NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Retrospective Post-Marketing Safety Surveillance Study of Tofacitinib in Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA)
Protocol number	A3921421
Protocol version identifier	2.0
Date	07 December 2022
European Union (EU) Post Authorization Study (PAS) register number	EUPAS46286
Active substance	L04AA29 – Tofacitinib citrate
Medicinal product	Xeljanz (Tofacitinib)
Research question and objectives	**Research question:** What are the types and reporting rates (RR) of adverse events (AE) in patients receiving tofacitinib for PsA or RA reported in the Pfizer safety database? **Objectives:** 1. To describe the demographics and clinical characteristics of PsA or RA patients treated with tofacitinib for whom adverse events have been reported in the Pfizer safety database. 2. To characterize the types and RR of AEs in patients receiving tofacitinib for PsA or RA captured within the Pfizer safety database.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AVDOS	average daily dose
bDMARD	biologic disease modifying anti-rheumatic drug
BID	twice daily
CI	confidence interval
CID	chronic inflammatory disease
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
DSMB	data safety monitoring board
DVT	deep vein thrombosis
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
ICD	International Classification of Diseases, Tenth Revision
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
IR	immediate release
IRB	Institutional Review Board
JIA	Juvenile Idiopathic Arthritis

Abbreviation	Definition
mg	milligram
N	Number
NA	North America
NMSC	non-melanoma skin cancer
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PE	pulmonary embolism
PMS	post-marketing surveillance
PR	prolonged release
PsA	psoriatic arthritis
QD	once daily
RA	rheumatoid arthritis
ROW	Rest of World
RR	reporting rate
SOC	system organ class
SAE	Serious Adverse Event
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic disease modifying anti-rheumatic drug
UC	ulcerative colitis
Unk	Unknown
US	United States

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Abbreviation	Definition
VTE	venous thromboembolism
XR	extended release

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Stand Alone document, see ANNEX 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	07 December 2022	Section 9.1 Study Design	Dates updated, references added, Cardiovascular risk added, MACE deleted, Exploratory Point added.	Administrative
		Section 9.2.Setting	Dates updated	Administrative
		Section 9.2.1.	Added word “regions”	Administrative
		Section 9.2.2.	Added new dates	Administrative
		Section 9.3 Variables	Added Cardiovascular risk and reference to the table, deleted MACE	Administrative
		Section 9.6. Data Management	Added word “regions”	Administrative
		Section 9.9 Limitations of the Research Methods	Added the word “regions”	Administrative

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	25 January 2022
Start of data collection	22 September 2022
End of data collection	06 October 2022
Registration in the EU PAS register	13 September 2022
Final study report	06 September 2023

7. RATIONALE AND BACKGROUND

Psoriatic arthritis (PsA) is a chronic inflammatory disease (CID) manifesting in skin and nail lesions, peripheral arthritis, inflammation of entheseal insertion points, swollen digits, and spondylitis.[1] The prevalence of PsA is approximately 133 per 100,000 subjects (95% Confidence Interval [CI], 107-167 per 100,000 subjects) worldwide, with wide geographical variation.[2] Patients with PsA have an increased risk of comorbid cardiovascular disease, obesity, Type 2 diabetes, hypertension, metabolic syndrome, infection, and health-related quality of life issues.[3,1]

International treatment guidelines for PsA recommend initial therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate.[4,5,6] In patients lacking sufficient clinical response from csDMARD treatment, advanced therapies such as biologic DMARDs (bDMARDs) or in certain scenarios, targeted synthetic DMARDs (tsDMARDs) are recommended. Studies of patients receiving certain bDMARDs for PsA have reported reductions of cardiovascular disease,[7,8] possibly due to control of systemic inflammation,[1] similar rates malignancies[9,10] and increased risk of infection,[11,8,12,13,14] compared to patient populations not receiving bDMARDs. However, results across studies are varied,[15,16,18] and evidence to date regarding treatment emergent adverse events (AEs) in PsA are not as strong as in other CIDs such as Rheumatoid Arthritis (RA).[8]

Tofacitinib, is an oral Janus Kinase inhibitor for the treatment of PsA, RA, ulcerative colitis (UC), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis.[17,18] Tofacitinib is available in immediate release (5 and 10 mg tablet), extended release (11 mg tablet) and oral solution (1 mg/mL, JIA only) formulations. The safety profile of tofacitinib in PsA has been characterized in two Global Phase 3 studies[19,20] and an open-label long-term extension study[21] and was comparable with the safety profile of tofacitinib in RA across Phase 1, 2, 3 and 3b/4 studies.[22]

