age and older who are at increased risk for meningococcal infection due to health risk factors; they are also recommended on a shared clinical decision making basis for healthy individuals 16 to 23 years of age (Mbaeyi 2020).

PENBRAYA is recommended for use when both ACWY and B vaccines are indicated to be given at the same visit (ACIP 2023). Due to the recommendations in place PENBRAYA is

expected to be used less frequently than serogroup ACWY vaccines. Furthermore, it is expected that only a very small proportion of pregnant individuals will receive the vaccine during pregnancy, if pregnancy status is known. This, in hand with prior meningococcal NIS experience (study B17910152) where vaccine uptake and enrollment were low, enrollment for this study is expected to be n=50 exposed pregnant individuals. Although it is possible for individuals to receive PENBRAYA during pregnancy (prior to knowing pregnancy status) and prior to pregnancy (within 30 days prior to LMP), the occurrence of this is expected to be uncommon as the US PI indicates that there are no clinical studies of PENBRAYA administered to pregnant individuals and available data on pregnant individuals are insufficient to inform vaccine-associated risks in pregnancy.

### 9.5.2. Target Enrollment

The frequency of PENBRAYA exposure in pregnant individuals is unknown, and their willingness to enroll in a pregnancy registry is challenging to predict with any degree of certainty. The registry aims to enroll 50 individuals with PENBRAYA exposure during pregnancy or within 30 days prior to LMP, which will allow the registry to estimate the proportion of the primary outcome, MCM, with a precision of ±7%.

### 9.5.3. Sample Size for Proportion Calculation

Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) and PASS 2021 Power Analysis and Sample Size software (version 21.0.3, CSS, LLC, Kaysville, Utah). For the calculations, general population proportion estimates were obtained for the outcomes of interest from various sources, including the Metropolitan Atlanta Congenital Defects Program (MACDP), National Vital Statistics System, and published literature.

Calculations were performed to determine the achievable precision of outcome proportion estimates for n=50 exposed pregnant women enrolled. Precision is calculated as the half-width of the two-sided 95% confidence interval (CI) using the Wilson (score) method for binomial proportions. Assuming that 90% of enrolled pregnancies result in a live birth and 10% of enrolled pregnancies are excluded from the analysis (as described in Section 9.7.1), the number of live births from n=50 enrolled exposed and pregnant individuals is estimated to be n=40 (50*0.9*0.9; Covington 2010; Veley 2020). Based on Table 3 below, precision for a proportion of MCM among n=40 live births is ±7.1%.

**Table 3. Sample Size-based Precision Calculations**

| Outcome | Reference proportion | Reference/ citation | Denominator (from rate in literature) | Outcome Denominator or N | Precision of outcome proportion obtained* |
|---|---|---|---|---|---|
| MCM | 4% | FDA 2002 | Livebirths | 40 live births | 7.1% |
| SAB | 14% | FDA 2002 | Pregnancies | 50 pregnancies | 9.6% |
| Elective termination | 22% | FDA 2002 | Pregnancies | 50 pregnancies | 11.2% |
| Stillbirth | 0.5% | FDA 2002 | Pregnancies | 50 pregnancies | 4.0% |
| Preterm birth | 8.5% | Martin 2021 | Singleton livebirths | 40 live births | 9.0% |
| SGA | 10% | By definition | Singleton livebirths | 40 live births | 9.6% |

MCM = major congenital malformation; reference proportion = proportion of outcome in general population for pregnant individuals of any age; SAB = spontaneous abortion; SGA = small for gestational age.

*Sample size calculations were performed in the PASS software for the outcomes of interest; precision is calculated as the half-width of the two-sided 95% CI using the Wilson (score) method for binomial proportions.

## 9.6. Data Management

Variables will be solicited and entered in the electronic data capture (EDC) by VRCC staff. Data provided by participants and/or their HCPs over the phone or on paper data collection forms, which can be submitted to the VRCC via mail, e-mail, or fax, will be reviewed for correctness and completeness and, if needed, entered into a database by VRCC staff.

If the number of enrolled patients warrants the use of an EDC platform, it will be compliant with 21 Code of Federal Regulations (CFR) Part 11 and data analyses will be performed using the statistical software program SAS (version 9.4 or higher; SAS Institute, Cary, NC).

### 9.6.1. Data Collection Tools

As used in this protocol, the term data collection tool (DCT) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed DCT is required for each included participant. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties,

except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. PPD shall ensure that the DCTs are securely stored in an electronic portal or secured in a locked room to prevent access by unauthorized third parties.

PPD has ultimate responsibility for the collection and reporting of all data entered on the DCTs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT serves as the source document. Any corrections to entries made in the DCTs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

### 9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, PPD agrees to keep all study-related records. The records should be retained by PPD according to local regulations or as specified in the vendor contract, whichever is longer. PPD must ensure that the records continue to be stored securely for so long as they are retained.

If PPD becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless PPD and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

PPD must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## 9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

### 9.7.1. Analytic Population

The analysis population will include participants who:

- Are valid (Section 9.7.1.1)
- Are prospectively enrolled (Section 9.7.1.2)
- Are not exposed to known teratogens or investigational medications during pregnancy (Section 9.7.1.3)
- Are not considered lost to follow-up (Section 9.7.1.4)

For the analyses of preterm birth and SGA, multiple-gestation pregnancies will be excluded from the analysis population (Section 9.7.1.6).

#### 9.7.1.1. Valid versus invalid participants

A valid participant will be defined as a pregnant individual with sufficient data, submitted or confirmed by an HCP, for determining and meeting inclusion/exclusion into the study. Participants who lack the minimum data required for determining inclusion or exclusion or who lack confirmation of exposure, or pregnancy, will be considered invalid. Invalid participants will be enumerated in each registry report but will not be included in statistical analyses.

#### 9.7.1.2. Prospectively enrolled versus retrospectively enrolled participants

The registry will encourage prospective registration; however, retrospective enrollment in the registry will be permitted as well. A prospectively enrolled participant is defined as a pregnant individual who enrolls prior to the pregnancy outcome. A retrospectively enrolled participant is defined as a pregnant individual who enrolls after the pregnancy outcome has occurred.

Retrospectively enrolled participants can introduce bias toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. They may also recall past drug exposures differently compared with prospectively enrolled patients. Therefore, retrospectively enrolled participants will be excluded from the analysis population but will be included in supplementary analyses (Section 9.7.5).

Diagnostic prenatal tests (e.g., ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. Therefore, inclusion of individuals who have had diagnostic prenatal testing in the analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrollment will be conducted (Section 9.7.6.1). For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

#### 9.7.1.3. Participants exposed to known teratogens or investigational medications

Participants will be considered exposed to known teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (time period equivalent to 5 times the product's half-life). A list of known teratogens (Annex 2) has been developed and will be continually updated based on the data available in the Teratogen Information System (TERIS) database

of teratogenic agents and publications (Polifka 2002; Feldkamp 2015; Zomerdijk 2015; TERIS 2021). Investigational medications include drugs that are not yet approved by the FDA. Participants who are exposed to known teratogens or investigational medications during pregnancy will be excluded from the analysis population but will be included in supplementary analyses (Section 9.7.5).

