NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Risk of Safety Events Among Patients with ulcerative colitis (UC) and psoriatic arthritis (PsA) Treated with Tofacitinib and Other Advanced Treatments in the United States (US)
Protocol number	A3921431
Protocol version identifier	3.0
Date	08 November 2024
EU Post Authorization Study (PAS) register number	EUPAS103443
Active substance	L04AA29 - Tofacitinib citrate
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	*Research questions:* What are the distributions of demographic and clinical characteristics of patients with UC and PsA treated with tofacitinib and other advanced treatments in the US? What is the risk of select safety events (major adverse cardiovascular events (MACE), venous thromboembolic disease (VTE, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE), malignancy (excluding (NMSC)) and serious infections) in UC and PsA patients receiving tofacitinib and other forms of advanced treatment in the US, and are these risks modified by factors of interest? What are crude and adjusted relative risks of select safety events when comparing mutually exclusive comparator groups of tofacitinib and other forms of advanced treatment within UC and PsA populations in the US? *Objectives*: • To estimate the frequency distributions of demographic and clinical characteristics among patients on tofacitinib and other forms of advanced treatment in UC and PsA populations.

	• To estimate crude incidence rates (IRs) of select safety events among UC and PsA populations on tofacitinib and other forms of advanced treatment. To estimate the crude and adjusted hazard ratios (HRs) of select safety events comparing tofacitinib and other forms of advanced treatment in UC and PsA populations.
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AS	Axial spondyloarthritis
BID	twice a day
CDC	Centers for Disease Control
CCI	Charlson Comorbidity Index
CDM	Clinformatics Data Mart
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPT	Current procedure terminology
CV	Cardiovascular
DVT	Deep vein thrombosis
EIMs	Extraintestinal Manifestations
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMR	Electronic medical records
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases – Ninth Revision

Abbreviation	Definition
ICD-10	International Classification of Diseases – Tenth Revision
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IP	Inverse probability
IRB	Institutional Review Board
IRs	Incidence Rates
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
KH	Komodo Health
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NDC	National Drug Center
NHIS	National Health Interview Survey
NMSC	Non-melanoma skin cancer
NSAIDs	Nonsteroidal anti-inflammatory drugs
PASS	Post-authorization safety study
PE	Pulmonary embolism
PsA	Psoriatic arthritis
PTCA/PCI	Percutaneous transluminal coronary angioplasty / percutaneous coronary intervention
RA	Rheumatoid arthritis
SAP	Statistical Analysis Plan
TNFi	Tumor necrosis factor inhibitor

Abbreviation	Definition
UC	Ulcerative colitis
US	United States
VTE	Venous thromboembolic disease

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

[redacted]			

4. ABSTRACT

Stand Alone document, see ANNEX 1.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	22 November 2023	Administrative	3. Responsible Parties	Peter Hur removed as Principal Investigator and replaced with You-Li Ling	Peter Hur no longer tofacitinib lead from Value and Evidence.
2.0	22 November 2023	Substantial	9.2 Setting 9.3 Variables 9.4 Data Sources 9.5 Study Size 9.7.3 Comparative Analyses 9.9 Strengths and Limitations of Research Methods	Remove Optum dataset and all associated analyses	Internal resourcing constraints do not allow for this analysis to be conducted internally; no funding for external vendor. Added value of additional analysis limited given small sample size and potential overlap with Komodo dataset. No Optum analysis had been conducted at the time of the amendment. Only Optum analysis included CV death as outcome, therefore that outcome as well as the MACE-3 composite which included CV death have been removed.
2.0	22 November 2023	Substantial	9.3 Variables	Variables list, except outcomes, moved to SAP	Given new sensitivity analysis with an extended list of variables, new list now included in the SAP.
3.0	08 November 2024	Substantial	6. Milestones	Update milestones to reflect updated end of data collection and study report due date.	Further sensitivity statistical analyses requested from the RMC required reconsideration of variables in the dataset and ongoing data analysis; therefore later end of data collection date than originally anticipated is needed.