Safety of tofacitinib is of heightened interest following availability of results from a Food and Drug Administration (FDA)-mandated post-authorization safety study (PASS), which enrolled RA patients ≥50 years of age with at least one additional cardiovascular risk factor (Study A3921133). On 18 February 2019 the data safety monitoring board (DSMB) for Study A3921133 notified Pfizer of a statistically and clinically important difference in the occurrence of pulmonary embolism in patients receiving tofacitinib 10 mg BID compared to patients receiving Tumor Necrosis Factor inhibitors (TNFi). The DSMB also noted an increase in overall mortality with tofacitinib 10 mg BID compared with tofacitinib 5 mg BID and TNFi. These interim findings were communicated via a Pfizer issued press release on 19 February 2019. In this randomized open label, safety event driven study non-inferiority criteria was not met in the comparison of tofacitinib and TNFi for the co-primary endpoints of adjudicated Major Adverse Cardiovascular Events (MACE) and malignancy (excluding non-melanoma skin cancer [NMSC])[23] Final top line results from Study A3921133 were communicated by Pfizer via a press release on 27 January 2021.

Post-marketing surveillance (PMS) monitors drug safety following market release and complements data from clinical trials. Spontaneous reports of adverse events are collected from patients, healthcare professionals, Regulatory Authorities, patient support and market research programmes, and reports extracted from the literature. PMS reports have been previously published for tofacitinib in UC[24] and RA,[25] although no similar report exists for PsA. To date, reports of real-world safety of tofacitinib are limited,[26] therefore, this study aims to further characterize the global real-world safety profile of tofacitinib in PsA through PMS data collected in the Pfzer safety database.

The overarching goal of this retrospective analysis of PMS data extracted from the Pfizer safety database is to help inform the real world safety profile of tofacitinib in PsA, and provide context with RA safety outcomes also from PMS reporting.

This retrospective non-interventional study is designated as a PASS and is voluntarily conducted by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

What are the types and RR of AEs in patients receiving tofacitinib for PsA or RA reported in the Pfizer safety database?

Objectives:

- To describe the demographics of PsA or RA patients treated with tofacitinib for whom AEs have been reported in the Pfizer safety database.

- To characterize the types and RR of AEs in patients receiving tofacitinib for PsA or RA captured within the Pfizer Safety database.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective analysis of worldwide PMS data collected from the Pfizer Safety database from 06 November 2012 (date of first regulatory approval [RA indication]) to 06 November 2021 in patients receiving tofacitinib for RA, and 14 December 2017 (first regulatory approval for PsA indication) to 06 November 2021.

Worldwide exposure estimates based on a combination of audited unit sales and prescription data will be used to estimate cumulative exposure of patients receiving tofacitinib for PsA or RA as denominator to calculate RR.

Endpoints of interest:

1. Demographics of patients with AEs reported in the PMS database by formulation (tofacitinib immediate release [IR], tofacitinib extended release [XR], unknown, tofacitinib all [tofacitinib IR and tofacitinib XR]) for PsA or RA:

    - Age (median, range);
    - Age ≥65 years/<65 years;
    - Sex (male/female/Unk);
    - Race (Black or African American/White/Asian/Other/Native Hawaiian or other Pacific Islander/American Indian or Alaska Native) and Ethnicity (Hispanic or Latino/Not Hispanic or Latino/Unknown);
    - Region (North America [NA][1]/Europe[2]/Rest of World [ROW].[3]

[1] Includes United States, Canada and Puerto Rico.

[2] Europe includes Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom.

[3] ROW includes Argentina, Australia, Brazil, Central America, Chile, China, Colombia, Ecuador, Egypt, Hong Kong, India, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Zealand, Peru, Philippines, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand, Tunisia, United Arab Emirates

2. Types and RR of treatment emergent AEs reported in the Pfizer Safety database[4] by formulation (tofacitinib IR, tofacitinib XR, unknown, tofacitinib All) for PsA or RA:

   - AEs as defined by MedDRA System Organ Class (SOC);
   - Serious adverse events (SAEs) as defined by MedDRA SOC;
   - Most commonly reported AEs (occurring ≥2%) by MedDRA preferred term (PT);
   - Discontinuations due to AEs;
   - Fatal cases;
   - Select adverse event of special interest (AESIs) as categorically defined by SOC/PT in Periodic Benefit Risk Evaluation Reports (PBRER):
     - Serious infections;
     - Herpes zoster (serious and non-serious);
     - Cardiovascular risk[5];
     - Malignancies (excluding NMSC);
     - NMSC;
     - Venous thromboembolism (VTE).

