# NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

**Study Information**

| | |
|---|---|
| **Title** | Retrospective Post-Marketing Safety Surveillance Study of Tofacitinib in Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA) |
| **Protocol Number** | A3921421 |
| **Version Identifier of the Final study Report** | 1.0 |
| **Date** | 13 November 2023 |
| **EU Post Authorization Study (PAS) Register Number** | EUPAS46286 |
| **Active Substance** | L04AA29 – Tofacitinib Citrate |
| **Medicinal Product** | Xeljanz (Tofacitinib) |
| **Research Question and Objectives** | **Research Question:**<br>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?<br><br>**Objectives:**<br>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.<br>2. To characterize the types and RR of Aes in patients receiving tofacitinib for PsA or RA captured within the Pfizer safety database. |
| **Author** | Redacted |

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# 1. ABSTRACT (STAND-ALONE DOCUMENT)

## 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 |
| bDMARD | Biologic Disease-Modifying Antirheumatic Drug |
| BID | Twice A Day |
| CI | Confidence Interval |
| CID | Chronic Inflammatory Disease |
| csDMARD | Conventional Synthetic Disease Modifying Antirheumatic Drug |
| CV | Cardiovascular |
| DMARD | Disease-Modifying Antirheumatic 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 |
| IEC | Independent Ethics Committee |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Institutional Ethics Committee |
| IR | Immediate Release |
| IRB | Institutional Review Board |

| Abbreviation | Definition |
|---|---|
| JIA | Juvenile Idiopathic Arthritis |
| N | Number |
| NA | North America |
| NMSC | Nonmelanoma 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 |
| ROW | Rest of World |
| RR | Reporting Rate |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| TNFi | Tumor Necrosis Factor Inhibitor |
| tsDMARDs | Targeted Synthetic Disease Modifying Antirheumatic Drug |
| UC | Ulcerative Colitis |
| Unk | Unknown |
| US | United States |
| VTE | Venous Thromboembolism |
| XR | Extended Release |

## 3. INVESTIGATORS

### Principal Investigator(s) of the Protocol

| Name, Degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
| Redacted | | | |
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## 4. OTHER RESPONSIBLE PARTIES

None.

## 5. MILESTONES

| Milestone | Planned Date | Actual Date | Comments |
|---|---|---|---|
| Completion of Feasibility | 25 January 2022 | 14-Jan-2022 | |
| Start of Data Collection | 22 September 2022 | 03 October 2022 | |
| End of Data Collection | 06 October 2022 | 23 December 2022 | |
| Registration in the EU PAS Register | 13 September 2022 | 21 September 2022 | |
| Final Study Report | 06 September 2023 | 13 November 2023 | |

## 6. 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 were 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 programs, 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 Pfizer 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.

## 7. 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?

### 7.1. Study Objectives

#### 7.1.1. Primary Study 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.

# 8. AMENDMENTS AND UPDATES

**Table 1. Amendments to the Protocol**

| Amendment Number | Date | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|
| 1 Administrative | 18 April 2022 | 6 Milestones | Milestones were updated. | The planned milestones were adjusted to align with information in sponsor's internal systems. |
| | | Annex 1 List of stand-alone documents | Date for statistical analysis plan (SAP) updated. | SAP date was updated to align with the actual date of the SAP. |

# 9. RESEARCH METHODS

## 9.1. Study Design

This was 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 in patients receiving tofa for PsA.

Worldwide exposure estimates based on a combination of audited unit sales and prescription data were used to estimate cumulative exposure of patients receiving tofacitinib for PsA or RA as the 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/not reported);

- 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/not reported);[1]
- Region (North America [NA][2]/Europe[3]/Rest of World [ROW][4]

2. Types and RR of treatment emergent AEs reported in the Pfizer Safety database[5] by formulation (tofacitinib IR, tofacitinib XR, unknown, tofacitinib all) for PsA or RA:
   - AEs as defined by MedDRA System Organ Class (SOC);[6]
   - Serious Adverse Events (SAEs) as defined by MedDRA SOC;
   - Most Commonly Reported AEs (occurring ≥2%) by MedDRA preferred term (PT);
   - 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[7];
     - Malignancies (excluding NMSC); NMSC;

[1] Race and demographic data are not reported in final study report due to high volume of missing data.

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

[3] 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.

[4] 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.

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

[6] AE data are reported in final study report as total number of AEs overall rather than by individual SOC.