6. MILESTONES

Milestone	Planned date
Start of data collection	31 March 2023
End of data collection	31 December 2024
Registration in the EU PAS register	10 March 2023
Final study report	30 November 2025

7. RATIONALE AND BACKGROUND

Tofacitinib is a Janus kinase (JAK) inhibitor approved for 5 indications in the US: adults with moderately to severely active rheumatoid arthritis (RA), adults with active PsA, adults with moderately to severely active UC, adults with active ankylosing spondylitis, and patients 2 years of age or older with polyarticular course juvenile idiopathic arthritis. As a commitment to the Food and Drug Administration (FDA), Pfizer conducted ORAL Surveillance Study (A3921133), a post-authorization safety study (PASS). Study A3921133 evaluated the risk of major adverse cardiovascular event (MACE) and malignancies excluding NMSC with tofacitinib (5 and 10 mg BID) versus tumor necrosis factor inhibitor (TNFi) in patients with moderately or severely active RA who had an inadequate response to methotrexate and who were 50 years of age or older and had at least 1 additional cardiovascular (CV) risk factor. For the combined tofacitinib doses (5 and 10 mg BID) versus TNFi, non-inferiority was not shown for either adjudicated MACE or malignancies (excluding NMSC).[1]

Given that the population enrolled into Study A3921133 were RA patients enriched for CV risk, it is important to contextualize the findings of the study and its implications for real world use of tofacitinib for its approved or proposed indications. Within the UC population, there is limited information on safety events related to tofacitinib using real world data that included an active comparator of other advanced therapies.[2-6] Previous studies included small sample sizes of UC patients on tofacitinib (n $\leq$300) and/or limited follow-up time (median 6-12 months). Further, only 2 of these studies were conducted in the U.S., and there are no active comparator studies examining malignancy outcomes in real world UC patients on tofacitinib. To date, within the PsA population, there are no real world, long-term (>6 months) studies examining safety outcomes in patients on tofacitinib compared to other therapies.[7]

This non-interventional study aims to provide additional insights into IRs of select safety outcomes in UC and PsA populations using active comparator groups in routine clinical practice in the U.S. The results are intended to provide epidemiologic context for interpreting and applying the relative risk estimates for safety events in clinical decision making for real-world UC and PsA patients eligible for tofacitinib receipt. This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

Research questions addressed by this study are as follows:

What are the distributions of demographic and clinical characteristics of patients with UC and PsA on tofacitinib and other forms of advanced treatment in the US?

What is the risk of select safety events (MACE, VTE (DVT and PE), malignancy excluding NMSC, and serious infections) in UC and PsA patients receiving tofacitinib and other forms of advanced treatment in the US, and are these risks modified by factors of interest?

What are the crude and adjusted relative risks of select safety events when comparing mutually exclusive comparator groups of tofacitinib and other forms of advanced treatment within UC and PsA populations in the US?

8.2. Study Objectives

8.2.1. Primary Objectives

The primary objectives for this study are:

a. To estimate the frequency distributions of demographic and clinical characteristics among tofacitinib and other forms of advanced treatment in UC and PsA populations.

b. To estimate crude incidence rates (IRs) of select safety events among UC and PsA populations on tofacitinib and other forms of advanced treatment.

c. To estimate the crude and adjusted HRs of select safety events comparing tofacitinib and other forms of advanced treatment in UC and PsA populations.

8.2.2. Secondary Objectives

Secondary study objectives are as follows:

To stratify estimated HRs of select safety events among populations of interest as stipulated in Section 8.2.1 Objective c, by the following factors:

1. Age < or ≥50 years.
2. Age < or ≥65 years.
3. Systemic glucocorticoid use at baseline.
4. Previous biologic or other advanced treatment use prior to baseline.
5. History of MACE or VTE.