[4] Includes initial and follow-up reports submitted to Pfizer Safety database.

[5] Referred to as Cardiovascular events for publication purposes

Exploratory Endpoints:

1. Types and RR of treatment emergent AEs reported in the Pfizer Safety database by formulation (tofacitinib IR, tofacitinib XR, tofacitinib All) for PsA or RA according to patient demographics (age ≥65/<65 years, gender [male and female]), and time intervals ,[6] December 2015 – November 2017,[7] December 2017 – November 2019, December 2019 – November 2021)[8].

2. Types and RR for treatment emergent AEs reported in the Pfizer Safety database by formulation (tofacitinib IR, tofacitinib XR, tofacitinib ALL) for PsA or RA during the first four years of approval for the respective indication. For PsA, the timeframe will be the same as the main analysis (ie, 14 December 2017 – 06 November 2021). For RA, the timeframe will be 06 November 2012 – 06 November 2016.

All analyses will be descriptive and no formal comparisons will be made.

[6] For RA indication only; Post Marketing Surveillance data for RA during this time interval was previously reported in Cohen et al 2018.[25]

[7] For RA indication only; PsA gained first worldwide approval in December 2017.

[8] Two year time interval analyses will only include initial reports submitted to Pfizer Safety database to avoid double reporting across time intervals.

9.2. Setting

Pfizer safety database

The Pfizer Safety database collects spontaneous reports of AEs occurring during or after exposure to Pfizer medicines from patients, healthcare professionals, Regulatory Authorities, post-marketing trials, non-interventional studies, solicited reports from patient support programs and market research programs, and reports extracted from the literature. Information on AEs are collected via case report forms based on information gathered by the reporter, and include at minimum, an identifiable patient/subject, a suspect product, an event and an identifiable reporter. Should case reports be incomplete attempts are made by Pfizer to collect additional relevant information pertaining to reported AEs. This information is collected for the purpose of ongoing pharmacovigilance.

Given the spontaneous nature of AE reporting within the Pfizer Safety database, some important limitations should be noted. Information on patient history and characteristics, concomitant medications, adverse event scenario, causality and status/outcome may not be complete for every AE report as these items are not compulsory. The potential for reporting bias exists, as not all AEs may be reported, temporal variation in volume of spontaneous AE reports (Weber effect), or certain types of AEs may be preferentially reported compared to others. Emergent safety signals and subsequent Regulatory activities regarding tofacitinib during the timeframe of 2019-2021 may impact the volume and type of reported spontaneous AEs.

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Cumulative exposure to tofacitinib for RA or PsA is calculated from a combination of audited unit sales from RedactedRedactedRedactedRedacted from RedactedRedactedRedacted. Patient-years for tofacitinib IR are calculated by taking the average daily dose (AVDOS) of 2 units daily for 5 mg BID tofacitinib and 10 mg BID tofacitinib sales combined, the patient-years for tofacitinib XR are calculated by taking AVDOS of 1 unit daily for 11 mg QD tofacitinib sales, then adding up the individual patient-years for each formulation separately to generate a cumulative exposure number for tofacitinib during the timeframe. The AVDOS was used to convert unit sales into patient-days (days of therapy) and further divided by 365.25 (days in a year) to obtain patient-years. Cumulative exposure data are available from Redacted Redacted from 06 November 2012 through the third quarter of 2021, and are reported by quarter. Cumulative exposure will be extrapolated to the end of reporting period (06 November 2021) using the average cumulative exposure from the respective previous three quarters. Cumulative exposure for the following time intervals will be calculated for tofacitinib All in patients with RA: 01 December 2015 – 30 November 2017, 01 December 2017 – 30 November 2019, 01 December 2019 – 06 November 2021 and 06 November 2021 – 06 November 2016. Cumulative exposure for the following time intervals will be calculated for tofacitinib All in patients with PsA: 14 December 2017 – 30 November 2019 and 01 December 2019 – 30 November 2021.

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Allocation of the patient population by indication, sex and age are derived through prescription share calculations from IQVIA Health's Prescriber Insights database. ICD-10 codes M06 Other Rheumatoid Arthritis and M05 Seropositive Rheumatoid Arthritis will be used to define RA indication. ICD-10 code L405 Arthropathic psoriasis will be used to define PsA indication. Patient-years exposure by region is based on audited unit sales by country from RedactedRedacted .