#### 9.7.1.4. Participants lost to follow up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant individuals without pregnancy outcome information and live-born infants without follow-up data after birth will be considered lost to follow-up. Annex 3 provides more information on the circumstances under which participants will be considered lost to follow-up. Information from these participants (e.g., demographic characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these participants will be excluded from the analysis population. While infants who are lost to follow-up will not contribute to the analysis of infant outcomes after the point in which they were lost to follow-up, the pregnancy information from their mothers will be included in the analysis of pregnancy outcomes.

#### 9.7.1.5. Subsequent pregnancies

Individuals who have previously enrolled in the registry with a prior pregnancy may enroll in the registry with subsequent pregnancies and contribute multiple pregnancies to the analysis population. Statistical non-independence due to multiple pregnancies from the same individual will be addressed in the analysis.

#### 9.7.1.6. Multiple-gestation pregnancies

Multiple-gestation pregnancies will be enrolled in the registry and included in the analysis population; however, for the analyses of preterm birth and SGA, multiple-gestation pregnancies will be excluded from the analysis population due to the higher risk of these outcomes in twins and higher-order multiples.

### 9.7.2. Descriptive Characteristics

Demographic and baseline characteristics (including the covariates listed in Section 9.3.4) will be summarized with descriptive statistics for the study population.

The number of observations, median, mean, standard deviation, minimum, and maximum will be reported for each continuous variable. The frequency and percentage per category will be reported for each categorical variable.

### 9.7.3. Outcome Proportion

Proportion of the outcomes of interest will be calculated according to the conventions described in Table 4. In general, the proportion of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge.

For most outcomes, the analysis population (denominator) will be the number of pregnant individuals with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the timepoint of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors (as noted in Table 4).

**Table 4. Outcome Proportion Calculations**

| Outcome | Numerator (among those in denominator) | Denominator | Relevant etiologic period (timing of exposure assessment) |
|---|---|---|---|
| MCM<br>Primary analysis | Live births with confirmed (i.e., adjudicated) MCMs (excluding MCMs not associated with medication exposure) | Live births | First trimester |
| MCM<br>Secondary analysis | Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure) | Live births and fetal losses | First trimester |
| SAB | Spontaneous abortions | Individuals with pregnancy outcome data who are enrolled before 20 completed gestational weeks[1] | Before 20 completed gestational weeks |
| Elective termination | Elective terminations | Individuals with pregnancy outcome data | Full pregnancy period |
| Stillbirth | Stillbirths | Individuals with pregnancy outcome data | Full pregnancy period |
| Preterm birth | Preterm births | Singleton live births without confirmed MCM among pregnant individuals who are enrolled before 37 completed gestational weeks[2] | Before 37 completed gestational weeks |
| SGA | SGA births | Singleton live births without confirmed MCM with weight data | Full pregnancy period |

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small-for-gestational-age.

1 By definition, SAB occurs prior to 20 gestational weeks (see Section 9.3.3).

2 By definition, preterm birth occurs prior to 37 gestational weeks (see Section 9.3.3).

### 9.7.4. Subgroup Analyses

If sample size permits, subgroup analyses will be conducted that consider:

- Timing of exposure (earliest trimester of exposure)
- Extent of exposure (cumulative vaccine doses during pregnancy, or relevant exposure window)
- Maternal age group at conception (10 to <18, 18 to 25 years)

Due to the expected low enrollment in the registry, the ability of the study to assess differences across subgroups will be limited.

### 9.7.5. Supplementary Analyses

Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population due to:

- Occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants)
- Exposure to a known teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants)

### 9.7.6. Sensitivity Analyses

The following sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results, if sample size permits, and presented in the final study report.

#### 9.7.6.1. Definition of prospective enrollment

As described in Section 9.7.1.2, a sensitivity analysis of MCM will be conducted that applies a stricter definition of prospective enrollment. For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

#### 9.7.6.2. Restriction of preconception exposure window

A sensitivity analysis will be conducted that restricts the preconception exposure window to 28 days prior to conception rather than 30 days prior to LMP.

### 9.7.7. Missing Data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As described in Annex 4, the registry will make multiple attempts to obtain

missing data for critical data points. The frequency and percentage of participants with missing data for each data point will be presented.

For start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing.

### 9.8. Quality Control

Ensuring high quality data will be an ongoing, multi-step process involving automatic programming of edit checks for critical data variables in the EDC system as well as visual review for completeness, logic, consistency, and accuracy by the VRCC staff. As recommended in regulatory guidance documents, data collection forms are carefully designed to ensure data quality and integrity. All participant-reported data will be verified by the appropriate HCP, where possible.

#### 9.8.1. Steering Committee

A steering committee will be established to oversee the scientific affairs of the study, including its ongoing monitoring. A charter for steering committee activities, roles and responsibilities, and meeting frequency will be established following study initiation. The steering committee will be composed of recognized experts including (but not limited to) the fields of teratology, epidemiology, maternal-fetal medicine, neonatology/pediatrics, and immunology/infectious disease. The steering committee and birth defect evaluators will be independent of one another.

The steering committee will meet regularly to review the accumulated body of data from the study, including review of reported MCMs, which have been classified by independent birth defect evaluators, and other study outcomes. The steering committee will provide consultation regarding recruitment and retention strategies and will also carry out any actions required, including review and interpretation of data analyses and reports and contribute to publications of study data. In addition to the above activities, the steering committee will support the design and implementation of strategies to heighten awareness of the study and will provide consultation regarding recruitment and retention strategies.

### 9.9. Strengths and Limitations of the Research Methods

Prospective pregnancy registries offer several advantages over retrospective primary data collection studies and secondary database studies. The prospective design mitigates the potential for recall bias, a bias that may be introduced in retrospective primary data collection studies. Additionally, this prospective registry offers the potential to capture rich patient information that would not be captured in secondary databases. Critical data are provided directly from the HCPs and participants, including information that may not be routinely captured in medical records. This direct capture of data can minimize the potential for

exposure, outcome, and covariate misclassification. Nonetheless, this study is subject to several limitations.

The general limitations of pregnancy registries with voluntary participation are well known, and these will apply to this study as well. Many individuals avoid medications and/or vaccines during pregnancy and the safety of PENBRAYA use in pregnancy is currently unknown. Hence, the number of enrolled PENBRAYA-exposed participants may be small, precluding the ability to derive meaningful conclusions. A multi-model recruitment campaign and flexible, evolving retention strategies will aim to maximize study size (Annex 3).