9. RESEARCH METHODS

9.1. Study Design

This is a population-based retrospective cohort study of adults (ages ≥18 years of age) with UC and PsA identified through a US data source.

9.2. Setting

The populations under study will be adult patients diagnosed with UC or PsA with an index date between 31 May 2018 and 30 September 2022 (for UC), or between 15 December 2017 and 30 September 2022 (for PsA). This study will use a US administrative database (Komodo's Healthcare Map). Identification of disease populations, safety outcomes of interest, and drugs prescribed will be implemented using International Classification of Diseases – Ninth Revision (ICD-9) or International Classification of Diseases – Tenth Revision (ICD-10) codes, current procedure terminology (CPT) procedure codes, and prescribing data (eg, national drug center (NDC) codes) in the patients' records.

9.2.1. Definition of Study Cohort

Upon establishing that a patient has an indication of interest, patients will be followed from subsequent date of new drug initiation (index date) until the earliest date of death, end of study period, the event of interest, treatment switch, treatment discontinuation (+ 90 days),[8] or end of enrollment in the database.

Exposure to therapies will be defined using the NDC for dispensed or administrated medications and, where relevant, procedure codes for injection or infusion. New users will be defined as those with a prescription for a drug they had not previously been prescribed during the 365 days baseline period. Patients who discontinue an index therapy are eligible for selection into a second category as of the date they begin one of the drugs in another category.

Treatment discontinuation will be defined as a period of >90 days without a dispensation of the same treatment after the period covered by the previous reimbursement, or switch date to another biologic or advanced treatment (ie, date of reimbursement). Further information is defined in the statistical analysis plan (SAP).

9.2.1.1. UC Exposure

Exposure within the UC population will be classified into 6 categories:

- Tofacitinib;
- Ustekinumab;
- Vedolizumab;
- Ozanimod*;
- TNFi (adalimumab, certolizumab pegol, golimumab, infliximab);
- TNFi (adalimumab only).

*If sample size is deemed insufficient, this variable will be removed as an exposure group.

9.2.1.2. PsA Exposure

Exposure in the PsA population will be classified into 6 categories:

- Tofacitinib;
- Ustekinumab (IL-12/-23i)**;
- Risankizumab (IL-23i)**;
- Secukinumab (IL-17i) or ixekizumab (IL-17i)**;
- TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab);
- TNFi (adalimumab only).

**If sample size is deemed insufficient, these exposure groups will be combined into a “non-TNFi” group.

9.2.2. Inclusion Criteria

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

1. Aged ≥18 years at index date.
2. Evidence of at least 1 inpatient diagnosis code or 2 outpatient diagnosis codes ≥30 days apart for UC or PsA on or prior to index date (index date is the date of drug initiation).
3. Evidence of initiation for at least 1 approved advanced treatment for the corresponding identified indication as defined in Section 9.2.1.
4. At least 365 days of continuous enrollment in database prior to index date.

9.2.3. Exclusion Criteria

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

1. Tofacitinib users with prescriptions of approved JAK inhibitors other than tofacitinib at or prior to index date.

2. Other advanced treatment users with a history of use of any JAK inhibitor.

For the PsA patient cohort, the following additional exclusion criteria apply:

3. Evidence of at least 1 inpatient diagnosis code or 2 outpatient diagnosis codes ≥30 days apart for RA.

9.3. Variables

Variables utilized in this study include baseline demographics and clinical characteristics, comorbidities, and medications. All variable definitions will be specifically defined in the statistical analysis plan (SAP), including code lists and time periods of interest. Outcomes of interest analyzed in the study are listed in Table 1.

