NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

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
Version identifier of the final study report	1.0
Date	10 February 2023
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

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Appendix 1. SIGNATURES

Appendix 2. PROTOCOL

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Not applicable.

Appendix 3.1. List of Investigators by Country

Not applicable.

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT))

Not applicable.

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Appendix 7.1 Withdrawn Subjects

Not applicable.

Appendix 7.2 Protocol Deviations

May be applicable.

Appendix 7.3 Subjects Excluded from the Analysis

Not applicable.

Appendix 7.4 Demographic Data

Not applicable.

Appendix 7.5 Medication/Treatment Data

Not applicable.

Appendix 7.6 Endpoint Data

Not applicable.

Appendix 7.7 Adverse Events

Not applicable.

Appendix 7.8 Laboratory listings

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

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 procedural terminology
CVA	cerebrovascular accident
csDMARD	conventional synthetic disease modifying antirheumatic drugs
DMARD	disease modifying antirheumatic drugs
DVT	Deep vein 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
IBD	Irritable bowel disease
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 Code
NI	Non-interventional
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
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
UC	ulcerative colitis
US/USA	United States/United States of America
VTE	Venous thromboembolism

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Redacted			

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	15 Feb 2021	15 Feb 2021	
End of data collection	08 March 2021	08 March 2021	
Final report of study results	19 January 2023	10 February 2023	Additional time needed to finalize study conclusions and interpretation with the medical leads.

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] Despite the availability of vaccines and antiviral therapy, influenza can have serious complications, including viral and bacterial pneumonia, acute respiratory decompensation, myocarditis, and exacerbation of underlying pulmonary disease, which often result in hospitalization and death.[1]

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 of the incidence of vaccine preventable infections concluded that persons with autoimmune inflammatory rheumatic disease are at higher risk for contracting influenza than the general population.[2] The most comprehensive description of influenza in persons with RA is from a retrospective cohort study using data from a US commercial health insurance database from 2000-2007. The study found that patients with RA, compared with patients without RA, had a 33% higher incidence of seasonal influenza and a 2.8-fold increase in incidence of influenza complications. Patients without RA were significantly more likely than those with RA 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 in patients with UC compared with age-, sex-, and date of entry-matched patients without UC.[6] Notably, use of biologics was not significantly associated with the rate of influenza or its complications in either study.[5,6] A study of influenza among RA patients 50 and older with chronic obstructive pulmonary disease (COPD) similarly concluded that use of biologic bDMARDs as a class (including a relatively small number of tofacitinib treated patients) was not associated with a higher risk of influenza infection. Although the risk of severe influenza was higher in bDMARD than in csDMARD patients, the difference was not statistically significant.[7] Apart from these above-mentioned studies, little is known about the association between treatment with immunosuppressive drugs, and the incidence of influenza and influenza-related complications in patients with RA, PsA and UC.

Tofacitinib has been approved in the US since November 2012 to treat adult patients with moderate to severe RA who have had inadequate response or intolerance to methotrexate. In December 2017, tofacitinib was approved in the US to additionally treat adult patients with active psoriatic arthritis with prior inadequate response or intolerance to methotrexate or other DMARDs. In May 2018, tofacitinib was further approved in the US to treat adult patients with moderately to severely active UC with prior inadequate response or prior intolerance to TNF blockers. 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]

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 uncertainty in 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. However, there is currently limited clinical evidence to guide these decisions (Howland et al., 2021).[20] In a small study of RA, PsA, and ankylosing spondyloarthritis patients with symptomatic COVID-19 illness, being on a JAKi (including tofacitinib) was a significant risk factor for hospitalization in the PsA and ankylosing spondyloarthritis patients but not the RA patients, after adjusting for age, sex, BMI, and comorbidities (Haberman et al., 2020).[18] The authors note that channeling of sicker patients to JAKi treatment (particularly for PsA patients) may partly explain this finding. In a study of IBD patients with COVID-19, no greater risk of COVID 19-related severe symptoms, hospitalization, or intensive care unit admission was identified in tofacitinib users (n=37) versus those on other medications.[19] Because these studies represent a small number of patients receiving JAKi treatment, and an even smaller number receiving tofacitinib, their results cannot be deemed conclusive regarding continued tofacitinib use in those with immune-mediated disease who are infected with SARS-CoV-2.[20] Nevertheless, the recommendation for patients exposed to SARS-CoV-2, or with active or presumptive COVID-19, is to stop treatment with tofacitinib, given the potential risks.[20] 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 who are asymptomatic.[16,17]

The overall goal of this retrospective observational study using a US database was 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 clinical outcomes.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The research question addressed by this study was:

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?

The objectives for this study were to:

- 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).
- Additionally, the frequencies and incidence rates of influenza infection and influenza like illness, and the frequencies of influenza-related outcomes, including mortality, will be reported by Northern hemisphere influenza season (defined as 01 June – 31 May). Influenza vaccine status will also be reported for each influenza season.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amend-ment number	Date	Substantial or administrative amendment	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

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					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

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					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 and influenza like illness and the frequencies and incidence proportions of influenza complications will be used.	In the previous version of the protocol, the research question and study objectives were unclear regarding which 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

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					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 characteristic/exposure"	The term "concomitant medication" is superfluous, and it is not used to describe the role of the other exposure groups.
				The "Role" of the following variables is simplified to "Baseline	None of these variables is described

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				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.	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"	Influenza vaccine was not described

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				to "Secondary Endpoint."	elsewhere in the protocol or in the SAP as a potential confounder, and it was not analyzed as a potential confounder. Both documents state that influenza vaccination will be "reported" for each influenza season, with no further 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.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study of structured longitudinal data from Optum EHR databases in the US.

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 focuses on the entire study period (01 June 2014 through 31 May 2019), as well as conducting frequency and incidence rate analyses for each influenza season (01 June through 31 May of the following year).

9.2. Setting

Optum's EHR repository is derived from records of 150,000 healthcare providers and more than 2,000 hospitals and 7,000 clinics in the United States and includes more than 103 million patients receiving care as of January 2020. The data are certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and is managed according to Optum 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. Optum 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, Optum 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.

All diagnostic, laboratory, 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 prescriptions written, medications administered, and procedure tables when appropriate (via ICD-9-CM/ICD-10-CM, NDC, CPT, and HCPCS codes where applicable).

9.3. Subjects

All study participants were individuals in the OPTUM EHR database who satisfied the study's inclusion and exclusion criteria as described below.

9.3.1. Inclusion Criteria

To be eligible for entry into the study, patients had to meet all 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 of 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 Optum database prior to index date.

9.3.2. Exclusion Criteria

Patients were excluded if they met the following criterion:

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

9.4. Variables

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.

Redacted

Variable	Role	Operational definition[a]
Baseline non-TNFi	Baseline Characteristic/Exposure	Evidence of non-TNFi prescribed within 180 days prior to index date.
Baseline csDMARD	Baseline Characteristic/Exposure (Concomitant medication)	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 Characteristic	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

Redacted

Variable	Role	Operational definition[a]
Heart disease (HD)	Baseline Characteristic	Diagnosis of HD (heart failure, hypertensive heart disease, pulmonary heart disease, valvular disorders, arrhythmia, congenital 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 vaccine	Secondary Endpoint	Yes/No, evidence of influenza vaccine corresponding to seasons: 2014-2015; 2015-2016; 2016-2017; 2017-2018; 2018-2019 This will only be reported for each influenza season
Influenza	Primary Endpoint	Clinical diagnosis of influenza
ILI	Primary Endpoint	Clinical diagnosis of ILI
Influenza Complications - Pneumonia	Secondary Endpoint	Clinical diagnosis of pneumonia on or up to 30 days after an influenza diagnosis
Influenza Complications - Stroke or myocardial infarction (MI)	Secondary Endpoint	Clinical diagnosis of stroke or MI on or up to 30 days after an influenza diagnosis

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Variable	Role	Operational definition[a]
Influenza Complications – Neurological Disorder	Secondary Endpoint	Clinical diagnosis of neurological disorder on or up to 30 days after an influenza diagnosis
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. Applicable codes and other definitions further defined in the SAP.

9.5. Data Sources and Measurement

The structured data within the Optum database were used to identify populations, baseline demographics and clinical characteristics, exposures, and endpoints of interest as described in Section 9.3 and Section 9.4 above.

9.6. Bias

Diagnoses of immune-mediated inflammatory diseases were identified using ICD-10-CM diagnosis codes in the Optum database, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes. Where possible, validated algorithms were used. The baseline period of this study was of limited duration thus baseline comorbidities and risk factors occurring outside of this baseline period may not have been captured, which may have led to misclassification.

Information on prescriptions for outpatients does not indicate that the medication was consumed or taken as prescribed; similarly, medications filled over-the-counter or provided as samples by the physician are not recorded in the database. Although data on vaccinations were collected from the database, they were likely undercounted as many 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 over-sampled more severe RA, PsA, and UC cases, as well as more severe cases of influenza and influenza-like illness.

The primary analyses are descriptive in nature and therefore there was no assessment of or adjusting for confounding.

9.7. Study Size

As this was a descriptive study, no predetermined sample size was calculated. The resulting sample size was dependent on the number of eligible participants in the Optum EHR database.

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical Methods

9.9.1. Main Summary Measures

For continuous variables, means, medians, and standard deviations are provided. For categorical variables, counts and percentages are provided.

For the primary outcomes of influenza and influenza-like illness, counts, person time, and incidence rates are provided. For the secondary outcomes of influenza cases' clinical outcomes, counts and incidence proportions are reported. For vaccinations, counts and proportions of patients vaccinated are reported. All results are stratified by indication (RA, PsA, and UC) and by treatments (tofacitinib, JAKi, TNFi, non-TNFi, and csDMARD) and in some cases by age (<65 and ≥65 years old). Follow-up started at each index date and continued until the date of the event of interest, drug era end date, death date, end of study period (or end of each influenza season for the "by flu season" analysis), or end of enrolment in the database, whichever came first.

9.9.2. Main Statistical Methods

All in the OPTUM database with two outpatient diagnoses, or one inpatient diagnosis, for an indication of interest (RA, PsA, or UC) after 1 June 2014 were eligible for the study. Those with two or more of these indications during the study period were ineligible. The first diagnosis date was set as the indication date. From the indication date, patients who were new users of any of five treatment categories were included in the study. Exposure to therapies was defined using the NDC for dispensed or administrated medications and, where relevant, procedure codes for injection or infusion. The five exposure categories were:

- 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) in RA and PsA patients and conventional UC treatments in UC patients (auranofin, aurothioglucose, azathioprine, chloroquine, cyclophosphamide, cyclosporin, gold salts, hydroxychloroquine, leflunomide, methotrexate, minocycline HCl, penicillamine, sulfasalazine, tacrolimus, thalidomide).

A patient's "drug era" was the period during which the patient was prescribed and presumably taking a drug in at least one of the five drug classes and was at risk of a study outcome (influenza or influenza-related illness) that would be attributed to that drug class. Any given patient may have had more than one drug era during the study period. Drug eras were constructed using the following algorithm:

1. Drug prescription date or administration date and the days of supply were used to obtain the drug start and end dates for each prescription/administration. If the days of supply was missing or the days of supply was 0, 30 days was used (based on days of supply investigation results).
2. If the number of refills for a prescription drug was available, the number of refills + 1 was multiplied by the days of supply and the resulting total was the days of supply used in the analyses.
3. If the gap between the end of previous drug episode and the start of the subsequent prescription was less than or equal to 60 days for the non-csDMARD treatment groups or 90 days for csDMARD treatment group, the episodes were linked. If the gap was more than 60 (or 90) days, then the subsequent prescription defined the start of a new drug era.
4. No stockpiling applied.
5. For each drug era, the drug discontinuation date was defined as the drug end date of the last prescription.
6. A 30-day surveillance window was added to the end of each drug discontinuation date, and the end of the 30-day surveillance window was defined as the drug era end date. The prescription date for the first prescription in this drug era was defined as the drug era start date.
7. Each drug within the same drug class was treated as if the same drug.

