NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	A Pregnancy and Birth Outcome Assessment in a Population-based Cohort After Exposure to Trumenba
Protocol number	B1971052
Version identifier of the final study report	1.0
Date	16 December 2021
EU Post Authorization Study (PAS) register number	EUPAS21984
Active substance	Bivalent rLP2086
Medicinal product	Trumenba
Research question and objectives	**Research Questions:** What are the pregnancy and birth/infant outcomes among Trumenba-exposed pregnancies? **Objectives:** To describe the following outcomes among Trumenba-exposed pregnancies using administrative claims data: (1) Pregnancy outcomes: live birth, spontaneous abortion, and stillbirth; (2) Birth/infant outcomes: major congenital anomalies, premature birth, and small for gestational age

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Not applicable

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Not applicable

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Not applicable

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CDM	Common Data Model
CPT	Current Procedural Terminology
DRN	Distributed Research Network
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	U.S. Food and Drug Administration
FISMA	Federal Information Security Management Act
HIPAA	Health Insurance Portability and Accountability Act of 1996
HCPCS	Healthcare Common Procedure Coding System
HPHC	Harvard Pilgrim Health Care, Inc
HPHCI	Harvard Pilgrim Health Care Institute
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
ICMJE	International Committee of Medical Journal Editors
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MCA	Major congenital anomaly
NIST	National Institute of Standards and Technology
PMC	Postmarketing commitment
SAB	Spontaneous abortion
SAS	Statistical Analysis System
SGA	Small for gestational age
QA	Quality Assurance
QC	Quality Control

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed below.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Cynthia de Luise, PhD, MPH	Senior Director; Safety Surveillance Research, Worldwide Medical and Safety	Pfizer, Inc.
Jeffrey S. Brown, PhD	Principal Researcher	Harvard Medical School Harvard Pilgrim Health Care Institute
Aaron B. Mendelsohn, PhD	Research Scientist III	Harvard Medical School Harvard Pilgrim Health Care Institute
Young Hee Nam, PhD	Research Fellow	Harvard Medical School Harvard Pilgrim Health Care Institute
Allison Naleway, PhD	Senior Investigator	Center for Health Research, Kaiser Permanente Northwest
Susan Andrade, ScD	Senior Investigator	Meyers Primary Care Institute University of Massachusetts Medical School
Aziza Jamal-Allial, PhD, MS	Research Partner Investigator	HealthCore, Inc.
Cheryl Walraven, MSW, PhD	Research Partner Investigator	CVS Health Clinical Trials Services
Audrey Djibo, PhD, MSBME	Research Partner Investigator	CVS Health Clinical Trials Services

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS Register	01 December 2017	12 December 2017	
Date of institutional review board (IRB) approval of protocol The IRB approval dates for the protocol and any amendments are provided in Appendix 3.2.	05 March 2021	12 March 2021	The study plan was submitted to IRB on 05 March 2021 and was approved by IRB on 12 March 2021.
Start of data collection	30 June 2021	29 June 2021	
End of data collection	01 October 2021	01 October 2021	
Final report of study results	31 December 2021	TBD	

6. 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 adolescents and young adults with 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-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).

As presented in the FDA-approved protocol amendment dated 20 March 2017 (Appendix 2), the planned comparative analyses were predicated under the assumption that sample size estimates could be met. In the abstract section under study size, the following text is included:
"Sample size will be affected by public health recommendations made by the US Advisory Committee on Immunization Practices, from other professional advisory committees, and possibly meningococcal disease outbreaks. Based on available data from national insurers participating in the Sentinel System, the expected sample size of Trumenba exposed pregnant women may was expected to range from 468- 936 over the 5-year study period between November 1, 2015 through October 31, 2020. Estimation using an uptake pattern similar to the meningococcal conjugate vaccine, a sample size of 468 would have allowed a minimal detection of increased risk ratios ranging from 1.39 to 1.78 depending on the outcome (range: 3% - 10%) with 80% power and alpha=0.05 (two-sided). A sample size of 936 would have allowed a minimal detection of increased risk ratios ranging from 1.27 to 1.54 depending on the outcome (range: 3% - 10%) with 80% power and alpha=0.05 (two-sided)."