Table 1. Variables Defining Outcomes, Exposures, and Covariates

Variable	Role	Operational definition[a]
OUTCOMES		
Stroke	Outcome	Inpatient diagnosis of ischemic or hemorrhagic stroke (fatal or non-fatal)
MI	Outcome	Inpatient diagnosis of acute MI (fatal or non-fatal)
Venous thromboembolism (VTE)	Outcome	Inpatient diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE)
DVT	Outcome	Inpatient diagnosis of DVT
PE	Outcome	Inpatient diagnosis of PE
Serious infections	Outcome	Hospitalized infections
Malignancy (excluding NMSC)	Outcome	Diagnosis of malignancy (excluding NMSC)
Colorectal cancer	Outcome	Diagnosis of colorectal cancer
Melanoma	Outcome	Diagnosis of melanoma
Lung Cancer	Outcome	Diagnosis of lung cancer
Breast Cancer	Outcome	Diagnosis of breast cancer
Lymphoma	Outcome	Diagnosis of lymphoma

Variable	Role	Operational definition[a]

a. Where applicable codes and other definitions to be further defined in the SAP.

9.4. Data Sources

Komodo's Healthcare Map is a real-world dataset which integrates disparate sources of patient-level data to map longitudinal patient journeys. Komodo Health (KH) pulls de-identified, patient-level claims data from Clearinghouse, Payer (150+ payer), and Provider data sources to follow patients as they move through the healthcare system. The patient-centric database includes both open and closed claims data and is enriched with data from EMR and other sources. While Komodo's closed dataset (payer complete dataset) allows researchers to conduct a robust claims-based analysis with a large sample size and long follow-up periods, Komodo's open dataset brings additional historical data. Regardless of the data source, continuous enrollment is the key criterion for research-grade data extraction. Komodo's closed dataset (payer complete dataset) will be used for this analysis.

Komodo currently has real world data on more than 325 million patients that are well-distributed geographically across the U.S. Table 2 illustrates this further by comparing Komodo's 2019 patient population (from closed dataset) with the CDC's 2019 National Health Interview Survey (NHIS) of insured patients. The database covers all the US census regions. The all-payer claims data is fully-adjudicated. Komodo's Healthcare Map is a patient-centered claims dataset that complies with HIPAA.

Table 2. Regional Distribution of Komodo Health Dataset (Updated June 6, 2022)

U.S. Region	Komodo Data	NHIS 2019
Northeast	19.5%	16.9%
South	38.0%	36.5%
Midwest	21.6%	22.2%
West	20.9%	24.4%

Table 3. Age Distribution of Komodo Health Dataset

Age Range	Komodo	NHIS 2019
0 – 9	11.7%	11.3%
10 – 19	12.0%	12.3%
20 – 29	10.9%	9.6%
30 – 39	11.6%	12.6%
40 – 49	11.5%	11.3%
50 – 59	13.7%	12.8%
60 – 69	13.8%	14.4%
70 – 79	9.4%	9.9%
80+	5.5%	5.6%

Table 4. Gender Distribution of Komodo Health Dataset

Gender	Komodo Data oi	NHIS 2019
Female	54.8%	54.0%
Male	45.2%	46.0%

KH research team strives to provide the highest quality of scientific rigor and accurate, quality results. The research process includes, but is not limited to:

- To ensure a study approach is of sound scientific design with appropriate clinical context, a clinical expert from KH is involved in this study. The clinical expert(s) provide background on the disease state, set up appropriate patient cohorts, and provide a list of validated codes to identify patients' relevant comorbidities, procedures, and treatments. KH ensures all work is reviewed by an additional secondary clinical expert to ensure high quality and accuracy of these codes.

- To generate the most accurate dataset for analysis, KH will incorporate quality assurance checks throughout the process, which may include individual-level record/element review and double programming, as needed.

- Analysis is performed by the data scientists or analysts under the supervision of the lead researcher, epidemiologist, and biostatistician. The lead researcher, epidemiologist, and biostatistician will review intermediary and final output to ensure accuracy. For any modeling, the variable distributions, model assumptions, and model fit will also be assessed by the research team.