New users were defined as those with any new drug eras. A new drug era was defined as no prescription of that drug in the 180 days prior to drug era start date (for the first drug era in each treatment group) or with more than 180 days since last drug discontinuation date to the subsequent drug era start date (for subsequent drug eras in the same treatment group). Patients needed to have at least one new drug era to be included in the study.

Patients who were on an index therapy were eligible for selection into a second category as of the date they began one of the drugs in another category. They were also eligible for selection into the same drug category on the date they re-started a drug in that category, provided that more than 180 days had passed since their most recent discontinuation date for a drug in that category. Therefore, patients may have had multiple drug eras and each drug era was assessed for endpoints of interests.

The date when a patient initiated a drug era was set as the drug era's index date. For each index date, the 180 days prior was set as the baseline period for that index date. The *first* index date for each treatment category was used to evaluate baseline demographics and clinical characteristics for that treatment category.

Patients were followed from a drug era's index date until the date of the event of interest, treatment discontinuation followed by a 30-day surveillance period, death date, study end date, or the patient's end of enrolment in the database, whichever came first. If an endpoint of interest happened in overlapping follow-up periods for more than one drug era, the endpoint was counted in each of the treatment categories. Endpoints occurring during monotherapy were not reported separately from those occurring during combination therapy.

9.9.3. Missing Values

No imputations for missing values were performed.

9.9.4. Sensitivity Analyses

None.

9.9.5. Amendments to the Statistical Analysis Plan

None.

9.10. Quality Control

Summary statistics were tabulated for all variables. These summary statistics were checked for errors by a member of the Quantitative Epidemiology and Analytics team at Pfizer other than the member performing the analysis.

9.11. Protection of Human Subjects

Subject information and consent

Not applicable.

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

IEC/IRB review was not required.

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 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. RESULTS

10.1. Participants

Using the Optum EHR database, structured data were used to identify patients meeting inclusion and exclusion criteria (Section 9.3). This resulted in 199,697 patients enrolled into the study: 137,910 with RA, 19,179 with PsA, and 42,608 with UC. These patients' exposures to the treatments of interest are shown in Table 2. Because patients could be exposed simultaneously or consecutively to more than one drug class during the study, the sum of patients exposed to the drug classes exceeds the number of patients with a given indication.

Table 2. Treatment Exposures of Persons Diagnosed with Rheumatoid Arthritis, Psoriatic Arthritis, and Ulcerative Colitis (01 June 2014 – 31 May 2019)

	Tofacitinib	JAKi	non-TNFi	TNFi	csDMARD	Total patients
RA	8,818	8,912	42,207	32,510	102,828	137,910
PsA	475	475	6,498	9,773	10,805	19,179
UC	260	260	15,170	7,582	30,101	42,608

10.2. Descriptive Data

At index date, RA patients had the oldest mean age (60.5) and UC patients the youngest mean age (52.1) (Table 2). White patients and non-Hispanic patients each comprised over 80% of all three diagnostic groups. In terms of treatment, more patients were prescribed csDMARDS than any other treatment category in all the diagnostic groups and JAKi's were the least prescribed drug class (Table 3). In the following sections and tables, demographics, comorbidities, outcomes, and vaccination rates are described within each of the diagnostic-by-treatment categories.

Table 3. Baseline Characteristics of Persons Diagnosed with Rheumatoid Arthritis, Psoriatic Arthritis, and Ulcerative Colitis (01 June 2014 – 31 May 2019)

	Baseline characteristics	RA	PsA	UC
	Overall Population	137,910 (69.06%)	19,179 (9.60%)	42,608 (21.34%)
Age at index date	N	137,910	19,179	42,608
	Mean (SD)	60.49 (14.35)	53.29 (13.45)	52.05 (18.04)
	Median (IQR)	61 (52-71)	54 (44-63)	53 (37-66)
Age group at index date	18-24	1,483 (1.08%)	329 (1.72%)	2,880 (6.76%)
	25-34	5,665 (4.11%)	1,525 (7.95%)	6,140 (14.41%)
	35-44	12,242 (8.88%)	3,135 (16.35%)	6,385 (14.99%)
	45-54	24,527 (17.78%)	4,817 (25.12%)	7,087 (16.63%)
	55-64	37,014 (26.84%)	5,455 (28.44%)	8,280 (19.43%)
	65-74	32,309 (23.43%)	2,903 (15.14%)	6,574 (15.43%)
	75-84	21,805 (15.81%)	914 (4.77%)	4,468 (10.49%)
	85+	2,865 (2.08%)	101 (0.53%)	794 (1.86%)
Age group at index date	18-64	80,931 (58.68%)	15,261 (79.57%)	30,772 (72.22%)
	65+	56,979 (41.32%)	3,918 (20.43%)	11,836 (27.78%)
Sex	Female	104,926 (76.08%)	10,741 (56%)	22,896 (53.74%)
	Male	32,917 (23.87%)	8,432 (43.96%)	19,697 (46.23%)
	Missing	67 (0.05%)	6 (0.03%)	15 (0.04%)
Race	Asian	2,053 (1.49%)	260 (1.36%)	568 (1.33%)
	Black	14,919 (10.82%)	409 (2.13%)	3,086 (7.24%)
	Caucasian	111,890 (81.13%)	17,410 (90.78%)	36,709 (86.16%)
	Missing	9,048 (6.56%)	1,100 (5.74%)	2,245 (5.27%)
Ethnicity	Hispanic	7,505 (5.44%)	733 (3.82%)	1,603 (3.76%)
	Not Hispanic	122,574 (88.88%)	17,276 (90.08%)	38,888 (91.27%)
	Missing	7,831 (5.68%)	1,170 (6.10%)	2,117 (4.97%)
Region	Midwest	63,908 (46.34%)	8,250 (43.02%)	20,833 (48.89%)
	Northeast	19,564 (14.19%)	4,283 (22.33%)	7,184 (16.86%)
	South	36,762 (26.66%)	4,532 (23.63%)	8,525 (20.01%)
	West	13,663 (9.91%)	1,528 (7.97%)	4,696 (11.02%)
	Missing	4,013 (2.91%)	586 (3.06%)	1,370 (3.22%)
Insurance	Commercial	59,433 (43.10%)	10,602 (55.28%)	21,924 (51.46%)
	Medicaid	8,668 (6.29%)	1,026 (5.35%)	2,680 (6.29%)
	Medicare	41,032 (29.75%)	3,048 (15.89%)	8,449 (19.83%)
	Other	3,846 (2.79%)	486 (2.53%)	1,215 (2.85%)
	Uninsured	3,214 (2.33%)	374 (1.95%)	1,116 (2.62%)
	Missing	21,717 (15.75%)	3,643 (18.99%)	7,224 (16.95%)

Note: Because tofacitinib was the only FDA-approved JAKi to treat RA until baricitinib was approved on 31 May 2018 (one year before the end of the study period), the tofacitinib and JAKi treatment groups largely overlap in the RA data, and because tofacitinib is the *only* FDA-approved JAKi to treat PsA and UC these treatment groups are identical and are merged and labeled "JAKi (tofacitinib)" in the PsA and UC tables below.

10.2.1. Demographics by Treatment Within Diagnostic Groups

10.2.1.1. Rheumatoid Arthritis

Among RA patients, (Table 4), non-TNFi and csDMARD users have an older mean age and a greater proportion were ≥65 years old compared with tofacitinib, JAKi, and TNFi users. Gender distributions are similar across treatment groups, with females comprising 76.2%-81.4% of patients in the five groups. Race distributions across the five drug groups are

mostly consistent, with Caucasian patients comprising between 78.9% and 82.4% of the groups.

Table 4. Baseline Characteristics of Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		Tofa[a]	JAKi[a]	TNFi	Non TNFi	csDMARD
Age at index						
	N	8,818	8,912	32,510	42,207	102,828
	Mean (SD)	57.10 (12.57)	57.11 (12.56)	55.67 (13.40)	61.44 (14.30)	60.54 (14.26)
	Median (IQR)	58 (50-65)	58 (50-65)	56 (47-65)	62 (52-72)	61 (52-71)
Age group at index date						
	18-24	93 (1.05%)	93 (1.04%)	483 (1.49%)	410 (0.97%)	1,046 (1.02%)
	25-34	339 (3.84%)	342 (3.84%)	1,949 (6%)	1,543 (3.66%)	4,119 (4.01%)
	35-44	923 (10.47%)	935 (10.49%)	4,040 (12.43%)	3,391 (8.03%)	9,148 (8.90%)
	45-54	2,080 (23.59%)	2,101 (23.57%)	7,656 (23.55%)	7,139 (16.91%)	18,243 (17.74%)
	55-64	3,017 (34.21%)	3,050 (34.22%)	10,131 (31.16%)	11,153 (26.42%)	27,555 (26.80%)
	65-74	1,650 (18.71%)	1,666 (18.69%)	5,772 (17.75%)	10,279 (24.35%)	24,410 (23.74%)
	75-84	655 (7.43%)	663 (7.44%)	2,304 (7.09%)	6,963 (16.50%)	16,425 (15.97%)
	85+	61 (0.69%)	62 (0.70%)	175 (0.54%)	1,329 (3.15%)	1,882 (1.83%)
Age group at index date						
	18-64	6,452 (73.17%)	6,521 (73.17%)	24,259 (74.62%)	23,636 (56%)	60,111 (58.46%)
	65+	2,366 (26.83%)	2,391 (26.83%)	8,251 (25.38%)	18,571 (44%)	42,717 (41.54%)
Sex						
	Female	7,175 (81.37%)	7,258 (81.44%)	25,047 (77.04%)	32,575 (77.18%)	78,395 (76.24%)
	Male	1,642 (18.62%)	1,653 (18.55%)	7,443 (22.89%)	9,613 (22.78%)	24,385 (23.71%)
	Missing	1 (0.01%)	1 (0.01%)	20 (0.06%)	19 (0.05%)	48 (0.05%)
Race						
	Asian	130 (1.47%)	131 (1.47%)	457 (1.41%)	599 (1.42%)	1,574 (1.53%)
	Black	842 (9.55%)	853 (9.57%)	3,185 (9.80%)	5,270 (12.49%)	10,844 (10.55%)
	Caucasian	7,268 (82.42%)	7,341 (82.37%)	26,579 (81.76%)	33,305 (78.91%)	83,814 (81.51%)
	Missing	578 (6.55%)	587 (6.59%)	2,289 (7.04%)	3,033 (7.19%)	6,596 (6.41%)
Ethnicity						
	Hispanic	434 (4.92%)	443 (4.97%)	2,115 (6.51%)	2,455 (5.82%)	5,593 (5.44%)
	Not Hispanic	7,762 (88.02%)	7,842 (87.99%)	28,340 (87.17%)	37,790 (89.53%)	91,311 (88.80%)
	Missing	622 (7.05%)	627 (7.04%)	2,055 (6.32%)	1,962 (4.65%)	5,924 (5.76%)
Region						
	Midwest	3,866 (43.84%)	3,904 (43.81%)	14,922 (45.90%)	16,492 (39.07%)	49,751 (48.38%)
	Northeast	1,410 (15.99%)	1,435 (16.10%)	4,945 (15.21%)	6,603 (15.64%)	14,234 (13.84%)
	South	2,690 (30.51%)	2,711 (30.42%)	8,830 (27.16%)	11,406 (27.02%)	27,020 (26.28%)
	West	594 (6.74%)	600 (6.73%)	2,776 (8.54%)	6,471 (15.33%)	8,847 (8.60%)
	Missing	258 (2.93%)	262 (2.94%)	1,037 (3.19%)	1,235 (2.93%)	2,976 (2.89%)

Redacted

		Tofa[a]	JAKi[a]	TNFi	Non TNFi	csDMARD
Insurance						
	Commercial	4,821 (54.67%)	4,864 (54.58%)	17,346 (53.36%)	17,214 (40.78%)	44,776 (43.54%)
	Medicaid	541 (6.14%)	548 (6.15%)	2,286 (7.03%)	3,300 (7.82%)	5,990 (5.83%)
	Medicare	2,144 (24.31%)	2,171 (24.36%)	6,924 (21.30%)	14,743 (34.93%)	30,204 (29.37%)
	Other	229 (2.60%)	230 (2.58%)	924 (2.84%)	1,254 (2.97%)	2,922 (2.84%)
	Uninsured	156 (1.77%)	163 (1.83%)	837 (2.57%)	985 (2.33%)	2,413 (2.35%)
	Missing	927 (10.51%)	936 (10.50%)	4,193 (12.90%)	4,711 (11.16%)	16,523 (16.07%)
Treatment history Tofa						
	N (%)	0 (0%)	0 (0%)	728 (2.24%)	1,112 (2.63%)	960 (0.93%)
Treatment history JAKi						
	N (%)	6 (0.07%)	0 (0%)	733 (2.25%)	1,122 (2.66%)	970 (0.94%)
Treatment history TNFi						
	N (%)	2,015 (22.85%)	2,041 (22.90%)	0 (0%)	5,273 (12.49%)	6,756 (6.57%)
Treatment history non-TNFi						
	N (%)	1,616 (18.33%)	1,636 (18.36%)	1,998 (6.15%)	0 (0%)	6,018 (5.85%)
Treatment history csDMARD						
	N (%)	4,693 (53.22%)	4,738 (53.16%)	18,447 (56.74%)	14,333 (33.96%)	0 (0%)

a. Because tofacitinib was the only FDA-approved JAKi to treat RA until baricitinib was approved on 31 May 2018 (one year before the end of the study period), the tofacitinib and JAKi treatment groups largely overlap in the RA data.

