NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Pregnancy and Birth Outcome Assessment in a Population-based Cohort After Exposure to Trumenba

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Keywords:
Trumenba; serogroup B meningococcal vaccine; pregnancy outcomes; birth/infant outcomes; US FDA Sentinel Distributed Research Network

Rationale and background: Trumenba®, a serogroup B meningococcal vaccine, was licensed in the United States (US) on 29 October 2014 for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10-25 years of age. Trumenba was licensed in the European Union on 24 May 2017 and is indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. Trumenba may be given as a two dose series (0 and 6 months) or a 3 dose series (0, 1-2, and 6 months).

Trumenba is indicated in an age group that includes women of childbearing age. There are limited safety data on Trumenba use in a real world setting among pregnant women. In order to obtain safety data regarding pregnancy exposure and birth outcomes with Trumenba, Pfizer has post approval commitments to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to conduct an observational pregnancy study (B1971052). The original study was intended to examine pregnancy and birth outcomes in women and infants, respectively, exposed to Trumenba up to 28 days prior to or during pregnancy. Specifically, the objectives were 1) to estimate the incidence and risk ratios of pregnancy outcomes, including live birth, spontaneous abortion, and stillbirth, in women exposed and not exposed to Trumenba in up to 28 days prior to or during pregnancy, and 2) to estimate the prevalence and risk ratios of birth outcomes (major congenital anomalies) among infants exposed and not exposed to Trumenba in utero. The study was designed under the assumption that there would be sufficient uptake of the vaccine necessary to perform a meaningful analysis. This study is designated as a post-authorization safety study (PASS) and is a postmarketing commitment (PMC) to the FDA and EMA.

From June 2016 through September 2017, Harvard Pilgrim Health Care, Inc. (HPHC) led a Pfizer-sponsored planning phase (Phase 1) to prepare for implementation of a full-scale study using data from selected Sentinel Research Partners to assess pregnancy and birth outcomes after exposure to Trumenba in a population-based cohort. During October 2017 through December 2020 (Phase 2), HPHC served as the Coordinating Center to implement the research study using the infrastructure and data from the FDA-funded Sentinel System.

Four Sentinel Research Partners, HPHC, CVS Health Clinical Trial Services (Aetna), HealthCore, Inc. (Anthem), and Meyers Primary Care Institute, were engaged to contribute data to the study. Coordinating Center activities during Phase 2 focused on monitoring pregnancy exposures to Trumenba to determine the feasibility of conducting a full analytic study (comparative analysis) in a subsequent phase of the study (Phase 3).

During Phase 2, queries from the four Research Partners identified nine (9) Trumenba exposures during pregnancy among women who delivered live births between 01 November 2014 and 31 December 2018 with ages 10-49 years at the start of pregnancy. The start date of observation was later amended to 01 November 2015 to be consistent with the date in the FDA-approved protocol amendment dated 20 March 2017.

Given the small number of Trumenba exposures during pregnancy identified over a 4 year period, it became apparent that none of the protocol objectives could be scientifically assessed. Pfizer informed the US FDA, the health authority with whom Pfizer held the safety commitment, of the status of the study and sought approval on 18 May 2020, to focus on submitting a final, descriptive report of available information for Study B1971052 rather than a comparative analysis as specified in the FDA-approved protocol amendment dated 20 March 2017. The FDA agreed with this approach in writing on 12 June 2020.

The EMA was informed on 16 November 2020 of the study status and that this descriptive report will be submitted to the FDA to fulfill the FDA PMC. This descriptive report will be submitted to the EMA.

Research question and objectives: The research questions for this descriptive report are: What are the pregnancy and birth/infant outcomes among Trumenba-exposed pregnancies? The objectives are to describe the following outcomes among Trumenba-exposed pregnancies using administrative claims data: 1) Pregnancy outcomes: live birth, spontaneous abortion, stillbirth; and 2) Birth/infant outcomes: major congenital anomalies, premature birth, small for gestational age.

Study design: A population-based, non-interventional cohort study using healthcare claims data.

Setting: Persons identified from healthcare claims data of a commercially-insured population from the US Sentinel distributed research network (DRN).

Subjects and study size: Pregnancy outcomes were identified from 01 November 2015 through 31 December 2020. All women who met the eligibility criteria were included in the analyses. Eligible pregnant women were 10-49 years of age on the date of pregnancy outcome occurrence, and were exposed to Trumenba during the exposure period, which was defined as 28 days prior to pregnancy through the end of gestation for live birth and stillbirth deliveries, and during a pre-specified period (20 weeks) for spontaneous abortions. Because this was a descriptive study, statistical power calculations were not performed.

Variables and data sources: The exposure of interest was receipt of at least one dose of Trumenba during the exposure period described above. The outcomes of interest were pregnancy outcomes (live birth, spontaneous abortion, stillbirth) and birth/infant outcomes (major congenital anomalies, premature birth, small for gestational age). Healthcare claims data from four large health plans that are data partners of the US Sentinel DRN were used.

Results: During the observation period from 01 November 2015 through 31 December 2020, and among 794,571 pregnancies in women of age 10-49, a total of 51 (51/794,571 or 0.006%) Trumenba-exposed pregnancies were identified, of which 30/617,605 or 0.005% resulted in live-birth deliveries and 21/171,405 or 0.012% resulted in spontaneous abortions. There were no stillbirths reported. One congenital anomaly (microencephaly) was identified through maternal records only as the mother-infant could not be linked. There were 4 premature births (gestational age 35-36 weeks on the delivery date). Medical record review of the available data was not performed, thus further limiting the interpretation of the data.

All Trumenba exposure during pregnancy occurred in women between the ages of 10-25. Most Trumenba-exposed pregnancies consisted of only one dose of Trumenba. The majority of Trumenba exposure occurred in the 1st trimester or in the 28 days prior to the start of pregnancy for live births. The mean age of women was 18.7 years (SD=1.8) among live birth deliveries and 18.3 years (SD=1.4) among spontaneous abortions.

Discussion: From 794,571 pregnancies over a 5-year period in a commercially insured population, an extremely small number of Trumenba-exposed pregnancies were identified (n=51; 0.006%). Given the small number of Trumenba exposures during pregnancy, low linkage rate and no confirmation of the accuracy of the structured data through medical record review, no conclusions can be drawn from the data.

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