Another key limitation of the registry, due to the voluntary nature of participation, relates to representativeness. Despite limiting the main analysis to prospectively enrolled participants, voluntary participation could still produce bias (e.g., if high- or low-risk individuals are more likely to enroll). A description of participant characteristics including comorbidities and pregnancy history will help assess the extent of such possible bias. To minimize the potential for selection bias, a multi-faceted recruitment strategy will be employed.

Early, prospective enrollment is key to reducing recall and selection bias; however, early pregnancy losses may be less likely to be included in a registry. Indeed, research suggests that 90% of pregnancies enrolled in registries result in a live birth (Covington 2010; Veley 2020), whereas national estimates suggest up to 28% of pregnancies end in early losses (i.e., approximately 70% result in a live birth) (Rossen 2018).

Background rates from population-based surveillance systems or the published literature will be used to put registry outcome proportions into context. Quantitative comparisons between the registry and external data may be difficult to interpret, as the studies may vary in methodology, ascertainment, and classification of birth defects or other pregnancy outcomes, as well as in geographic location, sample size, and other factors that could affect the results. Although these differences pose inherent challenges with comparing registry data with data from external sources, these comparisons are not unrealistic and are generally considered acceptable as long as the methodologies of the external comparators are taken into consideration during the analysis (Kennedy 2004; FDA 2019). For example, because the live birth rate in pregnancies is typically much higher than that of the general population, it will be important to carefully consider registry rates of live births and fetal losses relative to general population rates. It will also be important to ensure that registry outcome proportions are calculated using the same conventions used by the external comparators for these comparisons.

Those pregnancies that have reached EDD, but for which pregnancy outcome information was unobtainable, will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Due to differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis.

However, the characteristics of those lost to follow-up will be compared with those not lost to follow-up to understand this potential source of bias.

As the registry will enroll women only after recognition of pregnancy and in some cases may be much later in pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant women will include women with a shortened period at risk of the outcomes of interest and exclude women who have already had certain outcomes (e.g., SAB, elective termination). To minimize the impact of this potential bias, the registry's recruitment strategy will encourage recruitment of individuals as early in pregnancy as possible.

For this study, the outcome MCM is a heterogenous composite of any type of MCM. Individual drugs are more likely to have effects on specific MCM subtypes than all MCMs. However, the study is not powered to detect increases in the risk of individual defects.

Pregnancies that result in fetal losses (stillbirths, SABs, and elective or therapeutic abortions) without reported MCMs may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the fetal loss. However, the reporting physician may not know the condition of the lost fetus, which would increase the potential for outcome misclassification for MCMs.

Lastly, another potential limitation of this pregnancy registry is the lengthy preconception exposure window (30 days prior to LMP or approximately 6 weeks prior to conception). This exposure window may be unnecessarily long. Other pregnancy registries for vaccines have used a preconception exposure window about half as long (28 days prior to conception or 14 days prior to LMP). To explore the potential impact of this exposure definition, a sensitivity analysis will be conducted that restricts the preconception exposure window to 28 days prior to conception.

### 9.10. Other Aspects

Not applicable.

## 10. PROTECTION OF HUMAN PARTICIPANTS

### 10.1. Study Participant Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be stored at PPD in an electronic portal or secured in a locked room to ensure that only authorized study staff have access. PPD will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, PPD shall be responsible

for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any participant names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. PPD will maintain a confidential list of individuals who participated in the study, linking each participant's numerical code to their actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the vendor contract and applicable privacy laws.

### 10.2. Patient Consent

Informed consent will be obtained for each registry participant. Electronic consent will be available through the registry web-based application. Should individuals prefer to enroll via phone, this registry qualifies for a waiver of documentation of informed consent. Adults will be given the option to provide verbal consent under the waiver of documentation of informed consent, or signed informed consent through the web-based application or via courier. Adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definitions of a minor and an emancipated minor vary by state within the US. This registry will follow applicable laws for the state in which the individual resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based application or via courier. Written consent from both parent(s) or both guardian(s) will be obtained in the US states in which this is required by local laws and regulations.

At the initial screening with potential participants, the registry web-based application or registry associate will obtain consent to collect basic information about the individual, such as age and state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

#### 10.2.1. Additional Safeguards for Children in Clinical Investigations

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research). This registry will only ascertain maternal and infant information via maternal and pediatric HCPs, and no clinical specimens will be collected from mothers or infants; therefore, data collected on infants of individuals in this pregnancy registry involves

no greater than minimal risk to the infants. While the infants will be too young to provide assent, the registry protocol will require permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

### 10.2.2. Electronic Informed Consent Process

The study website will contain information about the registry and will provide access to the study's web-based application. The individual will register with their computer or mobile device using credentials (i.e., name, e-mail address, and password) via the web-based application.

Once the individual has registered, the application will automatically start the consent process. The application will present the contents of the consent in a scrollable window. The individual will review the document, and the application will present the following options: "Hold," "Disagree," and "Sign and Publish."

If the individual has questions during the consent process, they will be encouraged to stop the consenting process on the application via the "Hold" button and call the VRCC, where study specialists will assist with any questions. The individual can resume completion of the consent process at any time. If the individual does not wish to provide consent, she will be directed to choose the "Disagree" option, and the process will stop. If the individual wishes to provide consent, they will be directed to choose "Sign and Publish."

The application will provide an option for the individual to view or e-mail their completed consent form(s).

After the informed consent process, the individual will complete the medical release form(s) and answer some basic medical information questions.

### 10.2.3. Waiver of Documentation of Informed Consent

The following US regulations indicate that the waiver of documentation of informed consent is appropriate for this registry.

As is stated in US CFR, 21 CFR 56.109 [and additionally in 45 CFR 46.117(c)(2)]:

> (c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> > (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require PPD to provide subjects with a written statement regarding the research.

**The research involves no more than minimal risk to participants.** This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach. Extensive safeguards are in place to ensure that participants' privacy is protected:

1. An adequate plan is provided to protect the identifiers from improper use and disclosure (Section 10.1).
2. An adequate plan is provided to remove the identifiers at the earliest opportunity.
3. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

**The research involves no procedures for which written consent is normally required outside the research context.** Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time. The schedule of participant visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the participant's medical record.

### 10.3. Patient Withdrawal

Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time.

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of PPD for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document participant outcome, if applicable. PPD would inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved adverse events.

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

### 10.4. Institutional Review Board (IRB)/ Ethics Committee (EC)

It is the responsibility of PPD to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement to participate), and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained by PPD. Copies of IRB/EC approvals should be forwarded to Pfizer.

The protocol will be submitted to the applicable regulatory authority and central IRB for approval prior to registry implementation. The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to the sponsor before study initiation. Prior to study start, the PPD principal investigator will sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the VRCC is requested by a regulatory authority, the VRCC must inform the sponsor immediately of this request.