10.2.1.2. Psoriatic Arthritis

In PsA patients stratified by treatment group (Table 5), non-TNFi and csDMARD users have a slightly older mean age and are more likely to be ≥65 years old compared with tofacitinib, JAKi, and TNFi users. Females comprise between 53.5% and 64.8%, Caucasian patients between 90.5% and 93.9%, and non-Hispanic patients between 89.5% and 91.6% of the four treatment groups.

Table 5. Baseline Characteristics of Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		JAKi (tofacitinib)[a]	TNFi	Non TNFi	csDMARD
Age at index					
	N	475	9,773	6,498	10,805
	Mean (SD)	52.22 (11.66)	50.62 (12.75)	54.12 (13.04)	54.19 (13.44)
	Median (IQR)	53 (44-60)	52 (42-60)	55 (45-63)	55 (45-64)
Age group at index date					
	18-24	5 (1.05%)	202 (2.07%)	77 (1.18%)	163 (1.51%)
	25-34	31 (6.53%)	975 (9.98%)	437 (6.73%)	739 (6.84%)
	35-44	87 (18.32%)	1,896 (19.40%)	1,020 (15.70%)	1,697 (15.71%)
	45-54	140 (29.47%)	2,701 (27.64%)	1,679 (25.84%)	2,677 (24.78%)
	55-64	149 (31.37%)	2,722 (27.85%)	1,913 (29.44%)	3,045 (28.18%)
	65-74	53 (11.16%)	1,025 (10.49%)	1,010 (15.54%)	1,829 (16.93%)
	75-84	10 (2.11%)	235 (2.40%)	312 (4.80%)	600 (5.55%)
	85+		17 (0.17%)	50 (0.77%)	55 (0.51%)
Age group at index date					
	18-64	412 (86.74%)	8,496 (86.93%)	5,126 (78.89%)	8,321 (77.01%)
	65+	63 (13.26%)	1,277 (13.07%)	1,372 (21.11%)	2,484 (22.99%)
Sex					
	Female	308 (64.84%)	5,233 (53.55%)	3,766 (57.96%)	6,410 (59.32%)
	Male	167 (35.16%)	4,538 (46.43%)	2,731 (42.03%)	4,391 (40.64%)
	Missing		2 (0.02%)	1 (0.02%)	4 (0.04%)
Race					
	Asian	6 (1.26%)	132 (1.35%)	92 (1.42%)	158 (1.46%)
	Black	6 (1.26%)	204 (2.09%)	155 (2.39%)	221 (2.05%)
	Caucasian	446 (93.89%)	8,840 (90.45%)	5,878 (90.46%)	9,820 (90.88%)
	Missing	17 (3.58%)	597 (6.11%)	373 (5.74%)	606 (5.61%)
Ethnicity					
	Hispanic	15 (3.16%)	402 (4.11%)	253 (3.89%)	401 (3.71%)
	Not Hispanic	435 (91.58%)	8,749 (89.52%)	5,900 (90.80%)	9,755 (90.28%)
	Missing	25 (5.26%)	622 (6.36%)	345 (5.31%)	649 (6.01%)
Region					
	Midwest	176 (37.05%)	4,291 (43.91%)	2,408 (37.06%)	4,830 (44.70%)
	Northeast	131 (27.58%)	2,208 (22.59%)	1,623 (24.98%)	2,309 (21.37%)
	South	136 (28.63%)	2,299 (23.52%)	1,631 (25.10%)	2,499 (23.13%)
	West	20 (4.21%)	656 (6.71%)	672 (10.34%)	818 (7.57%)
	Missing	12 (2.53%)	319 (3.26%)	164 (2.52%)	349 (3.23%)
Insurance					
	Commercial	320 (67.37%)	5,862 (59.98%)	3,785 (58.25%)	5,781 (53.50%)

Redacted

		JAKi (tofacitinib)[a]	TNFi	Non TNFi	csDMARD
	Medicaid	22 (4.63%)	609 (6.23%)	371 (5.71%)	569 (5.27%)
	Medicare	59 (12.42%)	1,155 (11.82%)	1,191 (18.33%)	1,840 (17.03%)
	Other	10 (2.11%)	247 (2.53%)	166 (2.55%)	280 (2.59%)
	Uninsured	6 (1.26%)	173 (1.77%)	125 (1.92%)	211 (1.95%)
	Missing	58 (12.21%)	1,727 (17.67%)	860 (13.23%)	2,124 (19.66%)
Treatment history JAKi (tofacitinib)					
	N (%)	0 (0%)	27 (0.28%)	46 (0.71%)	33 (0.31%)
Treatment history TNFi					
	N (%)	134 (28.21%)	0 (0%)	1,810 (27.85%)	1,769 (16.37%)
Treatment history non-TNFi					
	N (%)	132 (27.79%)	459 (4.70%)	0 (0%)	666 (6.16%)
Treatment history csDMARD					
	N (%)	173 (36.42%)	3,230 (33.05%)	1,648 (25.36%)	0 (0%)

a. Because tofacitinib is the only FDA-approved JAKi to treat PsA and UC, these treatment groups are identical and are merged and labeled "JAKi (tofacitinib)" for the PsA and UC indications.

10.2.1.3. Ulcerative Colitis

In UC patients stratified by drug therapy (Table 6), non-TNFi and csDMARD users have an older mean age and are more likely to be ≥65 years old compared with tofacitinib, JAKi, and TNFi users. Females comprise between 50.7% and 55.1%, Caucasian patients between 83.5% and 87.7%, and non-Hispanic patients between 88.1% and 91.9% of the four therapy groups.

Table 6. Baseline Characteristics of Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		JAKi (tofacitinib)[a]	TNFi	Non TNFi	Conventional UC treatment
Age at index date					
	N	260	7,582	15,170	30,101
	Mean (SD)	45 (15.44)	43.06 (16.05)	54.83 (17.98)	51.24 (17.89)
	Median (IQR)	45 (32-57)	41 (30-56)	56 (40-69)	52 (36-65)
Age group at index date					
	18-24	24 (9.23%)	992 (13.08%)	719 (4.74%)	2,131 (7.08%)
	25-34	61 (23.46%)	1,791 (23.62%)	1,886 (12.43%)	4,566 (15.17%)
	35-44	42 (16.15%)	1,471 (19.40%)	2,026 (13.36%)	4,684 (15.56%)
	45-54	56 (21.54%)	1,303 (17.19%)	2,448 (16.14%)	5,041 (16.75%)
	55-64	50 (19.23%)	1,192 (15.72%)	3,021 (19.91%)	5,826 (19.35%)
	65-74	22 (8.46%)	590 (7.78%)	2,653 (17.49%)	4,476 (14.87%)

Redacted

		JAKi (tofacitinib)[a]	TNFi	Non TNFi	Conventional UC treatment
	75-84	4 (1.54%)	226 (2.98%)	1,977 (13.03%)	2,926 (9.72%)
	85+	1 (0.38%)	17 (0.22%)	440 (2.90%)	451 (1.50%)
Age group at index date					
	18-64	233 (89.62%)	6,749 (89.01%)	10,100 (66.58%)	22,248 (73.91%)
	65+	27 (10.38%)	833 (10.99%)	5,070 (33.42%)	7,853 (26.09%)
Sex					
	Female	140 (53.85%)	3,845 (50.71%)	8,354 (55.07%)	16,090 (53.45%)
	Male	120 (46.15%)	3,736 (49.27%)	6,810 (44.89%)	14,001 (46.51%)
	Missing		1 (0.01%)	6 (0.04%)	10 (0.03%)
Race					
	Asian	7 (2.69%)	95 (1.25%)	238 (1.57%)	385 (1.28%)
	Black	10 (3.85%)	503 (6.63%)	1,280 (8.44%)	2,066 (6.86%)
	Caucasian	228 (87.69%)	6,608 (87.15%)	12,671 (83.53%)	26,209 (87.07%)
	Missing	15 (5.77%)	376 (4.96%)	981 (6.47%)	1,441 (4.79%)
Ethnicity					
	Hispanic	12 (4.62%)	298 (3.93%)	643 (4.24%)	1,086 (3.61%)
	Missing	19 (7.31%)	321 (4.23%)	869 (5.73%)	1,348 (4.48%)
	Not Hispanic	229 (88.08%)	6,963 (91.84%)	13,658 (90.03%)	27,667 (91.91%)
Region					
	Midwest	109 (41.92%)	4,147 (54.70%)	5,970 (39.35%)	15,651 (51.99%)
	Northeast	81 (31.15%)	1,169 (15.42%)	3,320 (21.89%)	4,695 (15.60%)
	South	40 (15.38%)	1,397 (18.43%)	2,858 (18.84%)	6,072 (20.17%)
	West	20 (7.69%)	580 (7.65%)	2,571 (16.95%)	2,703 (8.98%)
	Missing	10 (3.85%)	289 (3.81%)	451 (2.97%)	980 (3.26%)
Insurance					
	Commercial	203 (78.08%)	5,092 (67.16%)	7,296 (48.09%)	15,850 (52.66%)
	Medicaid	9 (3.46%)	578 (7.62%)	1,325 (8.73%)	1,628 (5.41%)
	Medicare	14 (5.38%)	751 (9.91%)	3,871 (25.52%)	5,428 (18.03%)
	Other	4 (1.54%)	249 (3.28%)	457 (3.01%)	847 (2.81%)
	Uninsured	7 (2.69%)	186 (2.45%)	344 (2.27%)	829 (2.75%)
	Missing	23 (8.85%)	726 (9.58%)	1,877 (12.37%)	5,519 (18.33%)
Treatment history JAKi (tofacitinib)					
	N (%)	0 (0%)	18 (0.24%)	15 (0.10%)	16 (0.05%)
Treatment history TNFi					
	N (%)	73 (28.08%)	0 (0%)	1,402 (9.24%)	1,684 (5.59%)
Treatment history non-TNFi					
	N (%)	87 (33.46%)	746 (9.84%)	0 (0%)	1,730 (5.75%)
Treatment history csDMARD					

Redacted

		JAKi (tofacitinib)[a]	TNFi	Non TNFi	Conventional UC treatment
	N (%)	139 (53.46%)	4,037 (53.24%)	3,314 (21.85%)	0 (0%)

a. Because tofacitinib is the only FDA-approved JAKi to treat PsA and UC these treatment groups are identical and are merged and labeled "JAKi (tofacitinib)" for the PsA and UC indications.

