NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Effect of Trumenba on Gonococcal infections in adolescents and young adults in the United States: A retrospective cohort study
Protocol number	B1971066
Protocol version identifier	1.0
Date	18 April 2023
Medicinal product	Trumenba
Research question and objectives	To examine the effect of Trumenba on gonococcal infection in adolescents and young adults in the United States using a claims database.
Author	PPD (Pfizer): PPD (Pfizer): PPD PPD (Pfizer): PPD PPD (Pfizer): PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
4CMenB	bexsero vaccine
CIOMS	International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
CPT	current procedural terminology
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
fHBP	factor H binding protein
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HRs	hazard ratios
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficieny virus
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research
MenB	Meningococcal Serogroup B
MSM	men who have sex with men
NDC	National Drug Codes
OMV	outer membrane vesicle
PASS	Post-Authorization Safety Study

Abbreviation	Definition
SAS	statistical analysis system
US	United States
VE	Vaccine effectiveness

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not required.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	20 April 2023
End of data collection	30 April 2023
Final study report	31 October 2023

7. RATIONALE AND BACKGROUND

This study is not a Post-Authorization Safety Study (PASS) and is not a commitment to any regulatory authority.

Meningococcal B outer membrane vesicle (OMV) vaccines have been created, developed and used to control outbreaks of meningococcal B diseases in New Zealand, Norway and Cuba. Studies suggested that OMV vaccines could potentially protect against gonococcal infections in New Zealand and Norway.[1]

Recently 4 studies described the effect of Bexsero (4CMenB) on gonococcal infection in adolescents and young adults (2 studies in the United States (US), 1 in Australia and 1 in Italy). The vaccine coverage differed by studies (69% in Australia, 33% in men who have sex with men (MSM) living with human immunodeficiency virus (HIV) in Italy and 1.8% in New York City & Philadelphia. The direct effect of 4CMenB (vaccine effectiveness) ranged from 32 to 74% for 2 full doses and 33 to 71% for at least 1 dose.[2-5]

Abara et al studied the effectiveness of 4CMenB and factor H binding protein (fHbp) vaccines in 2 separate studies using the same methodology in New York and Philadelphia regions for the period of 2016-2018 (the first 2 years of meningococcal serogroup B [MenB] vaccines use in the US). The vaccine coverage was 7.4% and 1.6% for at least one dose for 4CMenB and fHbp vaccines respectively. The effectiveness of 4CMenB was 40% (95% CI 23; 53) for full dose and 26% (95% CI 12; 37) for only 1 dose. The effectiveness of fHbp vaccine was 3% (95%CI: +19; 21).[6] 6These results were based on data during the period where fHbp had extremely low vaccine coverage (<2%).

The vaccine effectiveness for 4CMenB varied highly according to study types, age of the study population and the vaccine coverage rate. The vaccine coverage had increased to 32% for any MenB vaccines in 2021 while it was 14% and 17% in 2017 and 2018 respectively. The effectiveness of fHbp vaccine observed in Abara et al study could be confirmed in a larger population with higher vaccine coverage. The purpose of the study will be to evaluate the effect of fHbp vaccine in prevention of gonococcal infection among 15-30 years in the US using the claim database.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Objectives

8.1.1. Primary Objective

To examine the effect of at least 1 dose of Trumenba on gonococcal infection in adolescents and young adults of 15-30 years in the US.

8.1.2. Secondary Objectives

1. To examine the effect of at least 2 doses of Trumenba on gonococcal infection in adolescents and young adults of 15-30 years in the US.

2. To examine the effect of at least 1 dose of Trumenba on chlamydial infection in adolescents and young adults of 15-30 years in the US.

3. To examine the effect of at least 2 doses of Trumenba on chlamydial infection in adolescents and young adults of 15-30 years in the US.

8.1.3. Exploratory Objectives

1. To examine the effect of at least 1 dose of Trumenba on gonococcal infection in adolescents and young adults of 16-23 years in the US.

2. To examine the effect of 1 dose of Trumenba on gonococcal infection in adolescents and young adults of 15-30 years in the US at 12 months, 24 months, 36 months and 48 months following the index vaccination.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study using health care administrative claims data as described in Section 9.4 Data Sources.