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 (Appendix 2).

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 (Appendix 2). 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.

7. RESEARCH QUESTION AND OBJECTIVE

What are the pregnancy and birth/infant outcomes among Trumenba-exposed pregnancies?

This report will describe the following outcomes among Trumenba-exposed pregnancies using administrative claims data:

(1) Pregnancy outcomes: live birth, spontaneous abortion, and stillbirth;

(2) Birth/infant outcomes: major congenital anomalies, premature birth, and small for gestational age

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	05 May 2021	Substantial amendment	5.1 Study Design (in the Study Plan, dated 06 November 2020)	The study period for identifying eligible pregnancy outcomes will be 01 November 2015 through the most recent data available for each Research Partner (up to 31 December 2020)	Change made to be consistent with the FDA-approved protocol amendment dated 20 March 2017, the 18 May 2020 communication to the FDA and in order to maximize sample size
			5.1 Study design (Figure 1 Study Schematic) 5.2 Study population 5.4.1 Exposure	Clarified the look back period (e.g., 20 weeks), for the identification of spontaneous abortion (SAB), as opposed to using the presumed start date of pregnancy.	The identification algorithm for SAB cannot estimate the start date of pregnancy, nor gestational age. Rather, a pre-specified look-back period (e.g., 20 weeks) to examine Trumenba exposure during pregnancy for SAB was applied.
			5.2 Study population	Added in the continuous enrollment requirement; 329 days for live birth or stillbirth deliveries and 140 days for SAB prior to the pregnancy outcome date	Reflected periods to be used by the Sentinel pregnancy outcome identification algorithms to identify eligible Trumenba exposure for each pregnancy outcome

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			5.4.2.3 Other variables of interest	Indicated that maternal age will be assessed on the date of the pregnancy outcome Removed gestational age as a variable of interest	As noted above, the identification algorithm for SAB cannot estimate the start date of pregnancy, nor gestational age
2	12 August 2021	Administrative Amendment	Appendix 1 Major Congenital Anomalies (MCAs) (in the Study Plan date 05 May 2021)	Added ICD-10 codes to Appendix 1 as well as a few additional MCAs of interest	The ICD-10 codes will be used in identifying the MCAs from the administrative claims data. There were MCAs that had not been initially included, but would be important to consider and were therefore added.
			Appendix 2 Teratogenic Medications (in the Study Plan date 05 May 2021)	Fixed minor issue in Appendix 2	Typographical error.

9. RESEARCH METHODS

9.1. Study design

This was a population-based, non-interventional cohort study using administrative healthcare claims data. The study period for identifying eligible pregnancy outcomes was 01 November 2015 through the most recent data available for each Research Partner, up to 31 December 2020. Birth/infant outcomes were identified through the most recent data available for each Research Partner up to six months after delivery. The study schematic is presented in Figure 1, and the time frame for the identification of Trumenba exposures, outcomes, and other variables of interest is presented in Figure 2.