KH runs data quality checks at all points in data ingestion/mastering/normalization and standardization process by developing tests of the data pipeline using data quality assurance tools.

For example, as data moves through the pipeline—from ingestion to deployment—KH runs analytics that report on: (1) data consistency, (2) data integrity and accuracy, (3) data

completeness, and (4) timeliness. A variety of different tests and acceptance criteria are completed to profile the quality of the data.

9.5. Study Size

Preliminary feasibility analyses indicate sample sizes range of approximately 2,391 and 3,411 new tofacitinib users with 12 months of continuous enrollment for UC and PsA populations, respectively, in the KH dataset (among open and closed claims). Detailed sample size requirements and available patient counts are described in a separate SAP.

9.6. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using statistical software such as SQL and Python. Versions of packages will be documented to assure reproducibility.

9.7. Data Analysis

An overview of the planned analyses is provided below.

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. Descriptive Analyses

Baseline demographic and clinical characteristics will be tabulated among the 2 cohorts of patients (UC and PsA), and each exposure category within the disease cohorts. Comorbidities and history of prescription medications will be measured and described with summary statistics for the look-back period of 12 months prior to the index date.

9.7.2. Incidence Rates

Number of events, person-years at risk, and crude- and age-standardized incidences will be calculated for each outcome. IRs for select safety events will be calculated with person-time at risk starting on the index date and ending on the date of a censoring event: 1) death, 2) end of study period which is 30 September 2022, 3) the event of interest, 4) treatment switch, 5) treatment discontinuation (+ 90 days),[8] or 6) end of enrollment in the database.

IRs per 100 person-years will be calculated based on the number of new events divided by the sum of the duration of patient exposures from the index date to censoring date during the risk period.

Details for handling observable person time will be detailed in the SAP.

9.7.2.1. Incidence Rates within UC Population

IRs for safety outcomes among the following groups within the UC population will be calculated:

- Tofacitinib, vedolizumab, ustekinumab, ozanimod*, and specific TNFi# new-users;
- Tofacitinib new-users;

- Vedolizumab new-users;
- Ustekinumab new-users;
- Ozanimod new-users*;
- New-users of a specific TNFi#;
- Adalimumab new-users.

*If sample size is deemed insufficient, this variable will be removed as an exposure group.

#Prior use of another TNFi is allowed.

9.7.2.2. Incidence Rates within PsA Population

IRs for outcomes among the following groups within the PsA population will be calculated:

- Tofacitinib, ustekinumab, risankizumab, secukinumab, ixekizumab, and TNFi# new-users;
- Tofacitinib new-users;
- Ustekinumab new-users**;
- Risankizumab new-users**;
- Secukinumab or ixekizumab new-users**;
- New- users of a specific TNFi#;
- Adalimumab new-users.

**If sample size is deemed insufficient, these exposure groups will be combined into a “non-TNFi” group.

#Prior use of another TNFi is allowed.

9.7.3. Comparative Analyses: Hazard Ratios using Propensity Score Matching to Control for Confounding

Hazard rates (hazard ratios) will be estimated using an inverse probability (IP) weighted Cox proportional hazards model with time since treatment start as timescale. All assumptions of the Cox proportional hazards model will be tested to ensure appropriate use. IP weighting will be used to control for potential confounding variables at baseline, and selected based on *a priori* knowledge and statistical properties of the cohorts under study. Statistical methods for IP weighting will be detailed in the SAP. Briefly, confounding variables in the weighting model will include: age, gender, year entered into cohort, number of prior biologics used (categorical: 0, 1, $\geq$2), baseline glucocorticoid use (yes/no), baseline conventional treatment use (yes/no), baseline NSAIDs use (yes/no), baseline anti-platelet use (yes/no), baseline anti-coagulant use (yes/no), baseline statin use (yes/no), baseline oral contraceptive or hormonal therapy use (yes/no), baseline diabetes (yes/no), baseline non-alcoholic fatty liver disease (yes/no), baseline CKD/dialysis (yes/no), other

