NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Retrospective Database Study to Evaluate Rates of Influenza and Related Diagnoses between Patients Treated with Tofacitinib and Other Systemic Therapies within Cohorts of RA, PsA, and UC Patients: A Post-Authorization Safety Study of Tofacitinib
Protocol number	A3921383
Protocol version identifier	2.0
Date	29 October 2021
EU Post Authorization Study (PAS) register number	EUPAS39242
Active substance	L04AA29
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	The research question addressed by this study is: What are the frequencies and incidence rates of influenza and influenza like illness and the frequencies and incidence proportions of influenza-related clinical outcomes, including mortality, among persons prescribed Xeljanz or other systemic therapies among cohorts of patients with RA, PsA and UC? Objectives: To describe demographics and clinical characteristics of RA, PsA, and UC patient cohorts overall and within each treatment strata.

	To describe the frequency and incidence rates of influenza infections and influenza like illness and the frequency and incidence proportions of influenza-related clinical outcomes, including mortality, in patients receiving tofacitinib and other systemic therapies within RA, PsA and UC cohorts, stratified by age (<65 and 65 and older)
Authors	Redacted Redacted Redacted RedactedRedacted RedactedRedacted Redacted Redacted RedactedRedacted

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
bDMARD	biologic disease modifying antirheumatic drug
CI	confidence interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPT	current proecedural terminology
CVA	cerebrovascular accident
csDMARD	conventional synthetic disease modifying antirheumatic drugs
DMARD	disease modifying antirheumatic drugs
DVT	Deep Vain Thrombosis
EHR	electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HD	Heart disease
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-9-PCS	International Classification of Diseases, Ninth Revision Procedure Classification System
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision Procedure Classification System
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHD	Instance Health Data
IL-6	interleukin 6
ILD	Interstitial lung disease
ILI	Influenza like illness
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JAK	janus kinase

Abbreviation	Definition
JAKi	janus kinase inhibitors
MI	Myocardial infarction
NDC	National Drug Center
NLP	Natural Language Processing
PASS	post-authorization safety study
PsA	psoriatic arthritis
PVD	Peripheral vascular disease
RA	rheumatoid arthritis
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNFi	tumor necrosis factor inhibitor
UC	ulcerative colitis
US/USA	United States/United States of America
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	29 October 2021	Title Page	EUPAS number added	EUPAS number received after final protocol submitted
			In the "research question and objectives," the terms "associated morbidity" and "complications" are replaced with "clinical outcomes."	The use of several terms to describe the study's clinical outcomes was confusing. The new term "clinical outcomes" is an efficient umbrella term that accurately describes the studies various secondary outcomes.
			The research question and study objectives are clarified to explicitly state that frequencies and incidence rates will be used to measure influenza and influenza-like illness outcomes and frequencies and incidence proportions will be used to measure influenza clinical outcomes.	The research question and study objectives were unclear regarding which measure(s) would be used to measure influenza, influenza-like illness, and influenza clinical outcomes.This amendment explicitly names the measures that will be used. These measures are now consistent with other statements in the protocol and with the Statistical Analysis Plan (SAP).
			New author added	The new study lead assumed the role of co-author.
		Section 3: Responsible Parties	Updating study personnel	To reflect personnel changes
		Section 6: Rationale and Background	The specific goals listed at the end of this section are removed.	The statement of the goals at the end of Section 6 is redundant with their statement in Section 7.
		Section 7: Research Questions and Objectives	The research question and study objectives were clarified to explicitly state that frequencies and incidence rates of influenza	In the previous version of the protocol, the research question and study objectives were unclear regarding which