### 10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in the following guidances:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891
- Postapproval Pregnancy Safety Studies: (Draft) Guidance for Industry issued by FDA https://www.fda.gov/media/124746/download
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml
- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ ucm071696.pdf
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance s/UCM243537.pdf

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## REQUIREMENTS

Table 5 summarizes the requirements for recording safety events on the data collection form and for reporting safety events on the NIS Adverse Event Monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: 1) serious adverse events (SAEs); 2) non-serious AEs (as applicable); and 3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in Section 11.3 (Definitions of Safety Events).

Note that SAEs requiring adjudication by the External Adjudication Committee (i.e., any malformation) are not reportable to Pfizer Safety.

**Table 5. Safety Event Reporting Requirements**

| Safety Event | Recorded on the data collection forms | Reported on the NIS AEM Report Form to Pfizer Safety within 1 Business Day/3 Calendar Days[a] of Awareness |
|---|---|---|
| Serious AE | All | All[b] |
| Non-serious AE | All | None |
| Scenarios involving exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy | All (regardless of whether associated with an AE) | All (regardless of whether associated with an AE/serious AE)<br>Note: Any associated AE is reported together with the exposure scenario. |
| Scenarios involving EDP | All AEs or serious AEs associated with EDP<br><br>Notification of EDP alone (i.e., not associated with an AE or serious AE) is not required when the study population is pregnant individuals. | All serious AEs[b] associated with EDP<br><br>Notification of EDP alone (i.e., not associated with a serious AE) is not required when the study population is pregnant individuals. |
| Scenarios involving occupational/environmental exposure | Not applicable | All (regardless of whether associated with an AE/serious AE) |

Abbreviations: AE = adverse event; AEM = adverse event monitoring; EDP = exposure to a drug during pregnancy; NIS = non-interventional study.
a Whichever is shorter. If a national or state holiday falls directly before or after a weekend (resulting in ≥3 consecutive calendar days of closure), the reporting will be done the next business day.
b Except for serious AEs judged by External Adjudication Committee [i.e., any malformations]). Of note, adjudicated serious AEs of which an HCP has indicated the serious AE to have a causal relationship with PENBRAYA are not included within this exception and must be reported to Pfizer Safety.

For each safety event, the PPD VRCC must pursue and obtain adequate information to determine the outcome and to assess whether it meets the criteria for classification as a serious AE (refer to Section 11.3.2).

Safety events must be reported per the process noted in Table 5 **regardless of whether the event is determined by the HCP to be related to PENBRAYA**. In particular, if the serious AE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. The timeframe noted in Table 5 also applies to additional, new (follow-up) information on previously forwarded safety event reports. In the rare situation that the PPD VRCC does not become immediately aware of the occurrence of a reportable safety event, the PPD VRCC must report the event within 1 business day/3 calendar days after learning of it and document the time of first awareness of the events on the NIS AEM Report Form.

For all safety events that are mentioned in the far-right column of Table 5, the PPD VRCC is obligated to pursue and to provide any additional information to Pfizer with the same reporting timeline. In addition, the PPD VRCC may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection forms. In general, this will include a description of the safety event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

This protocol will use an External Adjudication Committee wherein, to maintain scientific integrity, and adjudication of some clinical endpoints (i.e., any malformations) defined in the study objectives will be performed. The External Adjudication Committee is responsible for ongoing analysis of any MCMs and of their adjudication as endpoints. Any malformation that is not adjudicated as an endpoint by the External Adjudication Committee is reportable and is forwarded to Pfizer Safety. In addition, when the HCP has judged a malformation to have a causal relationship with PENBRAYA or other products used to treat meningococcal disease, the PPD VRCC must still report it to Pfizer Safety, even if that event is a component of the adjudicated endpoint.

## 11.1. Reporting Period

For each participant, the reporting period will begin at the time of the participant's first dose of PENBRAYA, or the time of the participant's informed consent if she is being vaccinated with PENBRAYA, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of the product under study; a report must be submitted to Pfizer Safety (or its designated representative) for any safety events (as per Table 5) occurring during this period. If a participant is administered PENBRAYA on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of

informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a participant provides informed consent but is never enrolled in the study (e.g., participant changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the participant.

If the PPD VRCC becomes aware of an SAE occurring at any time after completion of the study and the SAE has been reported as related to PENBRAYA, the SAE also must be reported to Pfizer Safety.

### 11.2. Causality Assessment

An HCP's causality assessment is the determination of whether there exists a reasonable possibility that PENBRAYA caused or contributed to the safety event. For all safety events, sufficient information should be obtained by the investigator to determine the causality.

In this study, unlike a trial design with sites and investigators, reporting HCPs will not have received formal training on providing causality assessments for the study drug. Further, given limited known information about the safety of PENBRAYA in pregnancy, it is expected that the HCPs will rarely provide a causality assessment for the reportable safety events, or they will report it as "unknown" as s/he cannot determine it. In this event, the applicable, reportable safety event must still be reported to Pfizer Safety per the process outlined in Table 5.

If the HCP cannot determine the etiology of the event but s/he determines that PENBRAYA did not cause the event, this should be clearly documented on the data collection forms and the NIS AEM Report Form.

For all safety events with a causal relationship to PENBRAYA, follow-up by the PPD VRCC is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the PPD VRCC, and Pfizer concurs with that assessment.

### 11.3. Definitions of Safety Events

#### 11.3.1. Adverse Events

An AE is any untoward medical occurrence in a participant administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE)
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Hypersensitivity

- Progression/worsening of underlying disease
- Lack of efficacy
- Drug abuse
- Drug dependency

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Off-label use
- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure during breast feeding
- Medication error
- Occupational exposure

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the HCP or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### 11.3.2. Serious Adverse Events

An SAE is any untoward medical occurrence in a participant administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute SAEs)

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported:

- Social admission (e.g., participant has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

### 11.3.3. Scenarios Necessitating Reporting to Pfizer Safety within 1 Business Day/ 3 Calendar Days

Scenarios involving exposure during pregnancy (EDP), exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An EDP occurs if:

- A female becomes, or is found to be, pregnant while receiving or having been exposed to the drugs under study, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the drugs under study *(maternal exposure)*
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of occupational or environmental exposure (e.g., a female family member or HCP reports that she is pregnant and has been exposed to the product)

This information must be submitted to Pfizer Safety following the same reporting timeline and using the NIS AEM Report Form and the EDP Supplemental Form. Prospective and retrospective exposure during pregnancy reports are reportable to Pfizer Safety following the requirement described in Table 5.