[7] Referred to as Cardiovascular events for publication purposes.

- Venous Thromboembolism (VTE).

**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:[8]For PSA, December 2017 – November 2019, December 2019 – November 2021; for RA, November 2015 – November 2017,[9] December 2017 – November 2019), December 2019 – November 2021.[10]

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 was the same as the main analysis (ie, 14 December 2017 – 06 November 2021). For RA, the timeframe was 06 November 2012 – 06 November 2016.

All analyses were descriptive, and no formal comparisons were made.

### 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

[8] For RA indication only; Post Marketing Surveillance data for RA during this time interval was previously reported in Cohen et al 2018.25.[25]

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

[10] Two-year time interval analyses only included initial reports submitted to the Pfizer Safety database to avoid double reporting across time intervals.

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.

## WORLDWIDE EXPOSURE ESTIMATES (PER IQVIA'S SALES AND PRESCRIPTION DATA)

Cumulative exposure to tofacitinib for RA or PsA was calculated from a combination of audited unit sales from IQVIA Health's MIDAS (Sales) database and prescription data from IQVIA Health's Prescriber Insights database. Patient-years for tofacitinib IR were 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 were calculated by taking AVDOS of 1 unit daily for 11 mg QD tofacitinib sales, then added up the individual patient-years for each formulation separately to generate a cumulative exposure number for tofacitinib during the timeframe. The AVDOS were 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 were available from IQVIA from 06 November 2012 through the third quarter of 2021 and are reported by quarter.

Cumulative exposure was 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 were 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 2012– 06 November 2016.

Cumulative exposure for the following time intervals were calculated for tofacitinib in all patients with PsA: 14 December 2017 – 30 November 2019 and
01 December 2019 – 6 November 2021.

Allocation of the patient population by indication, sex and age were 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 were be used to define PsA indication. Patient-years exposure by region is based on audited unit sales by country from IQVIA Health's MIDAS database.

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 IQVIA Health MIDAS 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 IQVIA Health MIDAS 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 IQVIA Health's MIDAS database and prescription share per indication from IQVIA Health's Prescriber Insights database, which may not accurately represent worldwide cumulative exposure to tofacitinib.

Prescription share data sourced from IQVIA Health's Prescriber Insights medical database are not available in all markets. Gender and age sub-analyses are also derived from IQVIA Health's Prescriber Insights medical database from a select set of countries/regions within the database (ie, more restricted versus prescription share data). Lastly, the patient-years metric was rounded and does not represent unique patient counts).

## 9.3. Subjects

### 9.3.1. Inclusion Criteria

All AEs reported in the Pfizer safety database in patients residing in countries/regions with available IQVIA Health MIDAS data[11] who were ≥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 were included. If an AE was reported during the study timeframe, but sequelae AE(s) occur following the study cut-off date (eg, 06 November 2021), sequelae AE(s) was not considered, and the event was marked as ongoing.

Unit sales data provided by IQVIA Health's MIDAS dataset during the timeframe of 06 November 2012 to 06 November 2021 were used for calculation of cumulative estimated exposure (in patient-years).

[11] United States, Canada, Puerto Rico, 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, 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.

### 9.3.2. Exclusion Criteria

The following reports of AEs occurring in patients meeting the following criteria were 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.[12]
- Sequelae AEs occurring outside of the study timeframe.

Worldwide unit sales data provided by IQVIA Health's MIDAS dataset prior to 06 November 2012 or after 06 November 2021 were out of scope for this analysis.

## 9.4. Variables

**Table 2. Variables Defining Outcomes, Exposures, & Covariates**

| Variable/Endpoint | Role | Operational Definition |
|---|---|---|
| Adverse Event (AE) | Endpoint | Report of AE During Study Timeframe |
| Adverse Event, Most Frequent | Baseline Characteristic/Stratifying Variable | Report of AE (by PT) during study timeframe with frequency ≥2% |
| Age Categories | Baseline Characteristic/Stratifying Variable | Age at time of event (≥65/<65) |
| Blood and Lymphatic System Disorders | Endpoint | System Organ Class MedDRA Classification |
| Cardiac Disorders | Endpoint | System Organ Class MedDRA Classification |