Figure 1. Study schematic

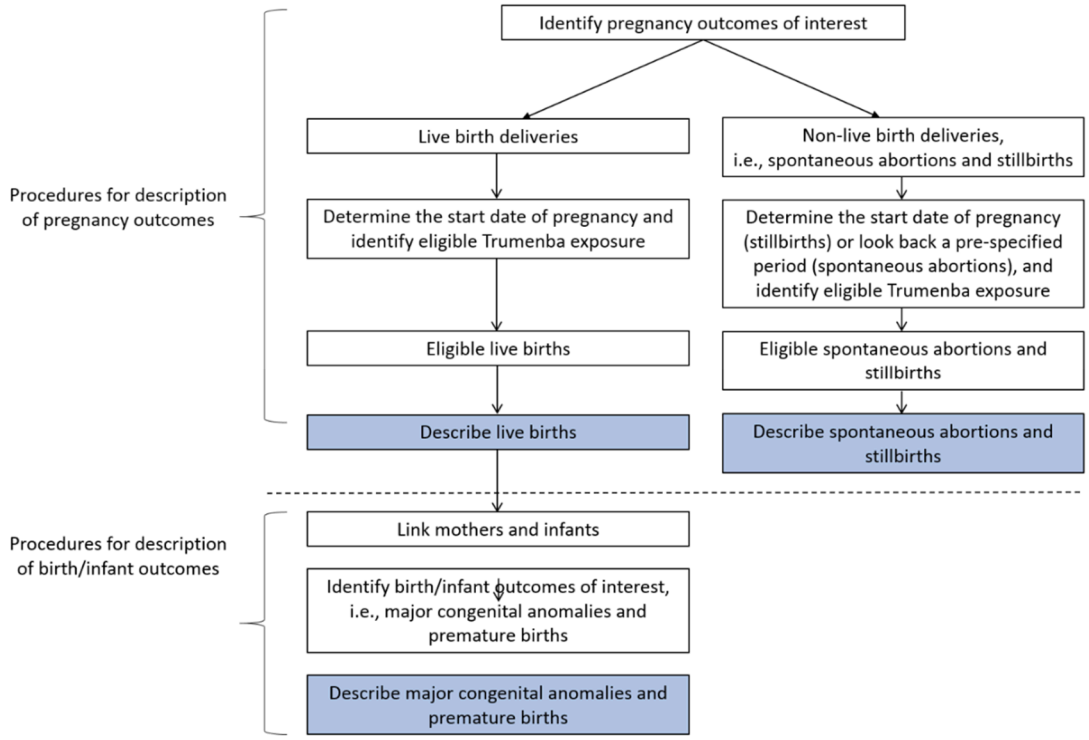
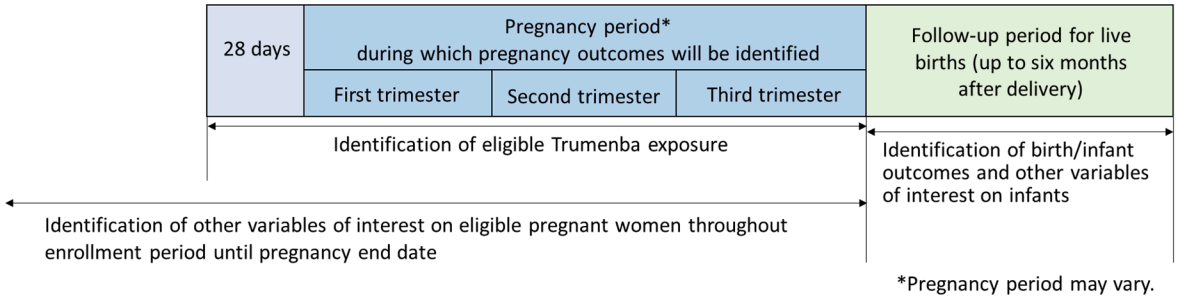


Figure 2. Identification of Trumenba exposures, outcomes and other variables of interest



9.2. Setting

Administrative healthcare claims data from selected Research Partners in the US Sentinel distributed research network (DRN) were used for this study. Further details about the Sentinel DRN are presented in Section 9.5 Data sources and measurements.

9.3. Subjects

Eligible pregnant women were 10-49 years of age on the date of pregnancy outcome occurrence, met a continuous enrollment criterion in the participating healthcare plans, and were exposed to Trumenba during the potential Trumenba 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, 140 days (i.e., 20 weeks) for spontaneous abortions (see the definition of spontaneous abortion in Section 9.4.2.1 Pregnancy outcomes). This pre-specified period for spontaneous abortions was used because the algorithm for identification of spontaneous abortion cannot estimate the pregnancy start date. Additionally, although most spontaneous abortions occur at 10-11 weeks of gestational age (Wilcox et al., 1981; Wilcox et al., 1988), a conservative period of 20 weeks was used to reduce the likelihood of missing Trumenba-exposed pregnancies resulting in spontaneous abortions.