10.2.2. Comorbidities

10.2.2.1. Comorbidities by Diagnostic Groups

The PsA group has the highest and the UC group the lowest mean BMI (Table 7). The RA group contains the highest proportions of current smokers and those with hypertension, hyperlipidemia, a range of heart and vascular conditions, interstitial lung disease/COPD/asthma, diabetes, of those on chronic kidney disease dialysis, and those using corticosteroids. The UC group is mostly likely to have a history of serious infection and malignancy.

Table 7. Baseline Comorbidities of Persons Diagnosed with Rheumatoid Arthritis, Psoriatic Arthritis, and Ulcerative Colitis (01 June 2014 – 31 May 2019)

		RA	PsA	UC
BMI				
	N	112,418	15,284	34,389
	Mean (SD)	30.17 (7.61)	32.16 (7.76)	28.09 (6.78)
	Median (IQR)	29 (24.80-34.40)	30.92 (26.70-36.38)	27.06 (23.32-31.60)
	Min-Max	5-70	8.70-70	5-70
BMI category				
	BMI ≥ 30	50,275 (36.45%)	8,576 (44.72%)	11,271 (26.45%)
	BMI < 30	62,143 (45.06%)	6,708 (34.98%)	23,118 (54.26%)
	Missing	25,492 (18.48%)	3,895 (20.31%)	8,219 (19.29%)
Smoking				
	Current smoker	14,589 (15.35%)	1,878 (14.68%)	3,184 (10.57%)
	Never smoked	40,756 (42.88%)	5,655 (44.20%)	14,852 (49.31%)
	Not recorded	1 (0%)		
	Previously smoked	32,757 (34.47%)	4,356 (34.05%)	10,026 (33.29%)
	Unknown/Missing	6,933 (7.30%)	904 (7.07%)	2,059 (6.84%)
Hypertension				
	N (%)	51,286 (37.19%)	5,502 (28.69%)	12,245 (28.74%)
Hyperlipidemia				
	N (%)	36,640 (26.57%)	4,440 (23.15%)	9,422 (22.11%)
Coronary artery disease				
	N (%)	14,414 (10.45%)	1,224 (6.38%)	3,570 (8.38%)

		RA	PsA	UC
History of SI				
	N (%)	11,245 (8.15%)	766 (3.99%)	9,402 (22.07%)
Malignancy				
	N (%)	7,934 (5.75%)	693 (3.61%)	3,293 (7.73%)
Pregnancy				
	N (%)	615 (0.45%)	70 (0.36%)	467 (1.10%)
ILD COPD asthma				
	N (%)	22,871 (16.58%)	1,737 (9.06%)	4,859 (11.40%)
VTE				
	N (%)	3,536 (2.56%)	269 (1.40%)	1,534 (3.60%)
Heart disease				
	N (%)	25,651 (18.60%)	2,138 (11.15%)	6,881 (16.15%)
CVA				
	N (%)	2,099 (1.52%)	133 (0.69%)	461 (1.08%)
PVD				
	N (%)	7,078 (5.13%)	546 (2.85%)	1,934 (4.54%)
Other immune deficiency				
	N (%)	5,405 (3.92%)	612 (3.19%)	1,268 (2.98%)
HIV AIDS				
	N (%)	160 (0.12%)	29 (0.15%)	120 (0.28%)
Diabetes				
	N (%)	22,194 (16.09%)	2,832 (14.77%)	5,290 (12.42%)
CKD dialysis				
	N (%)	20,574 (14.92%)	1,781 (9.29%)	5,431 (12.75%)
Liver disease				
	N (%)	4,154 (3.01%)	768 (4%)	2,259 (5.30%)
Corticosteroid use				
	N (%)	55,085 (39.94%)	5,566 (29.02%)	12,917 (30.32%)

10.2.2.2. Comorbidities by Treatment Groups Within Indicated Populations

In all three indicated patient groups (Table 8-Table 10), the non-TNFi treatment group has the highest prevalence of most of the comorbid conditions, followed by the csDMARD group; the other three treatment groups generally have the lowest prevalence of most of the conditions. The tofacitinib and JAKi treatment groups is most likely to use corticosteroids in all three indicated groups.

Table 8. Baseline Comorbidities of Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		Tofa	JAKi	TNFi	Non TNFi	csDMARD
BMI						
	N	7,754	7,837	28,002	37,177	83,192
	Mean (SD)	30.88 (7.69)	30.89 (7.72)	30.71 (7.70)	30.33 (7.84)	30.15 (7.53)
	Median (IQR)	29.80 (25.29-35.26)	29.80 (25.29-35.28)	29.52 (25.20-34.96)	29.10 (24.75-34.80)	29 (24.80-34.30)
	Min-Max	11.40-70	11.40-70	5-70	5-70	5-70
BMI Category						
	BMI ≥ 30	3,821 (43.33%)	3,863 (43.35%)	13,359 (41.09%)	16,909 (40.06%)	37,123 (36.10%)
	BMI < 30	3,933 (44.60%)	3,974 (44.59%)	14,643 (45.04%)	20,268 (48.02%)	46,069 (44.80%)
	Missing	1,064 (12.07%)	1,075 (12.06%)	4,508 (13.87%)	5,030 (11.92%)	19,636 (19.10%)
Smoking						
	Current smoker	995 (15.75%)	1,006 (15.75%)	3,862 (16.79%)	4,706 (15.15%)	10,658 (15.08%)
	Never smoked	2,806 (44.41%)	2,835 (44.38%)	10,129 (44.03%)	13,406 (43.15%)	30,233 (42.76%)
	Not recorded				1 (0%)	
	Previously smoked	2,098 (33.21%)	2,122 (33.22%)	7,333 (31.88%)	11,338 (36.49%)	24,284 (34.35%)
	Unknown/Missing	419 (6.63%)	425 (6.65%)	1,679 (7.30%)	1,619 (5.21%)	5,524 (7.81%)
Hypertension						
	N (%)	2,638 (29.92%)	2,665 (29.90%)	9,067 (27.89%)	19,430 (46.04%)	37,068 (36.05%)
Hyperlipidemia						
	N (%)	2,012 (22.82%)	2,031 (22.79%)	6,653 (20.46%)	13,386 (31.72%)	26,786 (26.05%)
Coronary artery disease						
	N (%)	578 (6.55%)	585 (6.56%)	1,723 (5.30%)	6,576 (15.58%)	9,781 (9.51%)
History of SI						
	N (%)	316 (3.58%)	320 (3.59%)	1,028 (3.16%)	5,785 (13.71%)	7,331 (7.13%)
Malignancy						
	N (%)	227 (2.57%)	229 (2.57%)	860 (2.65%)	3,733 (8.84%)	5,544 (5.39%)
Pregnancy						
	N (%)	14 (0.16%)	14 (0.16%)	129 (0.40%)	281 (0.67%)	368 (0.36%)
ILD COPD Asthma						
	N (%)	1,210 (13.72%)	1,222 (13.71%)	3,875 (11.92%)	9,556 (22.64%)	16,147 (15.70%)
VTE						
	N (%)	157	158 (1.77%)	525 (1.61%)	1,713 (4.06%)	2,412 (2.35%)

Redacted

		Tofa	JAKi	TNFi	Non TNFi	csDMARD
		(1.78%)				
Heart disease						
	N (%)	1,027 (11.65%)	1,037 (11.64%)	3,196 (9.83%)	11,477 (27.19%)	17,613 (17.13%)
CVA						
	N (%)	94 (1.07%)	94 (1.05%)	245 (0.75%)	932 (2.21%)	1,402 (1.36%)
PVD						
	N (%)	278 (3.15%)	280 (3.14%)	887 (2.73%)	3,184 (7.54%)	4,903 (4.77%)
Other immune deficiency						
	N (%)	442 (5.01%)	447 (5.02%)	1,489 (4.58%)	2,131 (5.05%)	4,025 (3.91%)
HIV AIDS						
	N (%)	1 (0.01%)	1 (0.01%)	23 (0.07%)	79 (0.19%)	105 (0.10%)
Diabetes						
	N (%)	1,190 (13.50%)	1,201 (13.48%)	4,165 (12.81%)	8,792 (20.83%)	15,675 (15.24%)
CKD dialysis						
	N (%)	916 (10.39%)	924 (10.37%)	3,288 (10.11%)	8,548 (20.25%)	14,431 (14.03%)
Liver disease						
	N (%)	245 (2.78%)	248 (2.78%)	894 (2.75%)	2,061 (4.88%)	2,642 (2.57%)
Corticosteroid use						
	N (%)	5,233 (59.34%)	5,285 (59.30%)	16,878 (51.92%)	19,195 (45.48%)	41,844 (40.69%)

Table 9. Baseline Comorbidities of Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		JAKi (tofacitinib)	TNFi	Non TNFi	csDMARD
BMI					
	N	428	8,003	5,621	8,574
	Mean (SD)	33.29 (8.31)	32.13 (7.62)	32.43 (7.97)	32.39 (7.87)
	Median (IQR)	32.50 (27.26-38.44)	31 (26.80-36.30)	31.16 (26.80-36.80)	31.24 (26.80-36.58)
	Min-Max	15.79-64.95	9.40-69.62	10-69.60	8.70-70
BMI category					
	BMI ≥ 30	263 (55.37%)	4,498 (46.02%)	3,191 (49.11%)	4,927 (45.60%)
	BMI < 30	165 (34.74%)	3,505 (35.86%)	2,430 (37.40%)	3,647 (33.75%)
	Missing	47 (9.89%)	1,770 (18.11%)	877 (13.50%)	2,231 (20.65%)
Smoking					
	Current smoker	52 (14.02%)	1,015 (15.25%)	650 (14.16%)	1,051 (14.62%)
	Never smoked	166 (44.74%)	2,988 (44.89%)	1,972 (42.97%)	3,173 (44.14%)

Redacted

		JAKi (tofacitinib)	TNFi	Non TNFi	csDMARD
	Previously smoked	127 (34.23%)	2,133 (32.05%)	1,705 (37.15%)	2,481 (34.51%)
	Unknown/Missing	26 (7.01%)	520 (7.81%)	262 (5.71%)	484 (6.73%)
Hypertension					
	N (%)	127 (26.74%)	2,346 (24%)	2,275 (35.01%)	3,110 (28.78%)
Hyperlipidemia					
	N (%)	94 (19.79%)	1,895 (19.39%)	1,706 (26.25%)	2,537 (23.48%)
Coronary artery disease					
	N (%)	15 (3.16%)	388 (3.97%)	584 (8.99%)	662 (6.13%)
History of SI					
	N (%)	4 (0.84%)	176 (1.80%)	427 (6.57%)	391 (3.62%)
Malignancy					
	N (%)	12 (2.53%)	171 (1.75%)	365 (5.62%)	389 (3.60%)
Pregnancy					
	N (%)	1 (0.21%)	32 (0.33%)	25 (0.38%)	28 (0.26%)
ILD COPD Asthma					
	N (%)	44 (9.26%)	670 (6.86%)	773 (11.90%)	1,000 (9.25%)
VTE					
	N (%)	2 (0.42%)	84 (0.86%)	125 (1.92%)	150 (1.39%)
Heart disease					
	N (%)	36 (7.58%)	723 (7.40%)	1,006 (15.48%)	1,159 (10.73%)
CVA					
	N (%)	1 (0.21%)	46 (0.47%)	64 (0.98%)	67 (0.62%)
PVD					
	N (%)	4 (0.84%)	161 (1.65%)	267 (4.11%)	288 (2.67%)
Other immune deficiency					
	N (%)	27 (5.68%)	333 (3.41%)	280 (4.31%)	342 (3.17%)
HIV AIDS					
	N (%)	1 (0.21%)	8 (0.08%)	15 (0.23%)	20 (0.19%)
Diabetes					
	N (%)	59 (12.42%)	1,197 (12.25%)	1,201 (18.48%)	1,587 (14.69%)
CKD dialysis					
	N (%)	32 (6.74%)	651 (6.66%)	782 (12.03%)	953 (8.82%)
Liver disease					
	N (%)	18 (3.79%)	366 (3.75%)	379 (5.83%)	348 (3.22%)
Corticosteroid use					
	N (%)	223 (46.95%)	3,061 (31.32%)	2,170 (33.39%)	3,471 (32.12%)