All reports submitted should include the anticipated date of delivery, as applicable, and should be managed as follows:

- Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown.
- A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report.
- In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth.
- In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for a serious AE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a

live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- SAB includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the HCP assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

For NIS conducted in pregnant individuals, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the study database. In such instances, only EDPs associated with an SAE are to be reported.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding individuals (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or participant harm while in the control of the HCP, participant, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a participant directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the HCP or the participant/consumer)
- Confusion with regard to invented name (e.g., trade name, brand name)

The PPD VRCC must submit the following medication errors to Pfizer Safety, irrespective of the presence of an associated AE/SAE:

1. Medication errors involving participant exposure to the product, whether or not the medication error is accompanied by an AE
2. Medication errors that do not involve a participant directly (e.g., potential medication errors or near misses)
    - When a medication error does not involve participant exposure to the product, the following minimum criteria constitute a medication error report:
        - An identifiable reporter
        - A suspect product
        - The event medication error

Overdose, misuse, extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy of a Pfizer product are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational/Environmental exposure

Reports of occupational exposure are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/SAE.

Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a data collection form; however, a copy of the completed NIS serious AE Report Form must be maintained in the PPD VRCC files.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if PPD is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, PPD will inform Pfizer immediately of any urgent safety measures taken by PPD to protect the study participants against any immediate hazard, and of any serious breaches of this NIS protocol which the investigator becomes aware of.

The registry will produce annual interim and final study reports that will be submitted to regulatory authorities. The reports will include a presentation of the registry design, methodology, results to date, and an interpretive discussion of the biostatistical analysis results. Additionally, this study will be disclosed and registered in the European Union (EU) Post-authorization Study (PAS) Register.

Submissions to scientific congresses and/or to peer-reviewed journals may be planned.

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## 14. LIST OF TABLES



## 15. LIST OF FIGURES



## 16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

## 17. ANNEX 2. LIST OF KNOWN TERATOGENS

Table 6 provides a list of known teratogens. This list has been developed and will be continually updated over the course of the study as new teratogens are identified.

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| **Androgens** | | |
| Methyltestosterone | 6 to 8 h | First, second, and third trimesters |
| Testosterone | Plasma half-life of testosterone ranges from 10 to 100 min. The cypionate and enanthate esters of testosterone have longer durations of action than testosterone. Cypionate half-life is about 8 d. | First, second, and third trimesters |
| Mesterolone | 12 to 13 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Nandrolone | 144 to 288 h | Unknown. Assumed window: first, second, and third trimesters |
| Oxandrolone | 13.3 h | Unknown. Assumed window: first, second, and third trimesters |
| Prasterone | 12 h | Unknown. Assumed window: first, second, and third trimesters |
| Fluoxymesterone | 9.2 h | Unknown. Assumed window: first, second, and third trimesters |
| **Angiotensin II receptor antagonists** | | |
| Candesartan | 9 h | First, second, and third trimesters |
| Eprosartan | 20 h | First, second, and third trimesters |
| Irbesartan | 11 to 15 h | First, second, and third trimesters |
| Losartan | 2 h | First, second, and third trimesters |
| Olmesartan | 13 h | First, second, and third trimesters |
| Tasosartan | Not available, but half-life of angiotensin II receptor antagonists ranges from 1 to 3 d | First, second, and third trimesters |
| Telmisartan | 24 h | First, second, and third trimesters |
| Valsartan | 6 h | First, second, and third trimesters |
| **Angiotensin-converting enzyme inhibitors** | | |
| Benazepril | 10 to 11 h | First, second, and third trimesters |