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			and influenza like illness and the frequenciesa and incidence proportions of influenza complications will be used..	measure(s) would be used for influenza, influenza like illness, and clinical outcomes of influenza illness. This amendment clearly identifies measures (frequencies and incidence rates and incidence proportions) that are consistent with other statements in the protocol and in the SAP.
			The terms "associated morbidity" and "complications" are replaced with "clinical outcomes."	The use of several terms to describe the clinical outcomes of influenza illness was confusing. The new term "clinical outcomes" is an efficient umbrella term that accurately describes the studies various outcomes of influenza illness.
			An assessment of the frequencies of influenza cases' clinical outcomes *in each influenza season* is added as a secondary objective of the study.	The protocol already identifies influenza cases' clinical outcomes as a secondary outcome for the *full study* period; this amendment adds this outcome to those outcomes already assessed *by influenza season,* which makes the protocol consistent with the SAP.
		Sub-section 8.2.2. Definition of Study Cohort	Removal of upadacitinib from the JAKi treatment group	Upadacitinib was approved for the RA indication after the end of the study period
		Sub-section 8.3. Variables	The "Role" of the Baseline csDMARD variable is changed from "Baseline characteristic/exposure (concomitant medication)" to "Baseline	The term "concomitant medication" is superfluous and it is not used to describe the role of the other exposure groups.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			characteristic/exposure"	
			The "Role" of the following variables is simplified to "Baseline characteristic" while the terms "Potential confounder" and/or "Risk factor" are removed from the "Role": age (continuous), age (categorical), gender, race, ethnicity, region, insurance, BMI, smoking, hypertension, hyperlipidemia, coronary artery disease, history of serious infections, malignancy, pregnancy, interstitial lung disease/COPD/Asthma, venous thromboembolism, heart disease, history of cerebrovascular accident, peripheral vascular disease, other immune deficiencies, HIV/AIDS, diabetes, chronic kidney disease/dialysis, liver disease, and corticosteroid use.	None of these variables was described elsewhere in the protocol or in the SAP as a potential confounder or risk factor, and they were not analyzed as potential confounders or risk factors.
			The "Role" of influenza-like illness is changed from "Endpoint" to "Primary Endpoint."	The SAP and elsewhere in the protocol clearly indicate that influenza-like illness is a primary endpoint, which is the term used in the protocol to describe the role of the study's other primary endpoint, influenza.
			The "Role" of influenza vaccine is changed from "Potential Confounder" to "Secondary Endpoint."	Influenza vaccine was not described elsewhere in the protocol or in the SAP as a potential confounder, and it was not analyzed as a potential confounder. In both documents, it is stated that influenza

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				vaccination will be "reported" for each influenza season, with no additional elaboration.
			The "Role" of the following variables is changed from either "Endpoint/Complication" or "Endpoint" to "Secondary Endpoint": Influenza complication - pneumonia, Influenza complication - stroke or myocardial infarction, Influenza complication - neurological disorder, corticosteroid use, methotrexate use, azathioprine use, influenza hospitalization, in-hospital death, and death.	The SAP and elsewhere in the protocol clearly indicate these variables are secondary endpoints – the other terms used to describe their roles in the protocol are superfluous or under-specified.
		Section 5	Updated Study Report Date	Administrative

5. MILESTONES

Milestone	Planned date
Start of data collection	15 Feb 2021
End of data collection	8 March 2021
<Registration in the EU PAS register>	TBD
Final study report	8 Jan 2023

6. RATIONALE AND BACKGROUND

Influenza is a seasonal acute respiratory illness caused by influenza A, B, or C viruses.[1] Annual incidence of influenza in the general population is estimated as 5%-10% of adults, according to the World Health Organization.[2] Influenza can be complicated with serious conditions, such as viral and bacterial pneumonia, acute respiratory decompensation, myocarditis and exacerbation of underlying pulmonary disease.[1] Despite the availability of vaccines and antiviral therapy, a large number of hospitalizations and deaths follow influenza each season.