Table 10. Baseline Comorbidities of Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

		JAKi (tofacitinib)	TNFi	Non TNFi	conventional UC treatment
BMI					
	N	237	6,861	13,072	23,888
	Mean (SD)	27.57 (7.14)	27.21 (6.69)	28.07 (7.01)	28.14 (6.67)
	Median (IQR)	26.50 (22.20-30.80)	26.09 (22.50-30.64)	27 (23.11-31.79)	27.10 (23.50-31.60)
	Min-Max	16.10-53.72	5-69	9.70-70	5.20-70
BMI category					
	BMI ≥ 30	70 (26.92%)	1,921 (25.34%)	4,290 (28.28%)	7,870 (26.15%)
	BMI < 30	167 (64.23%)	4,940 (65.15%)	8,782 (57.89%)	16,018 (53.21%)
	Missing	23 (8.85%)	721 (9.51%)	2,098 (13.83%)	6,213 (20.64%)
Smoking					
	Current smoker	10 (4.67%)	498 (8.21%)	1,503 (13.06%)	1,900 (9.11%)
	Never smoked	130 (60.75%)	3,225 (53.17%)	5,509 (47.88%)	10,483 (50.25%)
	Previously smoked	60 (28.04%)	1,886 (31.10%)	3,947 (34.31%)	6,956 (33.34%)
	Unknown/Missing	14 (6.54%)	456 (7.52%)	546 (4.75%)	1,522 (7.30%)
Hypertension					
	N (%)	48 (18.46%)	1,380 (18.20%)	5,556 (36.62%)	7,858 (26.11%)
Hyperlipidemia					
	N (%)	36 (13.85%)	1,081 (14.26%)	3,992 (26.32%)	6,299 (20.93%)
Coronary artery disease					
	N (%)	9 (3.46%)	285 (3.76%)	1,878 (12.38%)	2,151 (7.15%)
History of SI					
	N (%)	31 (11.92%)	2,233 (29.45%)	4,593 (30.28%)	5,494 (18.25%)
Malignancy					
	N (%)	6 (2.31%)	281 (3.71%)	1,913 (12.61%)	1,780 (5.91%)
Pregnancy					
	N (%)	0 (0%)	87 (1.15%)	179 (1.18%)	329 (1.09%)
ILD COPD Asthma					
	N (%)	22 (8.46%)	740 (9.76%)	2,309 (15.22%)	3,043 (10.11%)
VTE					
	N (%)	11 (4.23%)	299 (3.94%)	845 (5.57%)	896 (2.98%)
Heart disease					
	N (%)	21 (8.08%)	745 (9.83%)	3,544 (23.36%)	4,141 (13.76%)
CVA					
	N (%)	3 (1.15%)	43 (0.57%)	241 (1.59%)	284 (0.94%)
PVD					
	N (%)	1 (0.38%)	179 (2.36%)	1,088 (7.17%)	1,075 (3.57%)

Redacted

		JAKi (tofacitinib)	TNFi	Non TNFi	conventional UC treatment
Other immune deficiency					
	N (%)	16 (6.15%)	346 (4.56%)	635 (4.19%)	826 (2.74%)
HIV AIDS					
	N (%)	0 (0%)	9 (0.12%)	67 (0.44%)	64 (0.21%)
Diabetes					
	N (%)	17 (6.54%)	630 (8.31%)	2,499 (16.47%)	3,349 (11.13%)
CKD dialysis					
	N (%)	18 (6.92%)	667 (8.80%)	2,880 (18.98%)	3,110 (10.33%)
Liver disease					
	N (%)	9 (3.46%)	355 (4.68%)	1,127 (7.43%)	1,462 (4.86%)
Corticosteroid use					
	N (%)	174 (66.92%)	4,899 (64.61%)	5,156 (33.99%)	8,880 (29.50%)

10.3. Outcome Data

10.3.1. Influenza and Influenza-like Illness Frequencies

Among RA patients (Table 11), the following counts of incident influenza cases occurred during the study, listed by the drug class the patients were prescribed at the time: 105 (tofacitinib), 106 (JAKi), 284 (non-TNFi), 328 (TNFi), and 1,184 (csDMARD). Additionally, the following counts of incident influenza-like illnesses occurred during the study (by drug class): 1,207 (tofacitinib), 1,225 (JAKi), 3,243 (non-TNFi), 4,831 (TNFi), and 14,773 (csDMARD).

Table 11. Incident Cases of Influenza and Influenza-like Illness, and Person Time, in Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy and Age

Outcome	Tofa		JAKi		Non TNFi		TNFi		csDMARD	
Influenza										
Cases (N)	105		106		284		328		1,184	
Cases (N) by age (18-64/65+)	87	18	88	18	183	101	256	72	726	458
Person years	5,861.84		5,908.71		16,962.40		29,795.11		94,614.80	
Person years by age (18-64/65+)	4,452.30	1,409.54	4,488.60	1,420.11	10,840.76	6,121.65	22,916.03	6,879.08	58,530.73	36,084.07
Influenza-like illness										
Cases (N)	1,207		1,225		3,243		4,831		14,773	
Cases (N) by age (18-	970	237	986	239	2,234	1,009	3,887	944	9,815	4,958

Outcome	Tofa		JAKi		Non TNFi		TNFi		csDMARD	
64/65+)										
Person years	5,192.19		5,235.16		15,443.62		26,293.85		83,175.76	
Person years by age (18-64/65+)	3,920.28	1,271.92	3,953.53	1,281.63	9,731.01	5,712.61	20,093.59	6,200.26	50,753.36	32,422.39

Among PsA patients (Table 12), the following counts of incident influenza cases occurred during the study (by drug class): 1 (JAKi-tofacitinib), 36 (non-TNFi), 78 (TNFi), and 85 (csDMARD). Additionally, the following counts of incident influenza-like illnesses occurred during the study (by drug class): 29 (JAKi-tofacitinib), 566 (non-TNFi), 1,381 (TNFi), and 1,489 (csDMARD).

Table 12. Incident Cases of Influenza and Influenza-like Illness, and Person Time, in Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy and Age

Outcome	JAKi (tofacitinib)		Non TNFi		TNFi		csDMARD	
Influenza								
Cases (N)	1		36		78		85	
Cases (N) by age (18-64/65+)	1	0	31	5	69	9	68	17
Person years	194.31		3,096.39		8,989.60		9,446.07	
Person years by age (18-64/65+)	170.54	23.77	2,636.26	460.14	7,945.85	1,043.75	7,345.60	2,100.47
Influenza-like illness								
Cases (N)	29		566		1,381		1,489	
Cases (N) by age (18-64/65+)	28	1	494	72	1,259	122	1,196	293
Person years	184.82		2,863.64		7,991.58		8,383.73	
Person years by age (18-64/65+)	161.47	23.35	2,424.08	439.56	7,022.48	969.10	6,510.26	1,873.47

Among UC patients (Table 13), the following counts of incident influenza cases occurred during the study (by drug class): 2 (JAKi-tofacitinib), 85 (non-TNFi), 89 (TNFi), and 282 (csDMARD). Additionally, the following counts of incident influenza-like illnesses occurred during the study (by drug class): 17 (JAKi-tofacitinib), 814 (non-TNFi), 1,044 (TNFi), and 3,699 (csDMARD).

Table 13. Incident Cases of Influenza and Influenza-like Illness, and Person Time, in Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019)

Outcome	JAKi (tofacitinib)		Non TNFi		TNFi		conventional UC treatment	
Influenza								
Cases (N)	2		85		89		282	
Cases (N) by age (18-64/65+)	2	0	58	27	81	8	210	72
Person years	103.39		5,263.19		6,542.55		25,888.52	
Person years by age (18-64/65+)	95.16	8.24	3,918.37	1,344.82	5,957.77	584.78	19,917.77	5,970.74
Influenza-like illness								
Cases (N)	17		814		1,044		3,699	
Cases (N) by age (18-64/65+)	15	2	653	161	977	67	2,905	794
Person years	97.99		4,857.76		5,697.37		23,142.70	
Person years by age (18-64/65+)	90.20	7.80	3,574.51	1,283.25	5,167.96	529.42	17,738.46	5,404.24

Of note, the 1 and 2 counts of influenza cases among psoriatic arthritis and ulcerative colitis patients, respectively, in the tofacitinib-JAKi treatment class leads to highly unstable incident rate estimates in these groups.

Additional information on frequencies of influenza *clinical outcomes* is presented in Table 17-Table 19 below for the overall study period and in Source Tables S1-S29 (odd-numbered Source tables only) for each study year.

10.4. Main Results

Table 14-Table 16 show for each of the three indicated populations for the overall study period, incidence rates for both influenza and influenza-like illness, stratified by treatment and age. Source Tables S1-S30 show these results – not stratified by age – for each influenza season.

10.4.1. Rheumatoid Arthritis: Incidence Rates

10.4.1.1. Influenza

10.4.1.1.1. Full Study Period

In RA patients, the tofacitinib and JAKi treatment groups share the highest incidence rate for influenza (Incidence Rate [IR] 1.79, 95% Confidence Interval [CI] 1.48-2.17), followed in order by the non-TNFI, csDMARD, and TNFi groups (Table 14).

In the 18-64 age stratum, tofacitinib and JAKi users have the highest incidence rates for influenza (IR 1.95, 95% CI 1.59-2.41 and IR 1.96, 95% CI 1.59-2.42, respectively), followed in order by the rates for non-TNFi, csDMARD, and TNFi.

In the ≥65 age stratum, the non-TNFi group has the highest rate (IR 1.65, 95% CI 1.36-2.00), followed in order by the rates for the tofacitinib, JAKi, csDMARD, and TNFi groups.

10.4.1.1.2. By Influenza Season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S1-S10).

10.4.1.2. Influenza-Like Illness

10.4.1.2.1. Full Study Period

In RA patients, the JAKi group has the highest incidence rate of influenza-like illness (IR 23.40, 95% CI 22.13-24.75), followed in order by the tofacitinib, non-TNFi, TNFi, and csDMARD groups (Table 14).

In the 18-64 age stratum, the JAKi group has the highest incidence rate of influenza-like illness (IR 24.94, 95% CI 23.43-26.55), followed in order by the tofacitinib, non-TNFi, TNFi, and csDMARD groups.

In the ≥65 age stratum, the pattern of results is the same as in the 18-64 age stratum.

10.4.1.2.2. By Influenza Season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S1-S10).

Table 14. Incidence Rates, per 100 Person Years, of Influenza and Influenza-like Illness in Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy and Age

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
Treatment	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
Tofa: overall	1.79	1.48	2.17	23.25	21.97	24.60
18-64	1.95	1.59	2.41	24.74	23.24	26.35
65+	1.28	0.81	2.02	18.63	16.41	21.16
JAKi: overall	1.79	1.48	2.17	23.40	22.13	24.75
18-64	1.96	1.59	2.42	24.94	23.43	26.55
65+	1.27	0.81	2.00	18.65	16.43	21.17

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	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
Non TNFi: overall	1.67	1.49	1.88	21.00	20.29	21.73
18-64	1.69	1.46	1.95	22.96	22.03	23.93
65+	1.65	1.36	2.00	17.66	16.61	18.79
TNFi: overall	1.10	0.99	1.23	18.37	17.86	18.90
18-64	1.12	0.99	1.26	19.34	18.75	19.96
65+	1.05	0.83	1.32	15.23	14.29	16.23
csDMARD: overall	1.25	1.18	1.32	17.76	17.48	18.05
18-64	1.24	1.15	1.33	19.34	18.96	19.73
65+	1.27	1.16	1.39	15.29	14.87	15.72

10.4.2. Psoriatic Arthritis: Incidence Rates

10.4.2.1. Influenza

10.4.2.1.1. Full Study Period

Among PsA patients, the non-TNFi group has the highest incidence rate (1.16, 95% CI 0.84-1.61), followed in order by the csDMARD, TNFi, and tofacitinib-JAKi groups (Table 15). Of note, only one incident influenza case occurred in the tofacitinib-JAKi group.