## Table 6. List of Known Teratogens

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Captopril | 2 h | First, second, and third trimesters |
| Cilazapril | 9 h | First, second, and third trimesters |
| Enalapril | 11 h | First, second, and third trimesters |
| Fosinopril | 11.5 to 14 h | First, second, and third trimesters |
| Lisinopril | 12 h | First, second, and third trimesters |
| Moexipril | 12 h | First, second, and third trimesters |
| Perindopril | 0.8 to 1 h | First, second, and third trimesters |
| Quinapril | 3 h | First, second, and third trimesters |
| Ramipril | 13 to 17 h | First, second, and third trimesters |
| Trandolapril | 6 h | First, second, and third trimesters |
| **Anti-arrhythmics** | | |
| Amiodarone | 61 d | First, second, and third trimesters |
| **Antibiotic**s | | |
| Sulfamethoxazole/ Trimethoprim | 8 to 10 h | 3 months before conception and first trimester for MCMs and second trimester for preterm birth and low birth weight |
| **Anticoagulants** | | |
| Acenocoumarol | 8 to 11 h | First, second, and third trimesters |
| Dicumarol | 1 to 2 d | At least 2 weeks before conception and first, second, and third trimesters |
| Phenprocoumon | 4 to 6 d | First, second, and third trimesters |
| Warfarin | 40 h | At least 2 weeks before conception and first, second, and third trimesters |
| **Anti-epileptics** | | |
| Lamotrigine | Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy) | First, second, and third trimesters |
| Trimethadione/ Paramethadione | Paramethadione—12 to 24 h Trimethadione—11 to 16 h | First, second, and third trimesters |
| Valproic Acid, Valproate | 9 to 16 h | Primarily first trimester, but MCMs have been associated with second and third trimester exposures |
| Carbamazepine | 12 to 65 h | First, second, and third trimesters |
| Ethotoin | 3 to 9 h | First, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Phenytoin, fosphenytoin | Phenytoin: 7 to 42 h<br>Fosphenytoin: 15 min | First, second, and third trimesters |
| Primidone | 10 h | First, second, and third trimesters |
| Topiramate | 21 h | First, second, and third trimesters |
| Ethosuximide | 17 to 56 h | Unknown. Assumed window: first, second, and third trimesters |
| Oxcarbazepine | Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h<br>Active metabolite, 10–monohydroxy: 9 to 11 h | Unknown. Assumed window: first, second, and third trimesters |
| Sulthiame | 24 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Vigabatrin | 10.5 h | Unknown. Assumed window: first, second, and third trimesters |
| Phenobarbital | 70 to 140 h | First, second, and third trimesters |
| Methylphenobarbital | 34 h | Unknown. Assumed window: first, second, and third trimesters |
| **Antifungals** | | |
| Fluconazole | 30 h | 2 weeks before conception and first trimester |
| Flucytosine | 2.4 to 4.8 h | First trimester |
| **Antineoplastics** | | |
| Aminopterin | 12 to 24 h | First, second, and third trimesters |
| Asparaginase | 5.7 d | 3 months before conception and first, second, and third trimesters |
| Axitinib | 2.5 to 6.1 h | 1 week before conception and first, second, and third trimesters |
| Brentuximab vedotin | 4 to 6 d | 6 months before conception and first, second, and third trimesters |
| Methotrexate | 55 h | 6 months before conception and first, second, and third trimesters |
| Crizotinib | 42 h | 45 days before conception and first, second, and third trimesters |
| Cytarabine | 1 to 3 h | 6 months before conception and first, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Daunorubicin | The plasma half-life of daunorubicin averages 45 min in the initial phase and 18.5 h in the terminal phase. By 1 h after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has as average terminal plasma half-life of 26.7 h | 6 months before conception and first, second, and third trimesters |
| Exemestane | 24 h | 1 month before conception and first, second, and third trimesters |
| Mechlorethamine | 15 min | First, second, and third trimesters |
| Mercaptopurine | 10 h | 6 months before conception and first, second, and third trimesters. |
| Vinblastine | 24.8 h | First, second, and third trimesters |
| Cyclophosphamide | 3 to 12 h | 12 months before conception and first trimester |
| Altretamine | 4.7 to 10.2 h | Unknown. Assumed window: first, second, and third trimesters |
| Amsacrine | 8 to 9 h | 3 months before conception and first, second, and third trimesters |
| Bevacizumab | 480 h | 6 months before conception and first, second, and third trimesters |
| Bleomycin | 2 h | Unknown. Assumed window: first, second, and third trimesters |
| Bortezomib | 40 to 193 h | 7 months before conception and first, second, and third trimesters |
| Busulfan | 2.3 to 3.4 h | 6 months before conception and first, second, and third trimesters |
| Capecitabine | 0.75 h | 6 months before conception and first, second, and third trimesters |
| Carboplatin | 2.6 to 5.9 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Carmustine | IV, 15 to 75 min | 3 months before conception and first, second, and third trimesters |
| Cetuximab | 63 to 230 h | 2 months before conception and first, second, and third trimesters |
| Chlorambucil | 1.5 h | Not in TERIS. Assumed window: first, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Cisplatin | 20 to 30 min | 14 months before conception and first, second, and third trimesters |
| Cladribine | 1 d | 6 months before conception and first, second, and third trimesters |
| Clofarabine | 5.2 h | 6 months before conception and first, second, and third trimesters |
| Dacarbazine | 5 h | Unknown. Assumed window: first, second, and third trimesters |
| Dactinomycin | 36 h | 6 months before conception and first, second, and third trimesters |
| Dasatinib | 3 to 5 h | Unknown. Assumed window: first, second, and third trimesters |
| Docetaxel | 11.1 h | 6 months before conception and first, second, and third trimesters |
| Doxorubicin | 20 to 48 h | 6 months before conception and first, second, and third trimesters |
| Epirubicin | 31.1 h +/- 6 h to 35.3 h +/− 9 h | 6 months before conception and first, second, and third trimesters |
| Erlotinib | 36.2 h | 2 weeks before conception and first, second, and third trimesters |
| Estramustine | 10 to 20 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Etoposide | 4 to 11 h | 6 months before conception and first, second, and third trimesters |
| Fludarabine | 20 h | 6 months before conception and first, second, and third trimesters |
| Fluorouracil | 8 to 20 min | 3 months before conception and first, second, and third trimesters |
| Gemcitabine | 1.7 to 19.4 h | 6 months before conception and first, second, and third trimesters |
| Hydroxycarbamide | 2 to 4.5 h | Unknown. Assumed window: first, second, and third trimesters |
| Idarubicin | 20 to 22 h | 6.5 months before conception and first, second, and third trimesters |
| Ifosfamide | 15 h | Unknown. Assumed window: first, second, and third trimesters |
| Imatinib | 18 h | 2 weeks before conception and first, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Irinotecan | 6 to 12 h | 6 months before conception and first, second, and third trimesters |
| Lapatinib | 24 h | 1 week before conception and first, second, and third trimesters |
| Lomustine | 16 to 48 h | 2 weeks before conception and first, second, and third trimesters |
| Melphalan | 10 to 75 min | Unknown. Assumed window: first, second, and third trimesters |
| Mitomycin | 46 min | 6 months before conception and first, second, and third trimesters |
| Mitoxantrone | 23 to 215 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Nelarabine | Adults: prodrug: 30 min; ara-G: 3 h | Unknown. Assumed window: first, second, and third trimesters |
| Oxaliplatin | 392 h | 9 months before conception and first, second, and third trimesters |
| Paclitaxel | 13 to 52 h | 6 months before conception and first, second, and third trimesters |
| Pemetrexed | 3.5 h | 6 months before conception and first, second, and third trimesters |
| Pembrolizumab | 22 d | 4 months before conception and first, second, and third trimesters |
| Pentostatin | 5.7 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Procarbazine | IV, approximately 10 min | Not in TERIS. Assumed window: first, second, and third trimesters |
| Raltitrexed | 260 h | 6 months before conception and first, second, and third trimesters |
| Sorafenib | 25 to 48 h | 6 months before conception and first, second, and third trimesters |
| Streptozocin | Systemic: 35 min unchanged drug; 40 h metabolites | 1 months before conception and first, second, and third trimesters |
| Sunitinib | 40 to 60 h | 1 month before conception and first, second, and third trimesters |
| Tegafur | 6.7 to 11.3 h | 6 months before conception and first, second, and third trimesters |
| Temozolomide | 1.8 h | 6 months before conception and first, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Teniposide | 5 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Thioguanine | 80 min | Not in TERIS. Assumed window: first, second, and third trimesters |
| Thiotepa | 1.4 to 3.7 h | 6 months before conception and first, second, and third trimesters |
| Topotecan | 2 to 3 h | 6 months before conception and first, second, and third trimesters |
| Vincristine | 85 h | Unknown. Assumed window: first, second, and third trimesters |
| Vindesine | 2.9 h | Not in TERIS. Assumed window: first, second, and third trimesters |
| Vinorelbine | 27.7 to 43.6 h | 6 months before conception and first, second, and third trimesters |
| Lenalidomide | 3 h | 4 weeks before conception and first, second, and third trimesters |
| **Antithyroid** | | |
| Propylthiouracil | 1 to 2 h | First and second trimesters |
| Methimazole | 4.9 to 5.7 h | First, second, and third trimesters |
| Radioiodine | 192 h | 6-12 months before conception and first, second, and third trimesters |
| **Antivirals** | | |
| Ribavirin | 12 d | 6 months before conception and first, second, and third trimesters |
| **Estrogens** | | |
| Diethylstilbestrol | Diethylstilbestrol reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 d due to entero-hepatic circulation | First, second, and third trimesters |
| **Immunomodulatory agents** | | |
| Mycophenolate mofetil | 16 h | First, second, and third trimesters |
| Thalidomide | 5 to 7 h | 1 month before conception and first, second, and third trimesters |
| Penicillamine | 2 to 4 h | First, second, and third trimesters |