Eligible pregnant women were required to have continuous enrollment in their participating healthcare plan with medical and drug coverage from at least 329 days prior to the pregnancy outcome occurrence date for live birth and stillbirth deliveries and for at least 140 days prior to the outcome occurrence date for spontaneous abortion. The original B1971052 study protocol required continuous enrollment for at least 292 days prior to the start of pregnancy to examine whether there were Trumenba exposures before the eligible Trumenba exposure (i.e., to ascertain whether the eligible Trumenba exposure was the first dose, second dose, or third dose exposure) and also to measure baseline characteristics. This inclusion criterion of continuous enrollment was changed from 292 days to 28 days given that the present study is descriptive and to reduce the possibility of missing Trumenba-exposed pregnancies. A gap of up to 45 days in enrollment was allowed to account for administrative gaps without actual discontinuation of medical and drug coverage.

9.4. Variables

9.4.1. Exposure

The exposure of interest was receipt of at least one dose of Trumenba during the potential Trumenba exposure period (defined in Section 9.3. Subjects) in any care setting. Eligible Trumenba exposures and the exposure dates were identified using National Drug Codes (NDCs), Current Procedural Terminology (CPT) codes, and dates of Trumenba dispensing/administration appearing in the administrative healthcare claims data. The risk interval, i.e., the period during which a person was at risk for an adverse outcome following vaccination, was considered beginning from the time of vaccination. While women may have received more than one Trumenba dose during the enrollment period, only Trumenba exposure that occurred during the potential exposure period was considered to be an eligible Trumenba exposure. For example, if a woman received Trumenba before the potential exposure period but did not receive Trumenba during the potential exposure period, she was not considered as exposed to Trumenba for this study. The index exposure date was defined as the date of the first eligible Trumenba exposure during a pregnancy. Individuals were allowed to have multiple index exposure dates during their enrollment period.

9.4.2. Outcomes

The outcomes of interest were (1) pregnancy outcomes among eligible pregnant women, occurring during the study period and (2) birth/infant outcomes among the infants from the eligible Trumenba-exposed pregnancies, occurring during the study period up to six months after birth.

9.4.2.1. Pregnancy outcomes

Pregnancy outcomes of interest were live birth, stillbirth, and spontaneous abortion that occurred in any care setting. A stillbirth was defined as a spontaneous (non-deliberate) fetal death that occurred at or after 20 weeks gestation but prior to delivery. A spontaneous abortion was defined as a spontaneous (non-deliberate) embryonic or fetal death that occurred prior to 20 weeks gestation (Griebel et al., 2005).

Pregnancy outcomes were identified using diagnosis codes (International Classification of Disease, 10th revision, Clinical Modification [ICD-10-CM] codes) and procedure codes (CPT codes, Healthcare Common Procedure Coding System [HCPCS], and International Classification of Diseases, 10th Revision, Procedure Coding System [ICD-10-PCS] codes) in the administrative healthcare claims data. Pregnancies ending in a live birth were identified via validated algorithms that have been used in Sentinel and non-Sentinel projects (Sentinel Initiative, Validation, 2018; Andrade et al., 2012; Andrade et al., 2016). Pregnancies ending in a stillbirth or spontaneous abortion were identified via algorithms developed and validated through Sentinel (Andrade et al., 2021) and non-Sentinel (Naleway et al., 2021) efforts to update previously developed algorithms using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes (Centers for Disease Control and Prevention 2019).

9.4.2.2. Birth/Infant outcomes

Birth/infant outcomes of interest were major congenital anomalies, premature birth, and small for gestational age (SGA) that occurred in any care setting among live births. Major congenital anomalies were defined as birth defects that have either cosmetic or functional significance to the child (e.g., cleft lip). Premature birth was defined as a birth occurring before 37 weeks of gestation. A list of major congenital abnormalities was compiled from the National Birth Defects Prevention Study (Rasmussen et al., 2003) and the European Surveillance of Congenital Anomalies (Boyd et al., 2011).