In the 18-64 age stratum, the highest incidence rate is in the non-TNFi group (1.18, 95% CI 0.83-1.67), followed in order by the csDMARD, TNFi, and tofacitinib-JAKi groups.

In the ≥65 age stratum, the highest incidence rate is in the non-TNFi group (1.09, 95% CI 0.48-2.54), followed in order by the TNFi, and csDMARD groups. In the tofacitinib-JAKi group, there are no incident cases in this age group.

10.4.2.1.2. By Influenza Season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S11-S20).

10.4.2.2. Influenza-Like Illness

10.4.2.2.1. Full Study Period

In PsA patients, the non-TNFi group has the highest incidence rate of influenza-like illness (IR 19.77, 95% CI 18.20-21.46), followed in order by the csDMARD, TNFi, and tofacitinib-JAKi groups (Table 15).

In the 18-64 age stratum, the non-TNFi group has the highest incidence rate of influenza-like illness (IR 20.38, 95% CI 18.66-22.26), followed in order by the csDMARD, TNFi, and the tofacitinib-JAKi groups.

In the ≥65 age stratum, the pattern of results is the same as in the 18-64 age stratum, although the rates are higher in the non-TNFi and csDMARD groups than in the other two groups.

10.4.2.2.2. By influenza season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S11-S20).

Table 15. Incidence Rates per 100 Person Years of Influenza and Influenza-like Illness in Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019)

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
Treatment	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
JAKi (tofacitinib) overall	0.51	0.12	2.87	15.69	10.95	22.53
18-64	0.59	0.14	3.27	17.34	12.03	25.06
65+	0	0	15.52	4.28	1.04	23.86
Non-TNFi overall	1.16	0.84	1.61	19.77	18.20	21.46
18-64	1.18	0.83	1.67	20.38	18.66	22.26
65+	1.09	0.48	2.54	16.38	13.02	20.63
TNFi overall	0.87	0.70	1.08	17.28	16.39	18.22
18-64	0.87	0.69	1.10	17.93	16.97	18.95
65+	0.86	0.46	1.64	12.59	10.55	15.03
csDMARD overall	0.90	0.73	1.11	17.76	16.88	18.69
18-64	0.93	0.73	1.17	18.37	17.36	19.44
65+	0.81	0.51	1.30	15.64	13.95	17.54

10.4.3. Ulcerative Colitis: Incidence Rates

10.4.3.1. Influenza

10.4.3.1.1. Full Study Period

Among UC patients, the tofacitinib-JAKi group has the highest influenza incidence rate (IR 1.93, 95% CI 0.60-6.99), followed in order by the non-TNFi, TNFi, and conventional UC treatment groups (Table 16). Of note, only two incident influenza cases occurred in the tofacitinib-JAKi group.

In the 18-64 age stratum, the highest incidence rate is in the tofacitinib-JAKi group (IR 2.10, 95% CI 0.65-7.59), followed in order by the non-TNFi, TNFi, and csDMARD groups.

In the ≥65 age stratum, the highest incidence rate is in the non-TNFi group (IR 2.01, 95% CI 1.39-2.92), followed in order by the TNFi and csDMARD groups. In this age group, there were no incident cases in the tofacitinib-JAKi group.

10.4.3.1.2. By Influenza Season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S21-S30).

10.4.3.2. Influenza-Like Illness

10.4.3.2.1. Full Study Period

Among UC patients, the TNFi group has the highest influenza-like illness rate (IR 18.32, 95% CI 17.25-19.47), followed in order by the tofacitinib-JAKi, non-TNFi, and csDMARD groups (Table 16).

In the 18-64 age stratum, the highest incidence rate is in the TNFi group (IR 18.91, 95% CI 18.91, 95% CI 17.76-20.13), followed in order by the non-TNFi, tofacitinib-JAKi, and csDMARD groups.

In the ≥65 age stratum, the highest incidence rate is in the tofacitinib-JAKi group (IR 25.65, 95% CI 7.93-92.66) (based on two incident cases), followed in order by the csDMARD, TNFi, and non-TNFi groups.

10.4.3.2.2. By Influenza Season

No pattern emerged over the influenza seasons that markedly diverges from the full study period results (Source Tables S21-S30).

Table 16. Incidence Rates per 100 Person Years of Influenza and Influenza-like Illness in Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019)

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
Treatment	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
JAKi (tofacitinib) overall	1.93	0.60	6.99	17.35	10.89	27.78
18-64	2.10	0.65	7.59	16.63	10.14	27.43
65+	0	0	44.79	25.65	7.93	92.66
Non-TNFi overall	1.62	1.31	2.00	16.76	15.65	17.95
18-64	1.48	1.15	1.91	18.27	16.92	19.72
65+	2.01	1.39	2.92	12.55	10.76	14.64
TNFi overall	1.36	1.11	1.67	18.32	17.25	19.47
18-64	1.36	1.0947	1.69	18.91	17.76	20.13
65+	1.37	0.70	2.70	12.66	9.97	16.07
csDMARD overall	1.09	0.97	1.22	15.98	15.48	16.51
18-64	1.05	0.92	1.21	16.38	15.79	16.98
65+	1.21	0.96	1.52	14.69	13.71	15.75

10.4.4. Rheumatoid arthritis: clinical outcomes

Among influenza cases, the most common complication across all treatment and age groups is neurological disorder (Table 17). The most common auxiliary medication across treatment and age groups is corticosteroids. The risk of influenza-related hospitalization is greater in the older versus younger age group and appears greatest in the non-TNFi treatment group, with the numerically lowest rates in the tofacitinib and JAKi treatment groups.

Results by influenza seasons (Source Tables S1, S3, S5, S7, S9) are consistent with those from the full study period.

Table 17. Frequencies and Incidence Proportions of Clinical Outcomes Among Influenza Cases in Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019)

	Tofa		JAKi		Non TNFi		TNFi		csDMARD		Total	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
Influenza cases	87	18	88	18	183	101	256	72	726	458	1253	649
Pneumonia	8	3	8	3	37	39	32	20	96	128	173	190
	9.2%[a]	16.7%	9.1%	16.7%	20.2%	38.6%	12.5%	27.8%	13.2%	27.9%	13.8%	29.3%
MI or stroke	0	0	0	0	7	14	3	4	15	41	25	59
	0.0%	0.0%	0.0%	0.0%	3.8%	13.9%	1.2%	5.6%	2.1%	9.0%	2.0%	9.1%
Neurologic disorder	16	7	16	7	78	51	64	35	203	189	361	282
	18.4%	38.9%	18.2%	38.9%	42.6%	50.5%	25.0%	48.6%	28.0%	41.3%	28.8%	43.5%
Corticosteroid use[b]	42	7	43	7	114	67	104	40	361	287	622	401
	48.3%	38.9%	48.9%	38.9%	62.3%	66.3%	40.6%	55.6%	49.7%	62.7%	49.6%	61.8%
Methotrexate use[b]	11	3	11	3	22	11	53	12	171	163	257	189
	12.6%	16.7%	12.5%	16.7%	12.0%	10.9%	20.7%	16.7%	23.6%	35.6%	20.5%	29.1%
Azathioprine use[b]	0	0	0	0	1	2	1	0	13	12	15	14
	0.0%	0.0%	0.0%	0.0%	0.5%	2.0%	0.4%	0.0%	1.8%	2.6%	1.2%	2.2%
Influenza hospitalization	9	4	9	4	52	66	29	32	127	214	217	316
	10.3%	22.2%	10.2%	22.2%	28.4%	65.3%	11.3%	44.4%	17.5%	46.7%	17.3%	48.7%
In-hospital death	0	0	0	0	0	1	0	0	2	4	2	5
	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.3%	0.9%	0.2%	0.8%
Death within 90 days	1	0	1	0	4	13	5	3	13	43	23	59
	1.1%	0.0%	1.1%	0.0%	2.2%	12.9%	2.0%	4.2%	1.8%	9.4%	1.8%	9.1%

a. Complication risks were calculated by dividing the number of complications by the number of corresponding influenza or influenza-like illness cases.

b. The timeframe for medication use was 30 days before or after the diagnosis date of influenza or influenza-like illness, and therefore this medication use could reflect treatment of RA, PsA, or UC rather than treatment of influenza or influenza-like illness.

10.4.5. Psoriatic Arthritis: Clinical Outcomes

The results described here pertain only to the non-TNFi, TNFi, and csDMARD treatment groups, since only one influenza case arose in the tofacitinib-JAKi treatment group (Table 18). The most frequent complication across all treatment and age groups are

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neurological disorders. The most common auxiliary medication across all treatment and age groups is corticosteroids, although in the csDMARD group methotrexate use is nearly as frequent as corticosteroid use. The risk of influenza-related hospitalization is greater in the older versus younger age group.

The seasonal influenza results (Source Tables S11, S13, S15, S17, S19) are largely consistent with those from the full study period, despite small counts (<10) in most outcome cells.

Table 18. Frequencies and Incidence Proportions of Clinical Outcomes Among Influenza Cases in Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019)

	JAKi (tofacitinib)		Non TNFi		TNFi		csDMARD		Total	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
Influenza cases	1	0	31	5	69	9	68	17	169	31
Pneumonia	0	0	1	0	7	1	4	2	12	3
	0.0%a	0.0%	3.2%	0.0%	10.1%	11.1%	5.9%	11.8%	7.1%	9.7%
MI or stroke	0	0	0	0	0	0	1	0	1	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	0.6%	0.0%
Neurologic disorder	0	0	8	1	15	4	14	6	37	11
	0.0%	0.0%	25.8%	20.0%	21.7%	44.4%	20.6%	35.3%	21.9%	35.5%
Corticosteroid useb	1	0	17	4	20	1	30	6	68	11
	100.0%	0.0%	54.8%	80.0%	29.0%	11.1%	44.1%	35.3%	40.2%	35.5%
Methotrexate useb	0	0	2	1	9	1	28	7	39	9
	0.0%	0.0%	6.5%	20.0%	13.0%	11.1%	41.2%	41.2%	23.1%	29.0%
Azathioprine useb	0	0	0	0	0	0	1	0	1	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	0.6%	0.0%
Influenza hospitalization	0	0	4	3	7	3	7	5	18	11
	0.0%	0.0%	12.9%	60.0%	10.1%	33.3%	10.3%	29.4%	10.7%	35.5%
In-hospital death	0	0	0	0	0	0		0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Death within 90 days	0	0	0	0	0	0	0	1	0	1
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.9%	0.0%	3.2%

a Complication risks were calculated by dividing the number of complications by the number of corresponding influenza or influenza-like illness cases.
b The timeframe for medication use was 30 days before or after the diagnosis date of influenza or influenza-like illness, and therefore this medication use could reflect treatment of RA, PsA, or UC rather than treatment of influenza or influenza-like illness.

10.4.6. Ulcerative Colitis: Clinical Outcomes

The results described here pertain only to the non-TNFi, TNFi, and conventional UC treatment groups, since only two influenza cases arose in the tofacitinib-JAKi treatment group (Table 19). The most frequent complication across both treatment and age groups are neurological disorders. The most common auxiliary medication type across treatment and age groups is corticosteroids. Azapriothine use is more common in the TNFi and csDMARD groups than in the non-TNFi group. The risk of influenza-related hospitalization is greater in the older versus younger age group.

The seasonal influenza results (Tables S21, S23, S25, S27, S29) are largely consistent with those from the full study period, despite small counts (<10) in most outcome cells.