Adolescents and young adults approximately 15 to 30 years of age at their individual time zero (calculated based on birth year) will be identified from administrative claims during 01 January 2016 and 31 December 2021.

The exposure cohort will be the individuals who have received at least 1 dose of Trumenba and at least 1 dose of MenACWY (Menactra®, Menveo®, or MenQuadfi®) prior to the Trumenba vaccination, between 01 January 2016 and 31 December 2021. The index date (zero time) for the exposed cohort is the last date of vaccination, and the cohort will be followed from 14 days after vaccination to the end of the study period (31 December 2022). The individuals in the cohort will be censored by the event of interest, death date (if known), plan disenrollment (if known) or the end of the study period, whichever comes first.

The reference cohort will be those with at least 1 dose of MenACWY vaccine, but no doses of Trumemba during the observation period, received between 01January 2016 and 31 December 2021. The MenACWY-only vaccinated cohort is used as a reference cohort rather than an unvaccinated cohort in order to help control for theoretical differences in health seeking and risk behaviors between vaccinated and unvaccinated individuals. The index date (zero time) of the reference cohort is the last dose of MenACWY and these individuals will be followed from 14 days after zero time until the earliest occurrence of the following: outcome of interest, death date (if known), plan disenrollment (if known) or 31 December 2022 (end of study period).

The outcomes of interest are gonococcal and chlamydial infections and only the first episode within the study period will be considered as event in case of repeated infections.

9.2. Setting

IQVIA PharMetrics® Plus is a longitudinal health plan database of adjudicated medical and pharmacy claims, including patient enrollment data for national and sub-national health plans and self-insured employer groups in the US. Administrative claims and enrollment data available during 01 January 2016 and 31 December 2022 will be used in this study.

9.2.1. Inclusion Criteria

Patient records must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Individuals of approximately 15-30 years old (using July 1 of birth year) enrolled in a health plan available in PharMetrics Plus database during 01 January 2016 and 31 December 2021.

2. Individuals having at least 1 dose of MenACWY during 01 January 2016 and 31 December 2021.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

Individuals having any dose of Bexsero at any time during 01 January 2016 and 31 December 2021 and prior to the study

Individuals with missing demographic variables or dates of outcome diagnoses or vaccine administration (listed in Section 9.3).

9.3. Variables

In this study, the variables of interest are age, gender, state of residence, date of vaccination and the date of disease diagnosis.

Table 1. Variable List

Variable	Role	Operational Definition
Birth Year	Covariate	Birth year (age to be calculated based on July 1 of birth year)
Gender	Covariate	Male, Female, Unknown
Residence (ZIP code)	Covariate	First 3 digits of the zip code from individuals' most recent enrollment
MenACWY vaccination	Non-exposure	Current procedural terminology (CPT) codes and National Drug Codes (NDC) listed below
Trumemba vaccination	Exposure	CPT and NDCs listed below
Gonococcal infection	Primary Outcome	ICD-10-CM codes listed below
Chlamydial infection	Reference disease Outcome	ICD-10-CM codes listed below

Table 2. Diagnosis Codes for Identifying Gonococcal Infections

Code	Type
A540	ICD-10-CM
A5400	ICD-10-CM
A5401	ICD-10-CM
A5402	ICD-10-CM
A5403	ICD-10-CM
A5409	ICD-10-CM
A541	ICD-10-CM
A542	ICD-10-CM
A5421	ICD-10-CM
A5422	ICD-10-CM
A5423	ICD-10-CM
A5424	ICD-10-CM
A5429	ICD-10-CM
A543	ICD-10-CM
A5430	ICD-10-CM
A5431	ICD-10-CM
A5432	ICD-10-CM
A5433	ICD-10-CM
A5439	ICD-10-CM
A544	ICD-10-CM
A5440	ICD-10-CM
A5441	ICD-10-CM
A5442	ICD-10-CM
A5443	ICD-10-CM
A5449	ICD-10-CM
A545	ICD-10-CM
A546	ICD-10-CM
A548	ICD-10-CM
A5481	ICD-10-CM
A5482	ICD-10-CM
A5483	ICD-10-CM
A5484	ICD-10-CM
A5485	ICD-10-CM
A5486	ICD-10-CM
A5489	ICD-10-CM
A549	ICD-10-CM