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

| Variable/Endpoint | Role | Operational Definition |
|---|---|---|
| Cardiovascular risk /Cardiovascular Events | Endpoint | AESI; Report of Events Meeting Cardiovascular Risk Criteria[13] |
| Congenital, Familial and Genetic Disorders | Endpoint | System Organ Class MedDRA Classification |
| Cumulative Exposure | Endpoint | Estimated Cumulative Drug Exposure Based on Worldwide Unit Sales (IQVIA) |
| Death | Endpoint | Report of Death |
| 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 |
| 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 | System Organ Class MedDRA Classification |
| Metabolism and Nutrition Disorders | Endpoint | System Organ Class MedDRA Classification |
| Musculoskeletal and Connective Tissue | Endpoint | System Organ Class MedDRA Classification |

[13] 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 |
|---|---|---|
| Disorders | | |
| 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, Puerperium, 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 |
| 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 |
| Serious Adverse Event (SAE) | Endpoint | System Organ Class MedDRA Classification |
| 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 |

| Variable/Endpoint | Role | Operational Definition |
|---|---|---|
| Time Interval | Stratifying Variable | Discrete Period of Time within the Overall Study Timeframe |
| Vascular Disorders | Endpoint | System Organ Class MedDRA Classification |
| Venous Thromboembolism (VTE)[14] | Endpoint | System Organ Class MedDRA Classification |

### 9.5. Data Sources

See Section 9.2.

### 9.6. Bias

Limitations of this analysis include the potential for reporting bias (eg, favoring female and/or younger patients), varied reporter identity/training (eg, consumer versus physician; specialists may be more likely to report than general practitioners) and exposure estimation from commercial sales data (covering only 61 countries and one region, with indication-share derived from even fewer countries where prescription data were available. General biases/limitations of post-marketing surveillance data include under-reporting of nonserious AEs, difficulty identifying events with low frequency, and difficulty quantifying risk.

### 9.7. 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.[15]

Cumulative exposure during this timeframe was calculated as 20,706 patient years for PsA (Includes psoriasis)[16] and 439,370 patient years for RA.

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

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

[15] 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.

[16] Includes Psoriasis indication.

### 9.8. Data Transformation

Data transformations will not be conducted for this study.

Data from eligible case reports were extracted from the Pfizer Safety database and summarized in aggregate reports. Data to be reported as part of the study, including frequencies and RR calculations, were inputted into an excel file, QC checked and saved as final files in pdf form. Final data pdfs are stored in GDMS and GDMS location is documented within the relevant study folders.

### 9.9. Main Statistical Methods

Below is a synopsis of the analysis details. A SAP has not been developed for this study as the analysis plan is included in the study protocol.

### 9.10. Data Analysis

Number (N) and frequency of AEs with tofacitinib IR, tofacitinib XR, Unknown and tofacitinib all were calculated for patient demographic variables. N, frequency and RR with tofacitinib IR, tofacitinib XR, Unknown (no RRs calculated) and tofacitinib. All were calculated for AEs/SAEs/most frequent AEs (no RRs calculated)/AESIs/SAEs by SOC. N, frequency and RR for tofacitinib All were calculated for subgroup analyses by age (<65 years/ ≥65 years), gender (male/female) and time interval analyses.

RR was calculated by dividing the number of events by the estimated per 100 patient-years of exposure.

All analyses for this study are descriptive and no formal comparisons were made. Data output per indication was 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 were generated from the Pfizer safety database.

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

Cumulative exposure rates were generated using IQVIA databases as described in Section 9.2 RRs were calculated using the number of AE/SAEs/AESIs/SAEs by SOC reported within the study timeframe (06 November 2012 to 06 November 2021).

#### 9.10.1. Data Management

Patient demographics in patients reporting AEs/SAEs/death/AESIs in the Pfizer Safety database from 06 November 2012 to 06 November 2021 receiving tofacitinib for RA and 14 December 2017 to 06 November 2021 receiving tofacitinib for PsA were generated as aggregate frequencies. AE/SAEs/most frequent AEs/AESIs/SAEs by SOC reported in the Pfizer Safety database between 06 November 2012 and 06 November 2021 in patients

receiving tofacitinib for RA, and 14 December 2017 to 06 November 2021 in patients receiving tofacitinib for PsA, were aggregated and described in case listings.

AE/SAEs/most frequent AEs/AESIs/SAEs by SOC were also generated by patient demographics and time intervals described in Section 9.1. Adverse event data retrieved from the Pfizer Safety database were restricted to those reported in countries/regions with available IQVIA Health MIDAS sales data.