Table 19. Frequencies and Incidence Proportions of Clinical Outcomes Among Influenza Cases in Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019)

	JAKi (tofacitinib)		Non TNFi		TNFi		csDMARD		Total	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
Influenza cases	2	0	58	27	81	8	210	72	351	107
Pneumonia	0	0	5	9	4	1	10	17	19	27
	0.0%a	0.0%	8.6%	33.3%	4.9%	12.5%	4.8%	23.6%	5.4%	25.2%
MI or stroke	0	0	2	4	0	0	1	3	3	7
	0.0%	0.0%	3.4%	14.8%	0.0%	0.0%	0.5%	4.2%	0.9%	6.5%
Neurologic disorder	2	0	19	12	7	2	39	30	67	44
	100.0%	0.0%	32.8%	44.4%	8.6%	25.0%	18.6%	41.7%	19.1%	41.1%
Corticosteriod useb	1	0	33	14	36	6	79	34	149	54
	50.0%	0.0%	56.9%	51.9%	44.4%	75.0%	37.6%	47.2%	42.5%	50.5%
Methotrexate useb	0	0	2	0	0	0	2	0	4	0
	0.0%	0.0%	3.4%	0.0%	0.0%	0.0%	1.0%	0.0%	1.1%	0.0%
Azathioprine useb	0	0	0	1	8	1	20	7	28	9
	0.0%	0.0%	0.0%	3.7%	9.9%	12.5%	9.5%	9.7%	8.0%	8.4%
Influenza hospitalization	1	0	16	12	10	4	33	31	60	47
	50.0%	0.0%	27.6%	44.4%	12.3%	50.0%	15.7%	43.1%	17.1%	43.9%
In-hospital death	0	0	1	0	0	0	0	0	1	0
	0.0%	0.0%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%
Death within 90 days	0	0	1	2	0	0	0	5	1	7
	0.0%	0.0%	1.7%	7.4%	0.0%	0.0%	0.0%	6.9%	0.3%	6.5%

a Complication risks were calculated by dividing the number of complications by the number of corresponding influenza or influenza-like illness cases.
b The timeframe for medication use was 30 days before or after the diagnosis date of influenza or influenza-like illness, and therefore this medication use could reflect treatment of RA, PsA, or UC rather than treatment of influenza or influenza-like illness.

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10.4.7. Influenza Vaccine Rrequency and Proportions by Influenza Season

10.4.7.1. Rheumatoid Arthritis: Vaccinations

In all treatment groups and in all years, the older age stratum is more likely to be vaccinated than the younger stratum (Table 20). There are no marked differences in vaccination patterns between the treatment groups.

Table 20. Annual Influenza Vaccination Frequencies and Proportions Among Rheumatoid Arthritis Patients, Stratified by Drug Therapy (01 June 2014 – 31 May 2019)

	Tofacitinib		JAKi		non-TNFi		TNFi		csDMARD		Total[a]	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
2014												
patients	945	316	945	316	4,084	2,917	6,761	2,168	17,285	12,727	30,020	18,444
vaccinated	180	78	180	78	756	706	1,069	511	2,545	3,036	4,730	4,409
	19.0%	24.7%	19.0%	24.7%	18.5%	24.2%	15.8%	23.6%	14.7%	23.9%	15.8%	23.9%
2015												
patients	1,150	385	1,150	385	5,429	3,730	6,079	1,908	15,159	10,536	28,967	16,944
vaccinated	250	113	250	113	1,202	996	1,125	526	2,771	2,743	5,598	4,491
	21.7%	29.4%	21.7%	29.4%	22.1%	26.7%	18.5%	27.6%	18.3%	26.0%	19.3%	26.5%
2016												
patients	1,564	578	1,564	578	6,723	5,242	6,211	1,901	16,012	11,167	32,074	19,466
vaccinated	297	160	297	160	1,492	1,509	1,171	501	2,874	2,953	6,131	5,283
	19.0%	27.7%	19.0%	27.7%	22.2%	28.8%	18.9%	26.4%	17.9%	26.4%	19.1%	27.1%
2017												
patients	1,749	648	1,749	648	6,808	5,365	5,164	1,874	13,909	9,886	29,379	18,421
vaccinated	319	173	319	173	1,425	1,417	1,028	466	2,418	2,432	5,509	4,661

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	Tofacitinib		JAKi		non-TNFi		TNFi		csDMARD		Total[a]	
	18.2%	26.7%	18.2%	26.7%	20.9%	26.4%	19.9%	24.9%	17.4%	24.6%	18.8%	25.3%
2018												
patients	1,868	750	1,980	779	5,824	4,628	5,013	1,825	12,641	9,118	27,326	17,100
vaccinated	338	180	360	184	1,271	1,222	1,003	473	2,372	2,136	5,344	4,195
	18.1%	24.0%	18.2%	23.6%	21.8%	26.4%	20.0%	25.9%	18.8%	23.4%	19.6%	24.5%

a. Patients can contribute to more than one treatment group and therefore the total may not represent unique individuals.

10.4.7.2. Psoriatic Arthritis: Vaccinations

With one exception (a year with sparse data in the JAKi/tofacitinib group), the older age stratum is more likely to be vaccinated than the younger stratum across treatment groups and years (Table 21). There are no marked differences in vaccination patterns between the treatment groups. The JAKi/tofacitinib group consisted of very few PsA patients (<15) in each of the first three years of the study.

Table 21. Annual Influenza Vaccination Frequencies and Proportions Among Psoriatic Arthritis Patients, Stratified by Drug Therapy (01 June 2014 – 31 May 2019)

	JAKi (tofacitinib)		non-TNFi		TNFi		csDMARD		Total[a]	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
2014										
patients	4	1	492	121	2,381	290	2,217	617	5,094	1,029
vaccinated	0	0	77	37	364	67	299	147	740	251
	0.0%	0.0%	15.7%	30.6%	15.3%	23.1%	13.5%	23.8%	14.5%	24.4%
2015										
patients	7	0	890	219	2,151	299	1,972	590	5,020	1,108
vaccinated	0	0	171	60	352	72	346	171	869	303
	0.0%	NA%	19.2%	27.4%	16.4%	24.1%	17.5%	29.0%	17.3%	27.3%
2016										
patients	11	3	1,440	369	2,233	359	2,217	669	5,901	1,400
vaccinated	4	0	304	116	369	92	372	182	1,049	390
	36.4%	0.0%	21.1%	31.4%	16.5%	25.6%	16.8%	27.2%	17.8%	27.9%

Redacted

	JAKi (tofacitinib)		non-TNFi		TNFi		csDMARD		Total[a]	
2017										
patients	128	18	1,658	425	1,888	286	1,913	564	5,587	1,293
vaccinated	25	4	307	114	331	66	323	148	986	332
	19.5%	22.2%	18.5%	26.8%	17.5%	23.1%	16.9%	26.2%	17.6%	25.7%
2018										
patients	270	42	1,658	460	1,868	330	1,757	617	5,553	1,449
vaccinated	43	14	310	135	363	82	316	161	1,032	392
	15.9%	33.3%	18.7%	29.3%	19.4%	24.8%	18.0%	26.1%	18.6%	27.1%

a. Patients can contribute to more than one treatment group and therefore the total may not represent unique individuals.

10.4.7.3. Ulcerative Colitis: Vaccinations

With two exceptions (two years with sparse data in the JAKi/tofacitinib group), the older age stratum is more likely to be vaccinated than the younger stratum across treatment groups and years (Table 22). There are no marked differences in vaccination patterns between the treatment groups. The JAKi/tofacitinib group consisted of very few UC patients (<6) in each of the first three years of the study.

Table 22. Annual Influenza Vaccination Frequencies and Proportions Among Ulcerative Colitis Patients, Stratified by Drug Therapy (01 June 2014 – 31 May 2019)

	JAKi (tofacitinib)		non-TNFi		TNFi		csDMARD		Total[a]	
	18-64	65+	18-64	65+	18-64	65+	18-64	65+	18-64	65+
2014										
patients	2	1	1,463	760	1,271	132	5,722	1,918	8,458	2,811
vaccinated	0	0	258	176	216	41	807	465	1,281	682
	0.0%	0.0%	17.6%	23.2%	17.0%	31.1%	14.1%	24.2%	15.1%	24.3%
2015										
patients	3	0	2,264	1,075	1,591	183	5,942	2,062	9,800	3,320
vaccinated	1	0	487	260	300	58	952	627	1,740	945
	33.3%	NA	21.5%	24.2%	18.9%	31.7%	16.0%	30.4%	17.8%	28.5%
2016										
patients	5	0	2,528	1,280	1,720	201	6,045	2,255	10,298	3,736

Redacted

	JAKi (tofacitinib)		non-TNFi		TNFi		csDMARD		Total[a]	
vaccinated	1	0	526	374	334	67	1,064	661	1,925	1,102
	20.0%	NA	20.8%	29.2%	19.4%	33.3%	17.6%	29.3%	18.7%	29.5%
2017										
patients	22	3	2,867	1,463	1,538	191	5,564	2,095	9,991	3,752
vaccinated	3	0	542	400	313	51	947	592	1,805	1,043
	13.6%	0.0%	18.9%	27.3%	20.4%	26.7%	17.0%	28.3%	18.1%	27.8%
2018										
patients	204	23	2,633	1,317	1,513	196	4,909	1,838	9,259	3,374
vaccinated	41	8	528	358	289	53	864	504	1,722	923
	20.1%	34.8%	20.1%	27.2%	19.1%	27.0%	17.6%	27.4%	18.6%	27.4%

a. Patients can contribute to more than one treatment group and therefore the total may not represent unique individuals.

10.5. Other Analyses

None.

10.6. Adverse Events/Adverse Reactions

This study involves data that exist as structured data. 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 AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. DISCUSSION

11.1. Key Results

This retrospective database study included 199,697 patients 18 year of age and older with diagnoses of RA (n=137,910), PsA (19,179), and UC (42,608).

11.1.1. Demographics and Comorbidities

Patients with RA were older and more likely to be female than patients with PsA or UC. White patients comprised between 81-91% and non-Hispanic patients approximately 90% of each indicated population.

In all three indicated patient groups, those in the non-TNFi and csDMARD/conventional UC treatment groups were more likely to be ≥65 years old, and to have Medicare health insurance, than were those in the tofacitinib, JAKi, and TNFi treatment groups.

Also in all three indicated groups, those in the non-TNFi and csDMARD treatment groups had the highest prevalence of most of the assessed comorbid conditions; the other three treatment groups generally shared a similar lower prevalence of most of these conditions.

Line of treatment was not determined in this study. But RA, PsA, and UC patients in the JAKi treatment groups were more likely to have a history of treatment with TNFi and non-TNFi than the other treatment groups. Moreover, in all three indicated groups, the tofacitinib and JAKi treatment groups were more likely to use corticosteroids than were the other treatment groups. This difference in corticosteroid use was most pronounced in UC patients and least pronounced in the RA patients.

11.1.2. Influenza and Influenza-Like Illness Incidence Rates, Overall And By Season

11.1.2.1. RA Patients

Among RA patients in the full study period, the tofacitinib-JAKi group had the highest influenza incidence rate (IR 1.79 [1.48-2.17] in both the tofacitinib and JAKi groups) and the TNFi group the lowest rate (IR 1.10 [0.99-1.23]). The relatively high incidence rate in the tofacitinib-JAKi group was driven by a high rate in the 18-64 age stratum compared with a much lower rate in the ≥65 age stratum; the same age divergence was not observed in the other treatment groups' influenza rates. The seasonal influenza results – with smaller counts and correspondingly less stable rate estimates -- did not markedly diverge from the full study period results.

For influenza-like illness in the full study period, the tofacitinib-JAKi group had the highest incidence rates (IR 23.25 [21.97-24.60] and IR 23.40 [22.13-24.75], respectively) and the csDMARD group the lowest rate (IR 17.76 [17.48-18.05]). This pattern of results was essentially the same in both the 18-64 and ≥65 age strata. The seasonal influenza-like illness results did not diverge from the full study period results, except that in the final year (2018), the rates largely converged across treatment groups.

In this sample, RA patients taking tofacitinib and non-TNFi's had higher risks of influenza compared with the other treatment groups, though for tofacitinib this was driven by the 18-64 age stratum. Tofacitinib users also had a higher risk of influenza-like illness compared with all other treatment groups and the non-TNFi users had a higher influenza-like risk than the TNFi and csDMARD users.

11.1.2.2. PsA Patients

Among PsA patients in the full study period, the non-TNFi group had the highest influenza incidence rate (IR 1.16 [0.84-1.61]) and the tofacitinib-JAKi group the lowest rate (IR 0.51 [0.12-2.87]). The same pattern of findings obtained in both age strata. In the seasonal influenza results, small counts led to unstable estimates with broadly overlapping confidence intervals.