Note the following limitations when purposing IQVIA Health database data for calculations of cumulative exposure. Tofacitinib, like other treatments for CIDs, is often sold into specialty pharmacies, which are not captured in the Redacted audit for most markets outside of the US. This can often lead to significant under-reporting of units sold or in some markets, or no reporting at all. The unit data from Redacted audit reflect units sold to a distributor, but this does not necessarily mean the drug was prescribed to or taken by a patient. Cumulative exposure is derived from unit sales data from Redacted Redacted RedactedRedacted and prescription share per indication from Redacted RedactedRedacted , which may not accurately represent worldwide cumulative exposure for tofacitinib. Prescription share data sourced from RedactedRedacted Insights medical database are not available in all markets. Gender and age sub-analyses are also derived from RedactedRedactedRedactedRedacted from a select set of countries/regions within the database (ie, more restricted versus prescription share data). Lastly, the patient-years metric is rounded and does not represent unique patient counts.

9.2.1. Inclusion Criteria

All AEs reported in the Pfizer safety database in patients residing in countries/regions with available RedactedRedacted who are ≥18 years of age receiving tofacitinib for RA during the timeframe of 06 November 2012 to 06 November 2021, or PsA during the timeframe of 14 December 2017 to 06 November 2021 will be included. If an AE is reported during the study timeframe, but sequelae AE(s) occur following the study cut-off date (eg, 06 November 2021), sequelae AE(s) will not be considered and the event will be marked as ongoing.

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[9] United States, Canada, Puerto Rico, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Isreal, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, Argentina, Australia, Brazil, Central America, Chile, China, Columbia, Ecuador, Egypt, Hong Kong, India, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Zealand, Peru, Philippines, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand, Tunisia, United Arab Emirates.

Unit sales data provided by RedactedRedacted during the timeframe of 06 November 2012 to 06 November 2021 will be used for calculation of cumulative estimated exposure (in patient-years).

9.2.2. Exclusion Criteria

The following reports of AEs occurring in patients meeting the following criteria will be out of scope for the analysis:

- Dated prior to 06 November 2012 or after 06 November 2021 for RA.
- Dated prior to 14 December 2017 or after 06 November 2021 for PsA
- <18 years of age at time of event.
- Receiving tofacitinib for indications other than PsA or RA at time of event. RA indication will be defined using ICD-10 codes M06 Other Rheumatoid Arthritis and M05 Seropositive Rheumatoid Arthritis. PsA indication will be defined using ICD-10 code L405 Arthropathic psoriasis will be used to define PsA indication.[10]
- Sequelae AEs occurring outside of the study timeframe.

Worldwide unit sales data provided by RedactedRedacted prior to 06 November 2012 or after 06 November 2021 will be out of scope for this analysis.

9.3. Variables

Variable/Endpoint	Role	Operational definition
Adverse Event (AE)	Endpoint	Report of AE during study timeframe
Adverse Event, most frequent	Endpoint	Report of AE (by PT) during study timeframe with frequency ≥2%
Age categories	Baseline characteristic/Stratifying variable	Age at time of event (≥65/<65)
Age (median, range)	Baseline characteristic/Stratifying	Age at time of event

[10] In patients with multiple indications reported, the predominant indication at the time of the AE will be used.

Variable/Endpoint	Role	Operational definition
	variable	
Blood and lymphatic system disorders	Endpoint	System Organ Class MedDRA classification
Cardiac disorders	Endpoint	System Organ Class MedDRA classification
Cardiovascular risk / Cardiovascular events	Endpoint	AESI; Report of events meeting Cardiovascular risk criteria[11]
Congenital, familial and genetic disorders	Endpoint	System Organ Class MedDRA classification
Cumulative exposure	Endpoint	Estimated cumulative drug exposure based on world wide unit sales Redacted
Death	Endpoint	Report of death
Deep vein thrombosis (DVT)	Endpoint	AESI; Report of DVT
Discontinuation due to AE	Endpoint	Report of discontinuation of tofacitinib treatment due to AE
Ear and labyrinth disorders	Endpoint	System Organ Class MedDRA classification
Endocrine disorders	Endpoint	System Organ Class MedDRA classification
Eye disorders	Endpoint	System Organ Class MedDRA classification
Gastrointestinal disorders	Endpoint	System Organ Class MedDRA classification
General disorders and administration site conditions	Endpoint	System Organ Class MedDRA classification
Hepatobiliary disorders	Endpoint	System Organ Class MedDRA classification
Herpes zoster	Endpoint	AESI; Report of serious or non-serious herpes zoster
Immune system disorders	Endpoint	System Organ Class MedDRA classification

[11] Cardiovascular risk includes standardized MedDRA queries: central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and preferred terms: cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.