Birth/infant outcomes were identified using ICD-10-CM diagnosis codes in the administrative healthcare claims data among live births. Each Research Partner was responsible for linking mothers and infants using all available local data resources. In general, algorithms linking mothers and infants involve looking for equivalent subscriber numbers, dates of delivery and birth, names, and addresses. Sentinel Research Partners are able to link 70-80% of infants to their mothers (Sentinel Initiative, Validation, 2018). To allow adequate follow-up time to detect major congenital anomalies and to be consistent with other studies (e.g., Correa et al., 2007), claims data were examined for up to six months after birth, within each Research Partner's available data and the predefined study period. This study was designed to search both the infants' and mothers' claims for more complete

capture of these outcomes because the infant's diagnoses may be captured in the mother's claims data shortly after birth (generally ≤30 days after birth) if there is a delay in the enrollment of the infant in the health plan.

9.4.3. Other variables

In addition to the exposure and outcomes of interest described above, other variables of interest are listed below.

- **Maternal information**
  The following maternal information was collected from the administrative healthcare claims data.
  - Index date, pregnancy start date, pregnancy end date
  - Timing of each Trumenba exposure (first trimester, second trimester, third trimester, the 28-day period prior to the start of pregnancy, and prespecified 140 days prior to the end of pregnancy for spontaneous abortions)
  - Maternal age on the date of the pregnancy outcome occurrence
  - Teratogenic medication use
  - Comorbidities: diabetes, asthma, obesity, and conditions that may be associated with increased risk of meningococcal disease (e.g., sickle cell disease, splenic disease)
  - Pregnancy complications and health behaviors: alcohol use, drug dependence, gestational diabetes, gestational hypertension, maternal obesity, smoking
  - Health plan enrollment: Research Partner, health plan enrollment start date and end date

- **Infant information**
  Collection of the following infant information from the administrative healthcare claims data from the birth date until up to six months of age was planned.
  - Major congenital anomaly (presence of diagnosis, diagnosis code and date)
  - Premature birth
  - Small for gestational age
  - Sex
  - Birth date and follow-up end date

9.5. Data sources and measurement

As described above, administrative healthcare claims data used from the DRN comprised of four large national and regional health plans with electronic administrative healthcare databases that are members of the FDA Sentinel Initiative and participated in Phase 2 of this project to monitor pregnancy exposure to Trumenba: HPHC; CVS Health Clinical Trial Services (Aetna); HealthCore, Inc. (Anthem); and Meyers Primary Care Institute (Fallon Health). The FDA Sentinel is a national electronic system for active surveillance of the safety of drugs, biologics, vaccines, and medical devices in the US, established under the Sentinel Initiative (Food and Drug Administration, 2018). Sentinel uses a Common Data Model (CDM) (Food and Drug Administration, 2018) for standardization of demographic and clinical data elements and has routine analytical tools in place to permit rapid queries, including descriptive analyses and complex methodologies (e.g., comparative analyses),

across Research Partners. The use of a DRN enables assessment of large populations with well-defined demographic and clinical characteristics. The Research Partners that participated in this study have access to data on over 10 million patient-lives since 2014.

9.6. Bias

Not applicable because this is a descriptive study. See Section 11.2 Limitations for a description of the study's limitations.

9.7. Study Size

As presented in the FDA-approved protocol amendment dated 20 March 2017 (Appendix 2), the planned comparative analyses were predicated under the assumption that sample size estimates could be met. Based on available data from national insurers participating in the Sentinel System, the expected sample size of Trumenba exposed pregnant women was estimated to range from 468 to 936 over the 5-year study period from 01 November 2015 through 31 October 2020. This sample size was not achieved (only 51 cases compared to an expected range of 468 to 936 cases were observed) and agreement was reached with the FDA to submit a descriptive report of available data.

For this descriptive report, which has no specific hypotheses being tested, it is expected that statistical power with available data will be low. All individuals who met the eligibility criteria between 01 November 2015 through the most recent data available for each Research Partner, up to 31 December 2020, were included in the analyses. The extension to 31 December 2020 was implemented in an effort to increase sample size.