Influenza-like illness results for the full study period mirrored the influenza results. The non-TNFi group had the highest incidence rate (IR 19.77 [18.20-21.46]) and the tofacitinib-JAKi group the lowest (IR 15.69 [10.95-22.53]). This pattern of results obtained in both age strata. In the seasonal influenza-like illness results, small counts led to unstable estimates with broadly overlapping confidence intervals.

In this sample of PsA patients, the non-TNFi group had the highest influenza and influenza-like illness incidence rates, and the tofacitinib-JAKi group the lowest of both rates. The small number of PsA patients taking tofacitinib during the study period (475), yielding only one reported influenza case, led to an unstable influenza rate estimate (IR 0.51 [0.12-2.87]) and potentially uninformative influenza results concerning tofacitinib.

11.1.2.3. UC Patients

Among UC patients in the full study period, the tofacitinib-JAKi group had the highest influenza incidence rate (IR 1.93 [0.60-6.99]) followed by the non-TNFi group (IR 1.62 [1.31-2.00]). The conventional UC treatment group had the lowest rate (IR 1.09 [0.97-1.22]). The same pattern of findings obtained in the 18-64 age stratum; in the ≥65 age stratum, there were no cases in the tofacitinib-JAKi group, the non-TNFi group had the highest rate, and the conventional UC treatment group had the lowest rate. In the seasonal influenza results, small counts led to unstable estimates with broadly overlapping confidence intervals.

For influenza-like illness in the full study period, the TNFi group had the highest incidence rate (IR 18.32 [17.25-19.47]) and the conventional UC treatment group the lowest rate (IR 15.98 [15.48-16.51]). This pattern persisted in the 18-64 age stratum but in the ≥65 age stratum the tofacitinib-JAKi group had the highest incidence rate and the non-TNFi group the lowest. In the seasonal influenza-like illness results, the TNFi group had the highest rate in each of the five years.

In this sample of UC patients, the non-TNFi group had a higher influenza rate than the conventional UC treatment group. The small number of UC patients taking tofacitinib during the study period (260), yielding only two reported influenza cases, led to an unstable influenza rate estimate (IR 1.93 [0.60-6.99]) and potentially uninformative results concerning tofacitinib. For influenza-like illness, the risk was higher in the TNFi group than in the conventional UC treatment group.

11.1.3. Clinical Outcomes

In all patient groups and across treatments and age strata, the most frequent influenza complications were neurological and the most frequent auxiliary medications (ie, those medications taken within 30 days of the influenza diagnosis) were corticosteroids (although in PsA patients in the csDMARD group, methotrexate use nearly equaled corticosteroid use in both age strata). Older patients generally had higher rates of influenza complications than younger patients.

In patients with RA and in both age groups, the risk of influenza-related hospitalization, pneumonia, neurologic disorders, MI or stroke, and death within 90 days appeared higher in the non-TNFi group than in the other groups. Patients in the JAKi/tofacitinib groups had the numerically lowest rates of influenza complications. In patients with PsA and UC there were overall relatively few influenza cases and accordingly also a low number of complications, making it difficult to compare complication rates across treatment groups.

The seasonal results were consistent with the full study period results despite small counts (<10) in most clinical outcome cells in the PsA and UC diagnostic groups. In PsA patient there was only one influenza case in the tofacitinib-JAKi group and in UC patients only two influenza cases in the tofacitinib-JAKi group, thereby not contributing to these findings.

11.2. Limitations

The Optum database is large and covers all four US geographic regions; however, limitations that are general to all EHR database analyses as well as those specific to this study should be noted. Diagnoses of immune-mediated inflammatory diseases were 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 were used. The baseline period of this study was of limited duration and thus baseline comorbidities and risk factors occurring outside of this baseline period may not have been captured, leading to a potential undercount of these factors.

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 are not recorded in the database. Although data on vaccinations were collected from the database, they were likely undercounted as many 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 over-sampled more severe RA, PsA, and UC cases, as well as more severe cases of influenza; this may be particularly true for influenza-like illnesses.

The number of PsA and UC patients taking tofacitinib was small – 475 and 260, respectively – which led to unreliable influenza rate estimates.

The primary analyses did not adjust for potential confounding, nor did they distinguish between monotherapy and combination treatment exposures (eg, between methotrexate alone and methotrexate and tofacitinib used concurrently). Therefore, observed associations between drugs and outcomes may be due to confounding or to a drug used concurrently or to interaction with concurrently used drugs. These limitations make causal inference inappropriate regarding the associations between treatments and outcomes. Regarding the potential effects of combination therapy on the results, a sensitivity analysis assessed the extent to which the 108 influenza cases attributed to a tofacitinib drug era across the three indications may also have been attributed to another study drug era (Table 23). (By "attribution" we mean the influenza case occurred during a drug era of that drug class, as described in Section 9.9.2., and no causal attribution is intended.) Of these 108 influenza cases, 85 (78.7%) were diagnosed within 3 months of initiating tofacitinib, 99 (91.7%) within 6 months, and 107 (99.1%) within 12 months (Table 23, bottom row). Of the 85 influenza cases (of the 108 influenza cases attributed to a tofacitinib drug era) diagnosed within 3 months of initiating tofacitinib, 48 (57%) of these cases were also prescribed another drug class at some point during the period. Of the 107 influenza cases diagnosed within 12 months of initiating tofacitinib, 89 (83.2%) were also prescribed another drug class in the same period. Accordingly, a large proportion of influenza cases attributed to a tofacitinib drug era occurred with contemporaneous use of other study drugs and the individual versus joint effects of the drugs on influenza incidence cannot be discerned from the data.

An additional limitation is that the drug codes assigned to the non-TNFi drug category included HCPCS code J3490, which captures unclassified drugs typically administered by injection. To the extent this code captured drugs not in the non-TNFi category, the non-TNFi results may be biased. A sensitivity analysis (Table 24-Table 26) removing this code from the non-TNFi category did not change the overall conclusions. Removing the code resulted in decreased non-TNFi influenza incidence rates in each indication, but with no change in the relative results across drug classes. Regarding influenza-*like* illness rates, there was minimal change in the non-TNFi rates for RA and PsA patients and there was an increase among UC patients. However, no meaningful change in the relative results across drug classes occurred.

Finally, these study results may not be generalizable outside of the insured population.

Table 23. Sensitivity Analysis of all 108 Influenza Diagnoses Attributed to a Tofacitinib Drug era among RA, PsA, and UC Patients

	Influenza cases diagnosed during the following intervals after initiating tofacitinib			
	≤3 months N (%)	≤6 months N (%)	≤12 months N (%)	During study N (%)
csDMARD	42 (38.9%)	58 (53.7%)	72 (66.7%)	98 (90.7%)
TNFi	1 (0.9%)	12 (11.1%)	28 (25.9%)	55 (50.9%)
Non-TNFi	12 (11.1%)	19 (17.6%)	29 (26.9%)	58 (53.7%)
JAKi other	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)

Redacted

	Influenza cases diagnosed during the following intervals after initiating tofacitinib			
	≤3 months N (%)	≤6 months N (%)	≤12 months N (%)	During study N (%)
Any non-tofacitinib study drug	48 (44.4%)	70 (64.8%)	89 (82.4%)	105 (97.2%)
Tofacitinib	85 (78.7%)	99 (91.7%)	107 (99.1%)	108 (100%)

Table 24. Sensitivity Analysis of Removing Code J3490 From non-TNFi Drug Group: Incidence Rates, per 100 Person Years, of Influenza and Influenza-like Illness in Persons Diagnosed with Rheumatoid Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
Tofacitinib	1.79	1.48	2.17	23.22	21.95	24.57
JAKi	1.79	1.48	2.17	23.38	22.10	24.72
Non-TNFi (without J3490)	1.44	1.24	1.68	21.50	20.60	22.43
Non-TNFi (with J3490)	1.67	1.49	1.88	21.00	20.29	21.73
TNFi	1.10	0.99	1.23	18.38	17.87	18.90
csDMARD	1.25	1.18	1.32	17.76	17.48	18.05

Table 25. Sensitivity Analysis of Removing Code J3490 From non-TNFi Drug Group: Incidence Rates, per 100 Person Years, of Influenza and Influenza-like Illness in Persons Diagnosed with Psoriatic Arthritis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
Tofacitinib	0.51	0.12	2.86	15.64	10.92	22.47
JAKi	0.51	0.12	2.86	15.64	10.92	22.47
Non-TNFi (without J3490)	1.05	0.72	1.52	19.19	17.51	21.04
Non-TNFi (with J3490)	1.16	0.84	1.61	19.77	18.20	21.46
TNFi	0.87	0.70	1.08	17.27	16.39	18.21
csDMARD	0.90	0.73	1.11	17.75	16.88	18.68

Table 26. Sensitivity Analysis of Removing Code J3490 From non-TNFi Drug Group: Incidence Rates, per 100 Person Years, of Influenza and Influenza-like Illness in Persons Diagnosed with Ulcerative Colitis (01 June 2014 – 31 May 2019), Stratified by Drug Therapy

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
	IR	95% Confidence Interval		IR	95% Confidence Interval	
		Lower	Upper		Lower	Upper
Tofacitinib	1.93	0.60	6.97	17.31	10.86	27.72
JAKi	1.93	0.60	6.97	17.31	10.86	27.72

Redacted

	Influenza Incidence Rate			Influenza-like Illness Incidence Rate		
Non-TNFi (without J3490)	1.76	1.33	2.33	18.99	17.34	20.81
Non-TNFi (with J3490)	1.62	1.31	2.00	16.76	15.65	17.95
TNFi	1.36	1.10	1.67	18.27	17.19	19.41
conventional UC treatment	1.09	0.97	1.22	15.96	15.46	16.49

11.3. Interpretation

The results of this study, based solely on structured data analysis, suggest that in RA, PsA, and UC patient cohorts, certain treatments may be associated with higher rates of influenza and/or influenza-like illness than others. Specifically, in RA patients, the tofacitinib-JAKi treatment group (comprised mostly of tofacitinib users) had the highest rates of influenza and influenza-like illness compared with the other treatment groups. In contrast, risk of influenza complications appeared to be highest in the non-TNFi group, with the numerically lowest influenza complication rates in patients in the tofacitinib-JAKi treatment group.

In PsA patients, the non-TNFi treatment group had the highest rates of influenza and influenza-like illness compared with the other treatment groups. In UC patients, the non-TNFi group had the highest rate of influenza and the TNFi group had the highest rate of influenza-like illness. Tofacitinib-JAKi influenza counts were <3 in both PsA and UC patient groups and did not contribute meaningfully to these results.

As noted in the limitations section, these results are descriptive only, with no adjustment for potential confounding, including patient channeling, and no distinction between monotherapy and combination therapy. Accordingly, causal attributions to a particular drug class are not warranted. Higher influenza rates in a treatment group may be due to a higher severity of disease among those receiving the treatment rather than to the treatment itself. The unadjusted results reported here are therefore potentially inconsistent with *adjusted* results from other real-world evidence studies. In a study of influenza risk among IBD patients,[6] there was no significant risk difference between those treated with 5-ASAs, TNFi, and immunomodulators, after adjusting for demographics and comorbidities (though there was an increased risk in those treated with corticosteroids). Likewise, monotherapy and combination therapy were not distinguished in the present study and results observed in any one treatment group may reflect the effects of another drug class taken concurrently.

11.4. Generalizability

While these data are likely generalizable to insured populations in the United States, they may not be generalizable to uninsured populations in the United States or to populations in other countries.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In this study, some of the assessed treatments were associated with an increased rates of influenza or influenza-like illness or influenza-related complications in RA, PsA, and UC patients. However, given the absence of confounding control and no distinction between monotherapy and combination therapy, no causal attributions to these treatments are warranted. Therefore, these results do not provide any new information about the safety profile of tofacitinib. Finally, the number of PsA and UC patients exposed to tofacitinib was small, producing correspondingly unstable and possibly uninformative rate estimates.

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22. Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as September 4, 2012, as first released on November 26, 2012).

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