Variable/Endpoint	Role	Operational definition
Infections and infestations	Endpoint	System Organ Class MedDRA classification
Injury, poisoning and procedural complications	Endpoint	System Organ Class MedDRA classification
Investigations	Endpoint	System Organ Class MedDRA classification
Malignancies (excl. NMSC)	Endpoint	AESI; Report of malignancy (excl. NMSC)
Metabolism and nutrition disorders	Endpoint	System Organ Class MedDRA classification
Musculoskeletal and connective tissue disorders	Endpoint	System Organ Class MedDRA classification
Neoplasms benign, malignant and unspecified	Endpoint	System Organ Class MedDRA classification
Nervous system disorders	Endpoint	System Organ Class MedDRA classification
Non-melanoma skin cancer (NMSC)	Endpoint	AESI; Report of NMSC
Pregnancy, purperium and perinatal conditions	Endpoint	System Organ Class MedDRA classification
Product issues	Endpoint	System Organ Class MedDRA classification
Psoriatic arthritis (PsA)	Baseline Characteristic/Stratifying variable	Diagnosis if PsA
Psychiatric disorders	Endpoint	System Organ Class MedDRA classification
Pulmonary embolism (PE)	Endpoint	AESI; Report of PE
Race	Baseline Characteristic	Patient Race (Asian/Black or African American/Native Hawaiian or other Pacific Islander/American Indian or Alaska Native/White/Unknown/Other [specify])
Region	Baseline Characteristic	Regional location of patient (NA/Europe/ROW)
Renal and urinary disorders	Endpoint	System Organ Class MedDRA classification
Reproductive system and breast disorders	Endpoint	System Organ Class MedDRA classification
Respiratory, thoracic and mediastinal disorders	Endpoint	System Organ Class MedDRA classification
Rheumatoid Arthritis (RA)	Baseline Characteristic/Stratifying variable	Diagnosis of RA

Variable/Endpoint	Role	Operational definition
Serious Adverse Event (SAE)	Endpoint	Report of serious AE
Serious infection	Endpoint	AESI; Report of Serious infection
Sex/Gender	Baseline Characteristic/Stratifying variable	Patient sex (Male/Female)
Skin and subcutaneous tissue disorders	Endpoint	System Organ Class MedDRA classification
Social circumstances	Endpoint	System Organ Class MedDRA classification
Surgical and medical procedures	Endpoint	System Organ Class MedDRA classification
Time Interval	Stratifying variable	Discrete period of time within the overall study timeframe
Vascular disorders	Endpoint	System Organ Class MedDRA classification
Venous thromboembolism (VTE)	Endpoint	AESI; Report of VTE[12]

9.4. Data Sources

See Section 9.2.

9.5. Study Size

The cumulative worldwide exposure during the timeframe of 06 November 2012 to 05 November 2021 for tofacitinib across all indications was 541,996 patient-years.[13] Cumulative exposure during this timeframe was calculated as 22,833 patient years for PsA (includes psoriasis)[14] and 441,803 patient years for RA.

[12] Venous thromboembolism includes reports of deep vein thrombosis and pulmonary embolism.

[13] Indications include RA, PsA, Psoriasis, Juvenile Arthritis, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's disease, Other soft tissue disorders, not elsewhere classified, Other arthritis, Atopic dermatitis, Juvenile arthritis, Other arthritis, Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm, Alopecia areata.

[14] Includes Psoriasis indication.

As this is a descriptive, retrospective analysis of post-marketing surveillance adverse event reports, sample size calculations are not applicable.

9.6. Data Management

Patient demographics in patients reporting AE/SAEs/death/AESIs between 06 November 2012 to 06 November 2021 receiving tofacitinib for RA, and 14 December 2017 to 06 November 2021 receiving tofacitinib for PsA in the Pfizer Safety database will be generated as aggregate frequencies. AE/SAEs/most frequent AEs/AESIs/SOC AEs reported in the Pfizer Safety database within the timeframe of 06 November 2012 to 06 November 2021 in patients receiving tofacitinib for RA, and 14 December 2017 to 06 November 2021 in patients receiving tofacitinib for PsA will be generated in aggregate and described in case listings. AE/SAEs/most frequent AEs/AESIs/SOC AEs will also be generated by patient demographics and time intervals described in Section 9.1. Adverse event data retrieved from the Pfizer Safety database will be restricted to those reported in countries/regions with available RedactedRedacted .