Cumulative exposure (in patient-years) was generated using IQVIA Health's MIDAS database as described in Section 9.2. RRs for AE/SAEs/AESIs/SAEs by SOC were calculated by Pfizer statisticians using cumulative exposure retrieved from IQVIA Health's MIDAS database as described in Section 9.2.

### 9.10.2. Amendments to the Statistical Analysis Plan

Not applicable.

## 9.11. Quality Control

The protocol-specified analyses were performed. A second reviewer reviewed and validated the data output to ensure that the results and interpretation were correct. Standard quality control checks were performed prior to publication submission and the release of the final study report.

## 9.12. Protection of Human Subjects

Subject Information and Consent

In accordance with applicable legal requirements, Pfizer was not required to obtain informed consent from patients for this study because it did not involve data that was subject to privacy laws.

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

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.

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).

# 10. RESULTS

# 11. PARTICIPANTS

All case reports of subjects that met eligibility criteria were included in the analysis.

## 11.1. Descriptive Data

### Patient Characteristics

In total, 73,525 case reports were reviewed, comprising 5394 for PsA and 68,131 for RA. Of these, 368 (6.8%) and 4239 (6.2%), respectively, did not report a tofacitinib formulation and were excluded from the main analysis. In PsA, the number of case reports received for the IR vs XR formulations was similar, whereas in RA, the number of case reports received was higher for IR than for XR (Table 3). PY of exposure were higher for the IR than for the XR formulation for both indications. For both indications and formulations, AE reports were more commonly submitted for females, patients <65 years and patients from North America (Table 3). Similar trends in demographics were observed for the reports with no tofacitinib formulation specified (Table 4). Most XR reports originated from North America, and the proportion of reports originating from Europe and the rest of the world was higher with IR than with XR (Table 3).

**Table 3. Overall Patient Characteristics by Tofacitinib Formulation Among Patients with PsA and RA**

| PsA | Tofacitinib IR | | Tofacitinib XR | | All Tofacitinib | |
|---|---|---|---|---|---|---|
| | N | % of Case Reports | N | % of Case Reports | N | % of Case Reports |
| Case Reports | 2601 | | 2425 | | 5026 | |
| Sex | | | | | | |
| Male | 710 | 27.3 | 677 | 27.9 | 1387 | 27.6 |
| Female | 1850 | 71.1 | 1732 | 71.4 | 3582 | 71.3 |
| Not Reported | 41 | 1.6 | 16 | 0.7 | 57 | 1.1 |
| Age | | | | | | |
| Median (SD) [Range], Years | 56.0 (12.85) [8.0–90.0] | | 56.0 (12.48) [0.50–88.0] | | Not available | |
| <65 years | 1885 | 72.5 | 1866 | 76.9 | 3751 | 74.6 |
| ≥65 years | 575 | 22.1 | 525 | 21.6 | 1100 | 21.9 |

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| PsA | Tofacitinib IR | | Tofacitinib XR | | All Tofacitinib | |
|---|---|---|---|---|---|---|
| | N | % of Case Reports | N | % of Case Reports | N | % of Case Reports |
| Not Reported | 141 | 5.4 | 34 | 1.4 | 175 | 3.5 |
| Geographical Region | | | | | | |
| North America[a] | 1783 | 68.6 | 2352 | 97.0 | 4135 | 82.3 |
| Europe[b] | 421 | 16.2 | 13 | 0.5 | 434 | 8.6 |
| Rest of the World[c] | 397 | 15.3 | 60 | 2.5 | 457 | 9.1 |
| Case Reports | 39,744 | | 24,148 | | 63,892 | |
| Sex | | | | | | |
| Male | 6685 | 16.8 | 4156 | 17.2 | 10,841 | 17.0 |
| Female | 32,425 | 81.6 | 19,864 | 82.3 | 52,289 | 81.8 |
| Not Reported | 634 | 1.6 | 128 | 0.5 | 762 | 1.2 |
| Age | | | | | | |
| Median (SD) [Range], Years | 61.0 (12.63) [0.25–98.0] | | 60.0 (12.33) [0.50–97.0] | | Not available | |
| <65 years | 23,175 | 58.3 | 16,030 | 66.4 | 39,205 | 61.4 |
| ≥65 years | 14,631 | 36.8 | 7633 | 31.6 | 22,264 | 34.8 |
| Not Reported | 1938 | 4.9 | 485 | 2.0 | 2423 | 3.8 |
| Geographical Region | | | | | | |
| North America[a] | 28,730 | 72.3 | 22,468 | 93.0 | 51,198 | 80.1 |
| Europe[b] | 1903 | 4.8 | 19 | 0.1 | 1922 | 3.0 |
| Rest of the World[c] | 9111 | 22.9 | 1661 | 6.9 | 10,772 | 16.9 |