## Table 6. List of Known Teratogens

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| Azathioprine | 5 h | Primarily first trimester, but other outcomes have been associated with exposures "during pregnancy" |
| Leflunomide | 432 to 456 h | 2 years before conception and first, second, and third trimesters |
| Mycophenolic acid | 8 to 16 h | Primarily first trimester, but other outcomes have been associated with exposures "during pregnancy" |
| **Mood stabilizer** | | |
| Lithium | 24 h | First, second, and third trimesters |
| **NSAIDs** | | |
| Indomethacin | 4.5 h | Second and third trimesters; unlikely risk associated with first trimester exposure |
| **Prostaglandin analogues** | | |
| Misoprostol | 20 to 40 min | 1 month before conception and first, second, and third trimesters |
| **Retinoids** | | |
| Alitretinoin | 9 h | 1 month before conception and first, second, and third trimesters |
| Tretinoin | 0.5 to 2 h | Unknown. Assumed window: first, second, and third trimesters |
| Vitamin A | TERIS only notes "long half-life" | Doses above 10,000 IU/day may be teratogenic: First, second, and third trimesters |
| Acitretin | acitretin: 33 to 96 h<br>cis-acitretin: 28 to 157 h | 3 years before conception and throughout pregnancy, especially first trimester |
| Etretinate | 120 d to 3 y | 3 years before conception and throughout pregnancy, especially first trimester |
| Isotretinoin | 10 to 12 h | 1 month before conception and first, second, and third trimesters |
| Tazarotene | 18 h | First, second, and third trimesters |
| Retinol | 2 to 9 h | 12 months before conception and first trimester |
| **Steroids** | | |
| Danazol | 9.7 to 23.7 h | First, second, and third trimesters |

**Table 6. List of Known Teratogens**

| Drug class/generic name | Half-life | Relevant exposure window[a] |
|---|---|---|
| **Tetracyclines** | | |
| Demeclocycline | 10 to 17 h | Second and third trimesters |
| Oxytetracycline | 6 to 11 h | Second and third trimesters |
| Tetracycline | 6 to 11 h | Second and third trimesters; limited data for first trimester exposure |
| Chlortetracycline | 5.6 h | Unknown. Assumed window: second and third trimesters |
| Doxycycline | 18 to 22 h | Unknown. Assumed window: second and third trimesters |
| Methacycline | 14 to 22 h | Unknown. Assumed window: second and third trimesters |
| Minocycline | 11 to 24.31 h | Unknown. Assumed window: second and third trimesters |
| Tigecycline | 27 to 43 h | Unknown. Assumed window: second and third trimesters |

Abbreviations; d = day; h = hour; IV = intravenous; MCM = major congenital malformation; min = minute; NSAIDs = nonsteroidal anti-inflammatory drugs; TERIS = Teratogen Information System; y = year.

Sources: Eltonsy 2016; TERIS 2021; DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm; summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/; and product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.

a Teratogens with unknown relevant exposure windows will be assigned an exposure window equivalent to other product(s) in the same class.

## 18. ANNEX 3. RECRUITMENT AND RETENTION STRATEGY

- **Recruitment strategy**

An active, targeted, multi-pronged recruitment campaign will be employed to recruit participants for the registry. The campaign will focus on:

- Pregnant individuals
- Patients exposed to PENBRAYA
- Obstetric HCPs
- HCPs who are likely to prescribe/administer PENBRAYA

Obstetric HCPs and HCPs who are likely to prescribe/administer PENBRAYA may be identified via HCP directories and/or professional associations. Pregnant individuals, and patients who have received PENBRAYA may be identified through social media, and external data sources (e.g., pharmacy claims or electronic medical records). Pfizer's existing infrastructure for supporting stakeholders (e.g., the Pfizer medical information call center) may be leveraged to identify HCPs who are known to prescribe/administer PENBRAYA and pregnant individuals who have received PENBRAYA.

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to HCPs and patients. In addition, stakeholders may be identified and provided information regarding the registry via telephone through the Pfizer medical information call center and institutions that administer PENBRAYA.

- **Diversity**

Study materials (e.g., study website, data collection forms, information sheet, and informed consents) will be available in US English. In addition, a translation vendor will be available to engage in real-time translation for existing and potential participants. Campaign materials will also depict a diversity of individuals and families. Efforts will be made to recruit a patient population that is representative of the racial and ethnic distribution of individuals who have received PENBRAYA.

- **Direct-to-HCP outreach**

Direct-to-HCP outreach may be achieved by delivering recruitment materials to targeted HCPs via e-mail, fax, and/or hardcopy mail. In addition, Pfizer's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify potential registry participants and encourage their participation by speaking to them about the registry and providing them with the patient-directed registry recruitment materials.

- **Digital advertising**

Information regarding the registry and the registry recruitment materials will also be available online. A registry-specific website will be developed, where recruitment materials will be available for download. This website will be discoverable in any internet browser by performing a search related to pregnancy, PENBRAYA, and/or meningococcal vaccines. Information regarding the registry and/or a link to the registry website will also be available on the following websites:

- FDA listing of pregnancy registries on www.fda.gov
- EU PAS register (https://www.encepp.eu/encepp/studiesDatabase.jsp)
- Pfizer website

- PPD website (https://www.ppd.com/our-solutions/clinical/peri-and-post-approval/non-interventional-studies/pregnancy-and-lactation-studies/)

A web-based interface compatible with computers and mobile devices will also be developed to improve information accessibility and enable broader participation. As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant individuals) may be used to direct potential participants to the registry website.

The registry plans to partner with BabyCenter (worldwide), a leading digital resource, to aid in recruitment. This resource is one of the most commonly used digital resources for pregnant individuals, reaching more than 90% of first-time expectant individuals in the US and more than 13 million monthly visitors. They are committed to providing pregnancy and parenting information worldwide via website and mobile application. The content is evidence-based and includes a wealth of information for parents and pregnant individuals, including tools to track pregnancy and baby's growth, answers to common questions regarding pregnancy and childbirth, and online communities to connect with other pregnant individuals, moms, and dads. Because it is already used by so many pregnant individuals, it is an ideal means to help recruit participants into the registry.

- **Print advertising**

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The PENBRAYA prescribing information will provide registry information, including contact information. Information related to the registry may also be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics).

- **Recruitment materials**

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label. Materials may include the following:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation

- Registration form and sample participant consent form

- Participant consent-to-contact card (this card enables the VRCC to contact the potential participant and provide additional information about the registry)

- **Retention strategy**

A retention strategy will be facilitated by engaging the participant and HCP and seeks to minimize the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from patients and research-naïve HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up. To promote HCP engagement, status updates may be shared with HCPs through various means (i.e., e-mail, newsletters, and the registry website). Materials provided will emphasize the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on endpoints of interest to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, e-mail, website, web-based application) and a flexible follow-up schedule to enhance retention and maximize data reporting.

Finally, the registry will provide compensation to participants and their HCPs who serve as data reporters. Compensation will be sent to HCPs involved in pregnant individuals' care once pregnancy outcome data have been collected. Compensation will be sent to participants once pregnancy outcome data have been collected if fetal loss occurs or once 12-month infant outcome data have been collected if live birth occurs. Compensation will be sent to pediatric HCPs once 12-month infant outcome data have been collected.

- **Assessment of recruitment and retention**

To maximize recruitment and retention, the registry's recruitment and retention strategies will be flexible and will be continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (i.e., HCPs and participating individuals) on the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximize registry participation.