baseline immune deficiencies or immunological conditions (yes/no), history of MACE or VTE (yes/no) and history of malignancy (yes/no). The model will also incorporate censoring. Variables incorporated into the weighting may be reassessed if not successfully implemented (eg, model fails to converge). HRs will be calculated only if the smallest cell contains 5 or more events. Stabilized weights will be used to increase statistical efficiency of the HR estimate,[10] and weights will be truncated at the 1st and 99th percentiles of their distribution. Robust variance estimation will be used to calculate 95% CI to account for weighting.

9.7.3.1. Hazard Ratios within UC Population

- Tofacitinib (reference) vs. Vedolizumab.
- Tofacitinib (reference) vs. Ustekinumab.
- Tofacitinib (reference) vs. Ozanimod*.
- Tofacitinib (reference) vs. TNFi.
- Tofacitinib (reference) vs. TNFi (adalimumab only).

*If sample size is deemed insufficient, this variable will be removed as an exposure group.

9.7.3.1.1. Stratification Factors for UC

HRs will also be stratified by the following factors (see Section 8.2.2):

5. Age < or ≥50 years.
6. Age < or ≥65 years.
7. Systemic glucocorticoid use at baseline.
8. Previous biologic or other advanced treatment use prior to baseline.
9. History of MACE or VTE.

9.7.3.2. Hazard Ratios within PsA Population

- Tofacitnib (reference) vs. Ustekinumab**.
- Tofacitinib (reference) vs. Risankizumab**.
- Tofacitinib (reference) vs. Secukinumab or Ixekizumab**.
- Tofacitnib (reference) vs. TNFi.
- Tofacitinib (reference) vs. TNFi (adalimumab only).

**If sample size is deemed insufficient, these exposure groups will be combined into a “non-TNFi” group.

9.7.3.2.1. Stratification Factors for PsA

HRs will also be stratified by the following factors (see Section 8.2.2):

1. Age < or ≥50 years.
2. Age < or ≥65 years.
3. Systemic glucocorticoid use at baseline.
4. Previous biologic or other advanced treatment use prior to baseline.
5. History of MACE or VTE.

9.7.3.3. Sensitivity Analyses

Sensitivity analyses will also be conducted for comparative (HR) analyses and detailed in the SAP.

9.8. Quality Control

Analyses are programmed according to the specifications in the protocol, and if applicable, the SAP, and documented in a programming plan. Final deliverables will be reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks will be documented in the programming plan.

9.9. Strengths and Limitations of the Research Methods

The Komodo database is large and covers a wide geographic area; however, limitations that are general to all claims database analyses as well as those specific to this study should be noted. Diagnosis of UC and PsA will be identified using ICD-10-CM diagnosis codes, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes. Where possible, validated algorithms will be used. The baseline period of this study is of limited duration thus baseline comorbidities and risk factors occurring outside of this baseline period may not be captured, which may lead to misclassification.

Information on prescriptions for outpatients does not necessarily indicate that the medication was consumed or taken as prescribed; similarly, medications filled over-the-counter or provided as samples by the physician will not be recorded in the database.

Cases not requiring treatment or office visits tend to be systematically under-recorded in such databases; therefore, it is possible that this study will only capture severe manifestations of such disorders.

Outcomes were also captured by way of medical claims, which may have some degree of misclassification. To reduce the potential for misclassification of outcomes, outcomes were defined using definitions previously validated in healthcare data, such as claims databases where possible. Additionally, follow-up time may not be sufficient to capture outcomes such as malignancy, which may develop years after exposure.

Study results may not be generalizable outside of the insured population, or populations outside of the U.S.

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)

IEC/IRB review was 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

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

One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed.

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 the 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

Number	Document reference number	Date	Title
1	Section 4	22 November 2023	Abstract

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.