*IR* immediate release, *NR* not reported, *PsA* psoriatic arthritis, *PY* patient-years, *RA* rheumatoid arthritis, *SD* standard deviation, *XR* extended release.

a. Includes case reports from Canada, Puerto Rico and the United States
b. Includes case reports from Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.

| PsA | Tofacitinib IR | | Tofacitinib XR | | All Tofacitinib | |
|---|---|---|---|---|---|---|
| | N | % of Case Reports | N | % of Case Reports | N | % of Case Reports |

c. Includes case reports from Argentina, Australia, Brazil, Chile, China, Colombia, Ecuador, Egypt, Hong Kong, India, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Zealand, Peru, Philippines, Saudi Arabia, Singapore, South Africa, Thailand, Tunisia and United Arab Emirates

**Table 4. Patient Characteristics Among Patients with PsA and RA (tofacitinib formulation not reported)**

| | Tofacitinib NR PsA | | Tofacitinib NR RA | |
|---|---|---|---|---|
| | N | % of case reports | N | % of case reports |
| Case Reports | 368 | | 4239 | |
| Sex | | | | |
| Male | 94 | 25.5 | 638 | 15.1 |
| Female | 197 | 53.5 | 2778 | 65.5 |
| Not Reported | 77 | 20.9 | 823 | 19.4 |
| Age | | | | |
| Median (SD) [Range], Years | 57.0 (12.83) [12.0–86.0] | | 61.0 (13.3) [2.58–96.0] | |
| <65 years | 158 | 42.9 | 1700 | 40.1 |
| ≥65 years | 67 | 18.2 | 1176 | 27.7 |
| Not Reported | 143 | 38.9 | 1363 | 32.2 |
| Geographical Region | | | | |
| North America[a] | 222 | 60.3 | 2129 | 50.2 |
| Europe[b] | 84 | 22.8 | 532 | 12.6 |
| Rest of the World[c] | 62 | 16.8 | 1579 | 37.2 |

*NR* not reported, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation.

a. Includes case reports from Canada, Puerto Rico and the United States

b. Includes case reports from Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom

c. Includes case reports from Argentina, Australia, Brazil, Chile, China, Colombia, Ecuador, Egypt, Hong Kong, India, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Zealand, Peru, Philippines, Saudi Arabia, Singapore, South Africa, Thailand, Tunisia and United Arab Emirates

Approximately half of all reports were submitted by HCPs, with the remainder submitted by non-HCPs such as consumers (Table 5). A small percentage of reports included multiple indications (19.4% with PsA and 4.6% with RA) (Table 5). For PsA, the most reported co-indications were RA (46.5% of those with multiple indications), psoriasis (17.5%) and ankylosing spondylitis (3.7%). The most reported co-indications for RA were PsA (15.8% of those with multiple indications), osteoarthritis (10.1%) and arthritis (8.8%).

**Table 5. Top Co-indications and Reporter Identities by Formulation Among Patients with PsA and RA**

| | Tofacitinib IR | | Tofacitinib XR | | All Tofacitinib | |
|---|---|---|---|---|---|---|
| | N | % of Case Reports | N | % of Case Reports | N | % of Case Reports |
| **PsA** | | | | | | |
| Case Reports | 2601 | | 2425 | | 5026 | |
| Indications reported (most common indications reported) | | | | | | |
| RA | 4 | 0.2 | 4 | 0.2 | 8 | 0.16 |
| Multiple[a] | 337 | 13.0 | 636 | 26.2 | 973 | 19.36 |
| Unknown | 13 | 0.5 | 15 | 0.6 | 28 | 0.56 |
| PsA | 2265 | 87.1 | 1790 | 73.8 | 4055 | 80.68 |
| Psoriasis | 1 | 0 | 0 | 0 | 1 | 0.02 |
| Alopecia Universalis | 1 | 0 | N/A | N/A | N/A | N/A |
| AE Reporter Identity | | | | | | |
| HCP[b] | 1294 | 49.8 | 1844 | 76.0 | 3138 | 62.4 |
| Non-HCP[c] | 1307 | 50.3 | 581 | 24.0 | 1888 | 37.6 |
| **RA** | | | | | | |
| Case Reports | 39,744 | | 24,148 | | 63,892 | |
| Indications reported (most common indications reported) | | | | | | |
| RA | 38,372 | 96.6 | 22,616 | 93.6 | 60,988 | 95.45 |
| Multiple[d] | 1382 | 3.5 | 1542 | 6.4 | 2924 | 4.58 |