Table 3. Diagnosis Codes for Identifying Chlamydial Infections

Code	Type
A55	ICD-10-CM
A560	ICD-10-CM
A5600	ICD-10-CM
A5601	ICD-10-CM
A5602	ICD-10-CM
A5609	ICD-10-CM
A561	ICD-10-CM
A5611	ICD-10-CM
A5619	ICD-10-CM
A562	ICD-10-CM
A563	ICD-10-CM
A564	ICD-10-CM
A568	ICD-10-CM
A71	ICD-10-CM
A710	ICD-10-CM
A711	ICD-10-CM
A719	ICD-10-CM
A74	ICD-10-CM
A740	ICD-10-CM
A748	ICD-10-CM
A7481	ICD-10-CM
A7489	ICD-10-CM
A749	ICD-10-CM

Table 4. Current Procedural Terminal Codes and National Drug Codes for Identifying MenACWY Vaccination

Code	Type	Description
90734	CPT	Menactra/Menveo Vaccination
90619	CPT	Menquadfi Vaccine
49281-0589-05	NDC	Menactra Vaccine
46028-0208-01	NDC	Menveo Vaccine
58160-0955-09	NDC	Menveo Vaccine
49281-0589-58	NDC	Menactra Vaccine
49281-0590-58	NDC	Menquadfi Vaccine
46028-0218-11	NDC	Menveo Vaccine
58160-0958-01	NDC	Menveo Vaccine
58160-0959-01	NDC	Menveo Vaccine
46028-0219-11	NDC	Menveo Vaccine
54569-5687-01	NDC	Menactra Vaccine
50090-1890-01	NDC	Menactra Vaccine
49281-0590-05	NDC	Menquadfi Vaccine

Table 5. Current Procedural Terminal Codes and National Drug Codes for Identifying Trumemba (fHbp) Vaccination

Code	Type	Description
90621	CPT	Trumenba Vaccination
00005-0100-01	NDC	Trumenba Vaccine
00005-0100-02	NDC	Trumemba Vaccine
00005-0100-05	NDC	Trumenba Vaccine
00005-0100-10	NDC	Trumenba Vaccine

Table 6. Current Procedural Terminal Codes and National Drug Codes for Identifying Bexsero 4CMenB Vaccination

Code	Type	Description
90620	CPT	Meningococcal recombinant protein and outer membrane vesicle (OMV) vaccine, serogroup B (MenB-4C), 2 dose schedule, for intramuscular use
46028011401	NDC	Bexsero vaccine
46028011402	NDC	Bexsero vaccine
46028011411	NDC	Bexsero vaccine
58160097602	NDC	Bexsero vaccine
58160097606	NDC	Bexsero vaccine
58160097620	NDC	Bexsero vaccine

Additional details will be include in the Statistical Analysis Plan (SAP).

9.4. Data Sources

The data for this retrospective secondary data analysis is a large third party payer database, the IQVIA PharMetrics Plus (Pfizer 03 April 2023 version). PharMetrics Plus is a health plan claims database comprised of fully adjudicated medical and pharmacy claims for more than 210 million unique enrollees since 2006. Data contributors to the database are largely commercial health plans. It is representative of the commercially insured US national population for patients under 65 years of age. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs, and detailed enrollment information. All data are compliant to the Health Insurance Portability and Accountability Act (HIPAA) to protect patient privacy. The database is used in a variety of life sciences and commercial effectiveness studies. Over 250 peer reviewed publications have used PharMetrics Plus data.

9.5. Study Size

This is an exploratory study, thus no hypothesis was generated. All eligible individuals will be included in the study.

For the sample size estimation, we wished to detect a vaccine effectiveness against gonococcal infection of 20% or more with an onset from 14 days after receipt of both TRUMENBA and MenACWY. A Cox regression of the log hazard ratio on a covariate with a standard deviation of 1.50 to achieve 80% power at a 0.05 significance level to detect a regression coefficient equal to -0.2200, we need a sample of 15,669. The sample size was adjusted for an anticipated overall event rate of 0.0046. We will have 520,392 samples in the study database illustrating that we have adequate samples to conduct the analysis.