Patients with immune-mediated diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC) are known to have an increased risk of infections compared to the general population.[3,4] The increased overall infection risk in these patients has been attributed to immunological dysfunction associated with the etiology of the disease, presence of comorbid conditions and the impact of immunosuppressive drugs.[3]

A recent systematic review on the incidence of vaccine preventable infections concluded that patients with autoimmune inflammatory rheumatic disease are at higher risk for contracting influenza than the general population.[2] The most comprehensive description of influenza in RA patients is from a retrospective cohort study with data from a United States (US)commercial health insurance database from 2000-2007. This study found that incidence of seasonal influenza was 33% higher in RA patients than in matched controls and RA patients also had a 2.8-fold increase in incidence of complications. Controls were significantly more likely to have received influenza vaccination in this study.[5] A similarly designed study, with data from 2008-2011, found increased influenza incidence and hospitalization rates also in patients with UC.[6] Notably, in both these studies, use of biological drugs were not significantly associated with the rate of influenza or its complications.[5,6] A study of influenza among RA patients 50 and older with chronic obstructive pulmonary disease (COPD) similarly concluded that biologic disease modifying antirheumatic drugs (bDMARD) as a class (including a relatively small number of tofacitinib treated patients) were not associated with a higher risk of influenza infection, though power may have been limited to rule out risk of serious influenza infection where rates were numerically higher but the confidence interval (CI) included 1.[7] Apart from these above-mentioned studies, little is known about the association between treatment with immunosuppressive drugs, including Pfizer therapies, and the incidence of influenza and influenza-related complications in patients with RA, PsA and UC.
Tofacitinib has been approved to treat adult RA patients in the US since November 2012 and is currently also approved for the treatment of PsA and UC. Tofacitinib is an immunomodulating drug that inhibits the enzymatic activity of janus kinase (JAK)3, JAK1 and to a lesser extent JAK2, thereby inhibiting the cellular response to a wide range of inflammatory cytokines involved in immune regulation and inflammation.[7] Clinical trials and real-world evidence indicate that treatment with tofacitinib is associated with the same risk of infections as biological drugs.[8-13] An important exception is the risk of herpes zoster, ie, reactivation of the varicella zoster virus, which is higher with tofacitinib and the JAK inhibitor class than with other classes of advanced treatment.[12-15] There are currently no data

that indicate that the risk of other viral infections is increased with use of tofacitinib compared to other forms of advanced immunosuppression.

Guidelines on management of patients with immune-mediated disease in context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) indicate that there is uncertainty within the rheumatology and gastroenterology communities on the safety of JAK inhibitors (JAKi), including tofacitinib, in this setting.[16,17] Due to the broad immunosuppressive effect that includes impact on type I and type II interferons and the known risk of herpes zoster with JAK inhibitors, guidelines are based on a potentially increased risk of adverse outcome of viral infections, including respiratory viral infections, with this therapy compared to other classes. There is currently no clinical evidence to guide these decisions, but the recommendation for patients exposed to SARS-CoV-2 or with active or presumptive COVID-19 is to stop treatment with tofacitinib. Regarding alternative treatments, the recommendation is to stop them in patients with COVID-19 infection. The exception to the recommendation is for interleukin 6 (IL-6) inhibitors. There are some differences in the rheumatology and gastroenterology recommendations around the management of tumor necrosis factor inhibitors (TNFi) and other advanced therapies in patients exposed to SARS-CoV-2 but without symptoms.[16,17] A separate study (A3921380) is currently being conducted to evaluate the incidence and complications of COVID-19 infection in the same patient and treatment populations proposed for this study.

The overall goal of this retrospective observational study using a US real world database is to help inform prescribers and patients of the overall safety of tofacitinib and other treatments for RA, PsA and UC with respect to the development of influenza, influenza like illness (ILI) and associated complications.

7. RESEARCH QUESTION AND OBJECTIVES

The research question addressed by this study is:

What are the frequencies and incidence rates of influenza and influenza like illness and the frequencies and incidence proportions of influenza-related clinical outcomes, including mortality, among persons prescribed tofacitinib or other systemic therapies among cohorts of patients with RA, PsA and UC?

The objectives for this study are:

- To describe demographics, comorbidities and clinical characteristics of RA, PsA, and UC patient cohorts overall and within each treatment strata.