| | Tofacitinib IR | | Tofacitinib XR | | All Tofacitinib | |
|---|---|---|---|---|---|---|
| | N | % of Case Reports | N | % of Case Reports | N | % of Case Reports |
| Unknown | 106 | 0.3 | 88 | 0.4 | 194 | 0.30 |
| Arthritis | 2 | 0 | 3 | 0 | 5 | 0.01 |
| Juvenile Idiopathic Arthritis | N/A | N/A | 1 | 0 | 1 | 0.00 |
| PsA | 3 | 0 | 1 | 0 | 4 | 0.01 |
| UC | 1 | 0 | N/A | N/A | 1 | 0.00 |
| AE Reporter Identity | | | | | | |
| HCP[b] | 16,354 | 41.2 | 15,456 | 64.0 | 31,810 | 49.8 |
| Non-HCP[c] | 23,390 | 58.9 | 8692 | 36.0 | 32,082 | 50.2 |

Percentages are based on the total number of case reports by formulation.
N/A indicates that the indication was not included in the most common indications reported for the respective formulation.
*AE* adverse event, *HCP* healthcare provider, *IR* immediate release, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *XR* extended release.

a. Within the multiple indication category, the most common co-indications (as a proportion of the co-indication in which case reports were described) were: RA (46.5%), psoriasis (17.5%) and ankylosing spondylitis (3.7%)
b. HCP includes physicians, pharmacists and 'other HCPs'
c. Non-HCP includes consumers, lawyers and other non-HCPs.
d. Within the multiple indication category, the most common co-indications were: PsA (15.8%), osteoarthritis (10.1%) and arthritis (8.8%)

## 11.2. Outcome Data

See Section 11.2

## 11.3. Main Results

### AEs

For both PsA and RA, a higher number of AEs were reported for tofacitinib IR (PsA, n=8349; RA, n=137,476) vs XR (PsA, 7602; RA, n=82,153) (Table 6). For both indications, RRs for total AEs and SAEs were higher with the XR vs IR formulation, although the frequency of SAEs (% of AEs reported as serious) was similar. No clear trends across formulations were observed in the frequency or RR of AESIs and fatal cases (Table 6). Results for reports with no tofacitinib formulation specified are shown in Table 7. Over the full duration of data collection, a higher RR for total AEs was observed in PsA than in RA (Table 6).

**Table 6. Safety Outcomes by Tofacitinib Formulation Among Patients with PsA and RA**

| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Case Reports | 2601 | | | 2425 | | | 5026 | | |
| AEs | 8349 | | 59.64 | 7602 | | 113.36 | 15,951 | | 77.04 |
| SAEs | 1136 | 13.61 | 8.11 | 912 | 12.00 | 13.60 | 2048 | 12.84 | 9.89 |
| AESIs[c] | | | | | | | | | |
| Serious Infections | 239 | 2.86 | 1.71 | 200 | 2.63 | 2.98 | 439 | 2.75 | 2.12 |
| HZ (serious and nonserious) | 49 | 0.59 | 0.35 | 35 | 0.46 | 0.52 | 84 | 0.53 | 0.41 |
| Cardiovascular events[d] | 44 | 0.53 | 0.31 | 25 | 0.33 | 0.37 | 69 | 0.43 | 0.33 |
| Malignancies (excluding NMSC) | 30 | 0.36 | 0.21 | 27 | 0.36 | 0.40 | 57 | 0.36 | 0.28 |
| NMSC | 4 | 0.05 | 0.03 | 7 | 0.09 | 0.10 | 11 | 0.07 | 0.05 |
| VTE[e] | 27 | 0.32 | 0.19 | 12 | 0.16 | 0.18 | 39 | 0.24 | 0.19 |
| Fatal Cases | 22 | 0.85[f] | 0.16 | 19 | 0.78[f] | 0.28 | 41 | 0.82[f] | 0.20 |
| **RA** | **Tofacitinib IR 312,632 PY** | | | **Tofacitinib XR 126,738 PY** | | | **All Tofacitinib 439,370 PY** | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Case Reports | 39,744 | | | 24,148 | | | 63,892 | | |
| AEs | 137,476 | | 43.97 | 82,153 | | 64.82 | 219,629 | | 49.99 |
| SAEs | 24,966 | 18.16 | 7.99 | 11,978 | 14.58 | 9.45 | 36,944 | 16.82 | 8.41 |
| AESIs[c] | | | | | | | | | |
| Serious Infections | 4944 | 3.60 | 1.58 | 2467 | 3.00 | 1.95 | 7411 | 3.37 | 1.69 |
| HZ (Serious and Nonserious) | 1194 | 0.87 | 0.38 | 529 | 0.64 | 0.42 | 1723 | 0.78 | 0.39 |