Cumulative exposure (in patient-years) will be generated using IQVIA Health's MIDAS database as described in Section 9.2. RRs for AE/SAEs/most frequent AEs/AESIs/SOC AEs will be calculated by Pfizer statisticians using cumulative exposure retrieved from Redacted Redacted RedactedRedacted as described in Section 9.2.

9.7. Data Analysis

Number (N) and frequency of AEs with tofacitinib IR, tofacitinib XR, Unknown and tofacitinib All will be calculated for patient demographic variables assessed in the study. N, frequency and RR with tofacitinib IR, tofacitinib XR, Unknown and tofacitinib All will be calculated for AEs/SAEs/most frequent AEs/AESIs/SOC AEs. N, frequency and RR for tofacitinib All will be calculated for subgroup analyses by age (≤65 years/>65 years), gender (male/female) and time interval analyses.

RR will be calculated by dividing the number of events by the estimated patient-years of exposure (per 100 patient-years).

All analyses for this study will be descriptive and no formal comparisons will be made. Data output per indication will be in the form of Case Level Summaries (Demographics), Drug level summaries (AEs/SAEs/discontinuations due to AEs) and Adverse Event Reporting Proportion (Reported as SOC and Preferred Term [PT]; most frequent AEs; AESIs) and Case Listings (SAEs/death) from reports generated from the Pfizer safety database.

Select AESI category data will be generated using pre-defined PTs used in periodic safety update reports.

Cumulative exposure rates will be generated using Redacted as described in Section 9.2. RRs will be calculated using the number of AE/SAEs/most frequent AEs/AESIs/SOC AEs reported within the study timeframe (06 November 2012 to 06 November 2021).

9.8. Quality Control

Analyses will be programmed as specified in the protocol. Data output will be summarized, reviewed and validated by a second reviewer to ensure interpretation and results are correct. Prior to publication submission and release of final study report standard quality control checks will be performed.

9.9. Limitations of the Research Methods

Pfizer Safety Database

Given the spontaneous nature of AE reporting in the Pfizer safety database, information on patient history and characteristics, concomitant medications, adverse event scenario, causality and status/outcome may not be complete for every AE report as these items are not compulsory. The potential for reporting bias exists, as not all adverse events may be reported, temporal variation in volume of spontaneous AE reports (Weber effect), or certain types of adverse events may be preferentially reported compared to others. Emergent safety signals and subsequent Regulatory activities regarding tofacitinib during the timeframe of 2019-2021 may impact the volume and type of reported spontaneous AEs.

Redacted

RedactedRedactedRedactedRedactedRedactedRedacted cumulative worldwide exposure. Tofacitinib, like other treatments for CIDs, is often sold into specialty pharmacies, which are not captured in the Redacted audit for most markets outside of the US. This can often lead to significant under-reporting of units sold or in some markets, no reporting at all. The unit data from Redacted audit reflect units sold to a distributor, but this does not necessarily mean the drug was prescribed to or taken by a patient. Cumulative exposure is derived from Redacted unit sales data and Redacted Redacted Health Prescriber Insights prescription share per indication, which may not accurately represent worldwide cumulative exposure for tofacitinib. Prescription share data sourced from Redacted Redacted Health Prescriber Insights database are not available in all markets. Gender and age sub-analyses are also derived from Redacted Insights database from a select set of countries/regions within the database (i.e. more restricted versus prescription share data). Lastly, the patient-years metric is rounded and does not represent unique patient counts.

9.10. Other Aspects

Not Applicable.

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10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

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

The Post-marketing surveillance data used in this analysis were not collected as part of a clinical study and were non-interventional; therefore, ethics approval was not required.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves analysis of post-marketing safety surveillance data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more manuscripts will be developed based on the findings of this study and submitted to appropriate scientific journals for peer-review and publication. In addition, one or more abstracts will be developed based on the findings of this study and submitted to relevant scientific congress(es). Authorship will follow the International Committee of Medical Journal Editors (ICMJE; www.icmje.org) guidelines.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	30 August 2022	Abstract: Retrospective Post-Marketing Safety Surveillance Study of Tofacitinib in Psoriatic Arthritis and Rheumatoid Arthritis

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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