- To describe the frequency and incidence rates of influenza infections and influenza like illness and the frequency and incidence proportions of influenza-related clinical outcomes, including mortality, in patients receiving tofacitinib and other systemic therapies within RA, PsA and UC cohorts, stratified by age (<65 and 65 and older).

Additionally, the frequencies and incidence rates of influenza infection and influenza like illness, and the frequencies of influenza-related clinical outcomes, including mortality, will be reported by influenza season (annual datacut from 01 June – 31 May). Although there may be under-reporting and misclassification, presence of influenza vaccine in individual patient records will also be reported for each influenza season.

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective records-based cohort study involving secondary analysis of Redacted Redacted Electronic Health Record (EHR) databases in the US consisting of longitudinal health information about patients derived from participating healthcare provider organizations with details below.

This study period is 01 June 2014 through 31 May 2019. The June 2014 start date is intended to avoid potentially intractable channeling of patients with high unmet need into tofacitinib group given status as first in class to a new mechanism of action following US approval in November 2012.

This study first focuses on the whole study period (01 June 2014 through 31 May 2019), then perform frequency and incidence rate analysis for each influenza season (01 June through 31 May the next year).

8.2. Setting

8.2.1. Redacted

Redacted is derived from records of 150,000 healthcare providers in the United States, that include more than 2000 hospitals and 7000 clinics; treating more than 103 million patients receiving care as of January 2020. The data is certified as de-identified by an independent statistical expert following Health Insurance Portability and Accountability Act (HIPAA) statistical de-identification rules, and managed according to Redacted Redacted customer data use agreements.[18,19] Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory EHRs, practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Redacted Redacted data elements include: demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Redacted uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (ie, RAPID3 for RA, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

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All diagnosis data, laboratory data, and surgical procedure data for the study period of interest will be obtained from existing structured data (via International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification [ICD-9-CM/ICD-10-CM], International Classification of Diseases, Ninth Revision/Tenth Revision, Procedure Classification System [ICD-9-PCS/ICD-10-PCS], or Current Procedural Terminology[CPT] codes where applicable). All drug treatment data will be pulled from prescription written, medication administration, and procedure tables when appropriate (via ICD-9-CM/ICD-10-CM, National Drug Center [NDC], CPT, and Healthcare Common Procedure Coding System [HCPCS] codes where applicable).

8.2.2. 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 date of the event of interest, treatment discontinuation (defined in the statistical analysis plan [SAP]), death date, study end date, or end of enrolment in the database.

Exposure to therapies will be defined using the National Drug Code (NDC) for dispensed or administrated medications and, where relevant, procedure codes for injection or infusion. Exposure will be classified into five categories:

- Tofacitinib;
- JAKi, (tofacitinib, baricitinib);
- TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab);
- non-TNFi (abatacept, anakinra, rituximab, tocilizumab, sarilumab, ustekinumab, secukinumab, ixekizumab, vedolizumab);
- conventional synthetic disease modifying antirheumatic drugs (csDMARD) (auranofin, aurothioglucose, azathioprine, chloroquine, cyclophosphamide, cyclosporin, gold salts, hydroxychloroquine, leflunomide, methotrexate, minocycline HCl, penicillamine, sulfasalazine, tacrolimus, thalidomide).

New users will be defined as those with a prescription for a drug they had not previously been prescribed during the 180 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 or into the same category again as of the date they re-start the same drug after more than 180 days.

8.2.3. Inclusion Criteria

In order to be eligible for entry into an indicated patient cohort patients must meet all of the following inclusion criteria:

1. Aged ≥18 years at index date
2. Evidence of at least 1 inpatient diagnosis code or 2 outpatient diagnosis codes 7-365 days apart for RA, PsA, or UC.
3. Evidence of initiation for at least 1 approved systemic treatment (tofacitinib, JAKi, TNFi, non-TNFi, csDMARD) for the corresponding identified indication.
4. At least 180 days of continuous enrollment in Redacted prior to index date.

8.2.4. Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. Evidence of >1 indications of interest during the whole study period.

8.3. Variables

All variable definitions will be specifically defined in the SAP, including code lists, time periods of interest and data location.