9.8. Data transformation

The Harvard Pilgrim Health Care Institute (HPHCI) in Boston, Massachusetts, served as the data coordination center ("Coordinating Center") for this study. The Coordinating Center staff or contractors are responsible for writing and distributing Statistical Analysis Systems (SAS) programs that are used to collect data from the administrative healthcare claims databases at participating Research Partners. The Sentinel DRN allows Research Partners to maintain physical and operational control of their data while enabling use of the data to meet the study needs. The Coordinating Center uses a web-based portal that enables secure distribution of analytic queries, data transfer, and document storage. This system meets all required federal and state security guidelines for health data (e.g., Federal Information Security Management Act [FISMA], Health Insurance Portability and Accountability Act of 1996 [HIPAA]), specifically compliant for FISMA moderate risk security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53 [NIST, 2017]).

9.9. Statistical methods

Descriptive analyses were performed to characterize the pregnancy and birth/infant outcomes among the eligible pregnancies. See Section 9.9.1 Main statistical methods.

Descriptive statistics were used, namely, frequencies (counts), percentages for categorical variables (e.g., sex), and means and standard deviations for continuous variables (e.g., age).

9.9.1. Main statistical methods

The Sentinel Cohort Identification and Descriptive Analysis tools (FDA, 2018) and direct querying of the Research Partners' data were used to identify eligible pregnancies and women of childbearing age (10-49 years) exposed to Trumenba during the study period, obtain the data elements of interest, and perform the data analyses. The results were aggregated across the Research Partners (no Research Partner specific data are presented).

For informational purposes, the protocol amendment dated 20 March 2017 (Appendix 2) and the Statistical Analysis Plan (SAP) (Appendix 4) dated 27 April 2017 are included herein to describe the analytic plan of the originally planned study which could not be realized due to unexpectedly low Trumenba exposures during pregnancy.

9.9.2. Missing values

No attempt was made to impute missing values for this study.

9.9.3. Sensitivity analyses

None

9.9.4. Amendments to the statistical analysis plan

None

9.10. Quality control

As noted above, the Sentinel DRN utilizes a CDM that standardizes data across Research Partners, and each of the participating Research Partners has experience using this data model. This study used data quality assurance procedures of the Sentinel System (Sentinel Operations Center, 2017). The quality assurance procedures assess consistency with the Sentinel CDM, evaluate adherence to data model requirements, definitions, and logical relationships between data model tables, and review trends in medical and pharmacy services use within and across Research Partners. Details on the Sentinel quality assurance process and data curation are documented on the Sentinel website (FDA, 2018). The data curation process is consistent with the guidance set forth by the FDA in its current recommendations for data quality assurance, specifically "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC)", published in May 2013 (FDA, 2013). In addition to the data quality assurance procedures, the Coordinating Center adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables.

9.11. Protection of human subjects

Subject information and consent

Not Applicable

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an IRB for each site participating in the study. All correspondence with the IRB will be retained in the study files.

Ethical conduct of the study

The study was 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 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2018), Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (International Society for Pharmacoepidemiology, 2015), FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment (FDA, 2005); and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (FDA, 2013).

10. RESULTS

10.1. Participants

The number of pregnancies and pregnant women in the underlying source population identified during the period between 01 November 2015 through 31 December 2020, is shown in Table 2.

During this period there were a total of 794,571 pregnancies among women between the ages of 10-49 years.

Table 2. Number of pregnant women and pregnancies

	Number of unique pregnant women[a]	Number of pregnancies[b]
Live birth delivery	568,687	617,605
Stillbirth delivery	5,520	5,561
Spontaneous abortion	157,627	171,405
Total	**731,834**	**794,571**

a. Pregnant Women with 10-49 years of age on the date of live birth delivery, stillbirth delivery, or spontaneous abortion who met enrollment requirements (at least 329 days [140 days] of continuous enrollment with medical and drug coverage prior to the date of live birth delivery or stillbirth delivery [spontaneous abortion]; a up to 45-day gap was allowed).
b. Pregnancies incident with respect to live birth delivery or stillbirth delivery in the prior 183 days, and incident with respect to spontaneous abortion in the prior 140 days. Note: mutual exclusivity was not taken into consideration across the categories.

10.2. Descriptive data

Since this is a descriptive study, available data are presented in Section 10.4 Main results.

10.3. Outcome data

Provided in Section 10.4 Main results.