9.6. Data Management

This study will use secondary data collected in the PharMetrics Plus database, which is de-identified and HIPAA compliant. The data will be made accessible only to individuals working on the current study. No attempt will be made to identify individual patients, hospitals, or physicians. Analyses will be conducted using Statistical Analysis System (SAS) 9.4 (SAS Institute, Cary, NC).

The analytic files will include person-level data, including information on baseline demographic and clinical characteristics, study outcomes, and vaccination information as described in the variable section above. Data for this study will be processed and managed by Pfizer, Inc., and all analyses will be performed by Pfizer.

9.7. Data Analysis

The zero time is the date of Trumenba vaccination for the exposed group and the date of MenACWY for the unexposed group. We will assess gonococcal infections that occurred between i) 14 days after zero time and 365 days ii) 14 days after zero time and 730 days, iii) 14 days after zero time and 1095 days, and iv) 14 days after zero time and till end of the study period (31Dec2022). We will censor the data in the event of interest, death date (if known), plan disenrollment (if known), target end date, or the end of the study period, whichever comes first. In descriptive analyses, we will fit Kaplan-Meier curves. We will also create unadjusted and covariate adjusted Cox proportional hazard regression models verifying first that the proportionality assumption was satisfied for all independent variables. Hazard ratios (HRs) will be estimated by exponentiation of the coefficient for the vaccine variable in these models, with vaccine effectiveness estimated as (1–HR)×100%. SEs for the coefficients will be used to estimate p values and CIs for the HRs. If a covariate does not satisfy the assumption of proportionality, we will exclude the variable for the multivariable model and will perform the stratified analysis using the covariate.

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 Pfizer. 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.

9.8. Quality Control

Only observed data will be used in measuring study variables. It is anticipated that demographic information will be available for nearly all individuals in the study population. All other variables will be defined based on the presence of specific data (eg, diagnosis, procedure, and drug codes) in the analytic file; the absence of such data will be assumed to indicate the absence of the characteristic/event captured by the variable.

9.9. Strengths and Limitations of the Research Methods

Strengths

A significant strength of observational retrospective analyses is that they provide a better understanding of the study population in real world clinical practice as compared to the controlled conditions of a clinical trial.

Limitations

There are several limitations in this study. Given that this is an observational study using health care administrative claims data, residual confounding due to missing or unmeasured information is possible. To examine this, we will assess the effect of meningococcal vaccination on another sexually transmitted disease occuring, at the same age group, as reference disease outcome. If the HRs in any of these models are less than 1.0, it would indicate that residual confounding exists and may result in adjustment of our vaccine effectiveness (VE) estimates.

Second, health care administrative claims data will be available from 01 January 2016 through 31 December 2022. It is possible that some participants may have received a Trumenba vaccination prior to January 1, 2016 or during a period in which we do not have their claims data and be misclassified as unvaccinated with Trumenba. This may underestimate Trumenba vaccine effectiveness because the Men-ACWY-only cohort will include Trumenba vaccinated patients.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

The study databases will be de-identified prior to their release to study investigators, as set forth in the corresponding Data Use Agreement. The study databases have been evaluated and certified by an independent third party to be compliant with the HIPAA of 1996 statistical de-identification standards and to satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the HIPAA Privacy Rule regarding the determination and

documentation of statistically de-identified data. Use of the study databases for health services research is therefore fully compliant with the HIPAA Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects (45 Code of Federal Regulations [CFR] 46 §46.101) and IRB approval is not required.

10.4. 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 Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Formal communication of the results of this research will be done by Pfizer authors through peer-reviewed publications. For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if party responsible for collecting data from the participant 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.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

Document Approval Record

Document Name:	B1971066_Non Interventional Study Protocol_18April2023
Document Title:	B1971066_Non Interventional Study Protocol_18April2023

Signed By:	Date(GMT)	Signing Capacity
PPD	19-Apr-2023 19:31:05	Business Line Approver
	19-Apr-2023 21:52:10	Author Approval
	21-Apr-2023 16:33:13	Scientific Review