Variable	Role	Operational definition[a]
Rheumatoid Arthritis	Subcohort identification	At least 1 inpatient or 2 outpatient diagnoses 7-365 days apart
Psoriatic Arthritis	Subcohort identification	At least 1 inpatient or 2 outpatient diagnoses 7-365 days apart
Ulcerative Colitis	Subcohort identification	At least 1 inpatient or 2 outpatient diagnoses 7-365 days apart
Index date	Baseline characteristic	Date of initiation of index therapy
Baseline systemic therapy	Baseline Characteristic/Exposure	Evidence of therapy prescribed 180 days prior to index date. Categorical: , tofacitinib, JAKi, TNFi, non-TNFi, csDMARD
Baseline tofacitinib	Baseline Characteristic/Exposure	Evidence of tofacitinib prescribed within 180 days prior to index date.
Baseline JAKi	Baseline Characteristic/Exposure	Evidence of JAKi prescribed within 180 days prior to index date.
Baseline TNFi	Baseline Characteristic/Exposure	Evidence of TNFi prescribed within 180 days prior to index date.
Baseline Non-TNFi	Baseline Characteristic/Exposure	Evidence of Non-TNFi prescribed within 180 days prior to index date.

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Variable	Role	Operational definition[a]
Baseline csDMARD	Baseline Characteristic/Exposure	Evidence of csDMARD prescribed within 180 days prior to index date.
Age, continuous	Baseline Characteristic	Continuous age at index date
Age, categorical	Baseline Characteristic	Age at index date: 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+
Age, dichotomous	Stratifying variable	18-64 and ≥ 65
Gender	Baseline Characteristic	Female, Male, Unknown
Race	Baseline Characteristic	White, Black, Asian, Other
Ethnicity	Baseline Characteristic	Hispanic, non-Hispanic
Region	Baseline Characteristic	Distribution of geographic region at index date
Insurance	Baseline Characteristic	Insurance type
BMI	Baseline Characteristic	BMI<30 and BMI ≥30
Smoking	Baseline Characteristic	Current/former/non-smoker
Hypertension	Baseline Characteristic	Diagnosis of hypertension within baseline period
Hyperlipidemia	Baseline Characteristic	Diagnosis of hyperlipidemia within baseline period
Coronary artery disease	Baseline Characteristic	Diagnosis of coronary artery disease within baseline period
History of serious infections	Baseline Characteristic	Hospitalized infections within baseline period
Malignancy	Baseline Characteristic	Diagnosis of malignancy within baseline period
Pregnancy	Baseline C haracteristic	Diagnosis of pregnancy within baseline period
Interstitial lung disease (ILD)/COPD/Asthma	Baseline Characteristic	Diagnosis of ILD/COPD/Asthma within baseline period
Venous thromboembolism (VTE)	Baseline Characteristic	Diagnosis of pulmonary embolism (PE) or deep vein thrombosis (DVT) within baseline period
Heart disease (HD)	Baseline Characteristic	Diagnosis of HD (heart failure, hypertensive heart disease, pulmonary heart disease, valvular disorders, arrhythmia, congenital