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| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Cardiovascular Events[d] | 773 | 0.56 | 0.25 | 413 | 0.50 | 0.33 | 1186 | 0.54 | 0.27 |
| Malignancies (excluding NMSC) | 941 | 0.68 | 0.30 | 429 | 0.52 | 0.34 | 1370 | 0.62 | 0.31 |
| NMSC | 193 | 0.14 | 0.06 | 109 | 0.13 | 0.09 | 302 | 0.14 | 0.07 |
| VTE[e] | 318 | 0.23 | 0.10 | 150 | 0.18 | 0.12 | 468 | 0.21 | 0.11 |
| Fatal Cases | 839 | 2.11[f] | 0.27 | 279 | 1.16[f] | 0.22 | 1118 | 1.75[f] | 0.25 |

All cases reported at least one AE. Some cases reported >1 AE; therefore, the number of AEs exceeds the number of cases.

*AE* adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *IR* immediate release, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* non-melanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *VTE* venous thromboembolism, *XR* extended release.

a. Percentages are based on total AEs by formulation except where otherwise indicated.
b. Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)
c. Search criteria for AESI categories are described in Supplementary Methods.
d. Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
e. Pulmonary embolism events are captured in the cardiovascular events and VTE categories.
f. Percentages based on total case reports by formulation

**Table 7. Safety Outcomes Among Patients with PsA and RA (tofacitinib formulation not reported)**

| | Tofacitinib NR PsA | | Tofacitinib NR RA | |
|---|---|---|---|---|
| | N | %[a] | N | %[a] |
| Case Reports | 368 | | 4239 | |
| AEs | 905 | | 12,216 | |
| SAEs | 134 | 14.81 | 3163 | 25.89 |
| AESI[b] | | | | |
| Serious Infections | 29 | 3.20 | 582 | 4.76 |

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| | | | | |
|---|---|---|---|---|
| HZ (Serious and Nonserious) | 7 | 0.77 | 340 | 2.78 |
| Cardiovascular Events[c] | 9 | 0.99 | 130 | 1.06 |
| Malignancies (excluding NMSC) | 2 | 0.22 | 195 | 1.60 |
| NMSC | 2 | 0.22 | 23 | 0.19 |
| VTE[d] | 8 | 0.88 | 81 | 0.66 |
| Fatal Cases | 1 | 0.27[e] | 78 | 1.84[e] |

*AE* adverse event, *AESI* adverse events of special interest, *BID* twice daily, *HZ* herpes zoster, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *RA* rheumatoid arthritis, *SAE* serious adverse event, *VTE* venous thromboembolism.
[a]Percentages are based on total AEs by indication except where otherwise indicated.
[b]Search criteria for AESI categories are described in Supplementary Methods.
[c]Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
[d]Pulmonary embolism events are captured in the cardiovascular events and VTE categories.
[e]Percentages are based on the total case reports by indication.

For both indications, RRs and frequencies of SAEs by SOC were highest for infections and infestations, general disorders and administration site conditions, musculoskeletal and connective tissue disorders, investigations, and nervous system disorders (Table 8). The most frequently reported SAEs by SOC were generally similar between the XR and IR formulations. Results for reports with no tofacitinib formulation specified are shown in Table 9.