## 19. ANNEX 4. REGISTRY DATA COLLECTION DETAILS

- **Information collected at enrollment**

After obtaining informed consent, the following information will be collected on the ***Registration Form for Participants***, ***Registration Form for Healthcare Providers***, and ***Pregnancy Information Form***:

**Table 7. Information Collected at Enrollment**

| Data | Collected from Participants | Collected from HCPs |
|---|---|---|
| Reporter information | • Contact information for the participant, as well as alternate contact information<br>• HCP reporter contact information (pediatric HCP information may be provided around time of EDD if unknown at enrollment)<br>• Request for Release of Medical Information Form(s) (form may be completed for pediatric HCP around time of EDD if unknown at enrollment) | |
| Registration information | • Date of consent (enrollment)<br>• Recruitment source(s)<br>• Minimum data for study inclusion:<br>○ Country of residence<br>○ Pregnancy status<br>○ Exposure information<br>○ Prior enrollment status | • Minimum data for study inclusion:<br>○ Pregnancy status<br>○ Exposure information |
| Maternal demographics | • Maternal demographics | |
| Baseline pregnancy information | | • First day of LMP<br>• Method of conception |
| Maternal pre-pregnancy anthropomorphics | | *If not available from HCP, can be collected from participant*<br>• Pre-pregnancy anthropometrics (weight and height) |
| Maternal obstetrical history | | *If not available from HCP, can be collected from participant*<br>• Number of previous pregnancies (singleton or multiple) |

**Table 7. Information Collected at Enrollment**

| Data | Collected from Participants | Collected from HCPs |
|---|---|---|
| | | • Outcome of all previous pregnancies<br>• Complications of previous pregnancies<br>• Characteristics of previous live births (preterm, SGA)<br>• History of offspring with congenital anomalies |
| Family history of congenital malformations | | *If not available from HCP, can be collected from participant*<br>• Maternal and paternal history of congenital anomalies |
| Maternal exposures during pregnancy | | • Exposure to drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use, dose, route, frequency, and dates/duration of exposure<br>• Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure |
| Ongoing pregnancy information | | • Number of fetuses<br>• EDD and method of determination<br>• Prenatal tests performed, including type of test, date of test, and results/findings (e.g., congenital malformations)<br>• Concurrent maternal medical conditions, including but not limited to autoimmune/inflammatory disease, diabetes, hypertension, depression<br>• Concurrent pregnancy-related maternal medical conditions or pregnancy complications |

Abbreviations; EDD = estimated date of delivery; HCP = healthcare provider; LMP = last menstrual period; SGA = small for gestational age

- **Information collected at pregnancy follow-up**

At around the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***. For participants who enroll late in pregnancy, the end of second trimester follow-up might not be applicable. In the month of the EDD, the HCP(s) will be asked to complete another ***Pregnancy Information Form*** as well as the ***Pregnancy Outcome Form***. The participant is also contacted to provide authorization for medical release for the infant's pediatric HCP (if not previously obtained).

- **Follow-up at end of second trimester**

**Table 8. Information Collected at End of Second Trimester**

| Data | Collected from Participants | Collected from HCPs |
|---|---|---|
| Maternal exposures during pregnancy | | • Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available<br>• Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available |
| Ongoing pregnancy information | | • Number of fetuses<br>• EDD and method of determination<br>• Prenatal tests performed, including type of test, date of test, and results/findings (e.g., congenital malformations)<br>• Concurrent maternal medical conditions, including but not limited to autoimmune/inflammatory disease, diabetes, hypertension, depression<br>• Concurrent pregnancy-related maternal medical conditions or pregnancy complications |

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider

- **Follow-up at pregnancy outcome**

**Table 9. Information Collected at Pregnancy Outcome**

| Data | Collected from Participants | Collected from HCPs |
|---|---|---|
| Maternal exposures during pregnancy | | • Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use, dose, route, frequency, and dates/duration of exposure<br>• Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing |
| Ongoing pregnancy information | | • Number of fetuses<br>• EDD and method of determination<br>• Prenatal tests performed, including type, date, and results/findings<br>• Concurrent maternal medical conditions, including but not limited to autoimmune disease, inflammatory disease, diabetes, hypertension, depression<br>• Concurrent pregnancy-related maternal medical conditions or pregnancy complications |
| Pregnancy outcome information | | • Pregnancy outcome (spontaneous abortion, elective termination, live birth, stillbirth)<br>• Date of outcome of pregnancy<br>• Gestational age at outcome<br>• Fetal/infant characteristics, including sex, birth weight, length, head circumference<br>• Route of delivery<br>• Delivery/birth complications if any<br>• 5-minute Apgar score<br>• Congenital malformation(s) and potential contributing factors<br>• For a fetal loss (spontaneous abortion, stillbirth), factors that may have had an impact on the loss<br>• For elective termination, reason |

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider

- **Information collected at pediatric follow-up**

***Timing of pediatric follow-up***

If a live birth occurs, the mother is asked to provide authorization for medical release for the infant's pediatric HCP to provide follow-up information. If authorization for medical release is obtained, the pediatric HCP will be asked to complete the ***Infant Outcomes Form*** at 4 and 12 months of age. To reduce recall bias, pediatric HCPs will be asked to provide data that are routinely documented in the infants' medical records. This schedule follows the American Academy of Pediatrics infant well-child visit schedule (AAP 2022).

**Table 10. Information Collected at Pediatric Follow-up**

| Data | Collected from HCPs |
|---|---|
| Infant outcome information | • Date of follow-up evaluation<br>• Age of infant<br>• Gestational age at birth, if missing<br>• Weight, length, head circumference of infant at birth, if missing<br>• Congenital malformation(s) and potential contributing factors |

Abbreviation: HCP = healthcare provider

- **Targeted follow-up after report if an event of interest**

If there is a congenital malformation or other event of interest, to properly characterize the event, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form***.

**Table 11. Targeted Follow-up after Event of Interest Reported**

| Data | Collected from HCPs |
|---|---|
| Targeted follow-up information | • Details of the congenital malformation or other event of interest<br>• Etiology<br>• Maternal infections/conditions of relevance to event<br>• Other information considered relevant by the HCP<br>• Specific questions requested by the birth defect evaluator |

Abbreviation: HCP = healthcare provider

- **Attempts to obtain follow-up information**

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every 2 weeks via various modes of communication (e.g., phone, fax, e-mail, hardcopy mail). If no response is received from the HCP, additional attempts may occur at the next planned data collection timepoint. When appropriate, the participant will be asked to encourage their HCP to provide the missing data. After the 3 subsequent attempts, a final communication to obtain follow-up data will be sent to the HCP via certified mail indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

- **Follow-up process for clarification of information**

For critical data points (e.g., EDD, exposure, and outcome data), if there are outstanding questions, discrepancies between forms or missing data, the appropriate HCP will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

# Document Approval Record

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