Variable	Role	Operational definition[a]
		heart disease) within baseline period
History of cerebrovascular accident (CVA)	Baseline Characteristic	History of ischemic or hemorrhagic stroke within baseline period
Peripheral vascular disease (PVD)	Baseline Characteristic	Diagnosis of PVD within baseline period
Other immune deficiencies	Baseline Characteristic	Diagnosis of immunodeficiency within baseline period
Human immunodeficiency virus (HIV)/AIDS	Baseline Characteristic	Diagnosis of HIV/AIDS within baseline period
Diabetes	Baseline Characteristic	Diagnosis of diabetes within baseline period
Chronic kidney disease (CKD)/Dialysis	Baseline Characteristic	Diagnosis of CKD or dialysis procedure during baseline period
Liver Disease	Baseline Characteristic	Diagnosis or procedure during baseline period
Corticosteroid Use	Baseline Characteristic	Prescription during baseline period for systemic corticosteroids
Influenza Season	Stratifying variable	Annually June 1st – May 31st 2014-2015; 2015-2016; 2016-2017; 2017-2018; 2018-2019
Influenza	Primary Endpoint	Clinical diagnosis of influenza
ILI	Primary Endpoint	Clinical diagnosis of ILI
Influenza vaccine	Secondary Endpoint	Yes/No, evidence of influeza vaccine corresponding to seasons: 2014-2015; 2015-2016; 2016-2017; 2017-2018; 2018-2019 This will only be reported for each influenza season
Influenza Complications - Pneumonia	Secondary Endpoint	Clinial diagnosis of pneumonia on or up to 30 days after an influenza diagnosis
Influenza Complications - Stroke or myocardial infarction (MI)	Secondary Endpoint	Clinial diagnosis of stroke or MI on or up to 30 days after an influenza diagnosis
Influenza Complications – Neurological Disorder	Secondary Endpoint	Clinial diagnosis of neurological disorder on or up to 30 days after an influenza diagnosis

Variable	Role	Operational definition[a]
Corticosteroid Use	Secondary Endpoint	Corticosteroid use within 30 days [-30,30] around an influenza diagnosis
Methotrexate Use	Secondary Endpoint	Methotrexate use within 30 days [-30,30] around an influenza diagnosis
Azathioprine Use	Secondary Endpoint	Azathioprine use within 30 days [-30,30] around an influenza diagnosis
Influenza Hospitalization	Secondary Endpoint	Yes/No: hospitalization within 30 days post influenza diagnosis
In-hospital death	Secondary Endpoint	Death that happened during influenza hospitalization
Death	Secondary Endpoint	Death within 90 days post influenza diagnosis

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

8.4. Data Sources

The structured data within Redacted will be used to identify populations, exposures, confounders and endpoints of interest as described in Section 8.2.2 and Section 8.3.

8.5. Study Size

As this is a descriptive study, no predetermined sample size has been calculated. The resulting sample size is dependent on the number of eligible participants in the Redacted Redacted

8.6. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using statistical platform RedactedRedactedRedactedRedacted.

8.7. Data Analysis

Detailed methodology will be documented in a 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. Descriptive analysis will be performed for this study. Baseline demographics, comorbidities and clinical characteristics will be analyzed using baseline data for RA, PsA and UC patients, then stratified by index treatment group, and age (<65 and 65 and older). Means, medians, and standard deviations will be provided for continuous variables. Counts and percentages will be provided for dichotomous variables or categorical variables.

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The frequency and incidence rates for influenza and influenza like illness, the frequency of influenza complictions, influenza-related hospitalization and mortality among patients treated for RA, PsA, and UC in subsets of patients defined by different index treatments will be reported stratified by age (<65 and 65 and older).

8.8. Quality Control

Analyses are programmed according to the specifications in the protocol, and if applicable, the statistical analysis plan, 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.

8.9. Limitations of the Research Methods

The Redacted 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 autoimmune conditions 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. Although information on vaccinations will be collected if contained in the database; this is likely to be under-reported as many vaccinations are given at alternative locations; however, this is not likely to be differential.

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; this may be particularly true for ILI.

The primary analyses are descriptive in nature and inferences regarding association of treatment or indication are not possible. Feasibility of comparative analyses will depend on the number of infected patients with indications/treatments of interest.

Study results may not be generalizable outside of the insured population.

8.10. Other Aspects

Not Applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

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

9.2. 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.

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

IEC/IRB review was not required.

9.4. 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.

10. 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.

11. 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.

12. REFERENCES

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13. LIST OF TABLES

None.

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Study abstract.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921383 Non-Interventional Protocol Study Amendment 1 (CLEAN) 29 October 2021
Document Title:	A3921383 Non-Interventional Protocol Study Amendment 1 (CLEAN) 29 October 2021

Signed By:	Date(GMT)	Signing Capacity
Redacted	Redacted	Redacted
Redacted	Redacted	Redacted