10.4. Main results

10.4.1. Characteristics of pregnancy outcomes

During the observation period from 01 November 2015 through 31 December 2020, and among 794,571 overall pregnancies, a total of 51 (51/794,571 or 0.006%) Trumenba-exposed pregnancies were identified, of which 30 (30/617,605 or 0.005%) resulted in live-birth deliveries and 21 (21/171,405 or 0.012%) resulted in spontaneous abortions. There were no stillbirths reported. One congenital anomaly was identified through maternal records only as the mother-infant pair 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 years. 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) for live birth deliveries and 18.3 years (SD=1.4) for spontaneous abortions.

10.4.2. Characteristics of birth/infant outcomes

Regarding birth/infant outcomes, the mother and infant pair could be linked for only one of the 30 live birth deliveries by Research Partners (linkage rate ≈3.3%). There was one major congenital malformation identified from maternal records only. The mother's age upon delivery was 18 years and the timing of Trumenba exposure was during the 28 days prior to the pregnancy start date. There were no cases of small for gestational age among live birth deliveries.

10.5. Other analyses

None

10.6. Adverse events/adverse reactions

This study involves a combination of existing structured data and unstructured data, which was converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. DISCUSSION

11.1. Key results

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 and no confirmation of the accuracy of the structured data through medical record review, no conclusions can be drawn from the data.

11.2. Limitations

Given the very low number of Trumenba exposures during pregnancy and no confirmation of the accuracy of the structured data through medical record review, no conclusions can be drawn from the data. No comparison group of pregnancies unexposed to Trumenba was similarly evaluated, nor were any inferential statistics conducted.

This study has limitations inherent to observational studies using administrative health care claims databases. The performance of the algorithms used to identify data for study variables relies on the accuracy and completeness of coding. As a result, misclassification of both exposures and outcomes may have occurred (e.g., Trumenba-exposed pregnancies may have been missed or inaccurately coded). In this study which used administrative healthcare data, the identification of pregnancy exposure was conducted indirectly by observing codes for pregnancy outcomes such as live births, etc. and then looking backward in time to ascertain exposure as there is no ability to ascertain the start of gestation. Furthermore, three of the 21 cases of spontaneous abortion also had claims for other pregnancy outcomes (live birth for 1 and elective termination of pregnancy for 2). As medical record review was not performed, it is not possible to determine the accuracy of the codes for spontaneous abortion or which claims are correct for these 3 pregnancies that had more than one type of claim.

The mother-infant pair linkage rate was much lower in this study (eg. 3.3%) than the general linkage rate in the Sentinel DRN, which may be because the mothers were young. Hence, no meaningful conclusions are possible in terms of birth/infant outcomes. Although Sentinel Research Partners are usually able to link 70-80% of infants to their mothers in general, the linkage rates tend to be much lower among younger, relative to older, patients (Sentinel Initiative, 2021). It is possible that commercially-insured women of younger ages are likely to be enrolled in their parents' health plan, and after delivery, they and/or their babies may enroll in state Medicaid or switch to another commercial insurance plan, which may reduce the likelihood that the Sentinel Research Partners can link mothers and infants within their data.

Individuals enrolled in health plans of the participating Research Partners were commercially insured people. Therefore, the study results may not be generalizable to other populations or the US population at large. In addition, Trumenba use that occurred in the settings that are not included in the Sentinel DRN (e.g., university health clinics) was not captured.

11.3. Interpretation

Based on the results of this descriptive report which relied on administrative healthcare claims data of women of childbearing age, Trumenba receipt linked to exposure during pregnancy was extremely uncommon. Given the limited data available, no conclusions can be drawn.

11.4. Generalizability

As mentioned above in Section 11.2 Limitations, data from commercially insured individuals enrolled in health plans of the participating Research Partners were used for this study. Therefore, the results may not be generalizable beyond this population (e.g., non-commercial health plan enrollees, the US population at large or populations from other geographic regions).

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

From 794,571 pregnancies, a very small number of Trumenba-exposed pregnancies were identified (n=51). Given the small number of Trumenba exposures, low linkage rate and no confirmation of the accuracy of the structured data with medical record review, no conclusions can be drawn from the data.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable

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