**Table 8. Serious Adverse Events by SOC and Tofacitinib Formulation Among Patients with PsA and RA**

| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Total Number of AEs (serious and non-serious) | 8349 | | 59.64 | 7602 | | 113.36 | 15951 | | 77.04 |
| Blood and Lymphatic System Disorders | 18 | 0.22 | 0.13 | 9 | 0.12 | 0.13 | 27 | 0.17 | 0.13 |
| Cardiac Disorders | 35 | 0.42 | 0.25 | 21 | 0.28 | 0.31 | 56 | 0.35 | 0.27 |
| Congenital, Familial, and | 2 | 0.02 | 0.01 | | | | 2 | 0.01 | 0.01 |

| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Genetic Disorders | | | | | | | | | |
| Ear and Labyrinth Disorders | 4 | 0.05 | 0.03 | 3 | 0.04 | 0.04 | 7 | 0.04 | 0.03 |
| Endocrine Disorders | 7 | 0.08 | 0.05 | 2 | 0.03 | 0.03 | 9 | 0.06 | 0.04 |
| Eye Disorders | 25 | 0.30 | 0.18 | 19 | 0.25 | 0.28 | 44 | 0.28 | 0.21 |
| Gastrointestinal Disorders | 91 | 1.09 | 0.65 | 46 | 0.61 | 0.69 | 137 | 0.86 | 0.66 |
| General Disorders and Administration Site Conditions | 124 | 1.49 | 0.89 | 99 | 1.30 | 1.48 | 223 | 1.40 | 1.08 |
| Hepatobiliary Disorders | 22 | 0.26 | 0.16 | 11 | 0.14 | 0.16 | 33 | 0.21 | 0.16 |
| Immune System Disorders | 28 | 0.34 | 0.20 | 16 | 0.21 | 0.24 | 44 | 0.28 | 0.21 |
| Infections and Infestations | 238 | 2.85 | 1.70 | 200 | 2.63 | 2.98 | 438 | 2.75 | 2.12 |
| Injury, Poisoning, and Procedural Complications | 79 | 0.95 | 0.56 | 102 | 1.34 | 1.52 | 181 | 1.13 | 0.87 |
| Investigations | 27 | 0.32 | 0.19 | 16 | 0.21 | 0.24 | 43 | 0.27 | 0.21 |
| Metabolism and Nutrition Disorders | 15 | 0.18 | 0.11 | 10 | 0.13 | 0.15 | 25 | 0.16 | 0.12 |
| Musculoskeletal and Connective Tissue Disorders | 141 | 1.69 | 1.01 | 116 | 1.53 | 1.73 | 257 | 1.61 | 1.24 |
| Neoplasms Benign, Malignant and Unspecified | 32 | 0.38 | 0.23 | 30 | 0.39 | 0.45 | 62 | 0.39 | 0.30 |
| Nervous System Disorders | 62 | 0.74 | 0.44 | 52 | 0.68 | 0.78 | 114 | 0.71 | 0.55 |

| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Pregnancy, Puerperium and Perinatal Conditions | 1 | 0.01 | 0.01 | | | | 1 | 0.01 | 0.00 |
| Product Issues | | 0.00 | 0.00 | 3 | 0.04 | 0.04 | 3 | 0.02 | 0.01 |
| Psychiatric Disorders | 15 | 0.18 | 0.11 | 10 | 0.13 | 0.15 | 25 | 0.16 | 0.12 |
| Renal and Urinary Disorders | 23 | 0.28 | 0.16 | 26 | 0.34 | 0.39 | 49 | 0.31 | 0.24 |
| Reproductive System and Breast Disorders | 5 | 0.06 | 0.04 | 6 | 0.08 | 0.09 | 11 | 0.07 | 0.05 |
| Respiratory, Thoracic and Mediastinal Disorders | 53 | 0.63 | 0.38 | 40 | 0.53 | 0.60 | 93 | 0.58 | 0.45 |
| Skin and Subcutaneous Tissue Disorders | 33 | 0.40 | 0.24 | 16 | 0.21 | 0.24 | 49 | 0.31 | 0.24 |
| Social Circumstances | 1 | 0.01 | 0.01 | 1 | 0.01 | 0.01 | 2 | 0.01 | 0.01 |
| Surgical and Medical Procedures | 4 | 0.05 | 0.03 | 24 | 0.32 | 0.36 | 28 | 0.18 | 0.14 |
| Vascular Disorders | 51 | 0.61 | 0.36 | 34 | 0.45 | 0.51 | 85 | 0.53 | 0.41 |
| **RA** | **Tofacitinib IR 312,632 PY** | | | **Tofacitinib XR 126,738 PY** | | | **All Tofacitinib 439,370 PY** | | |
| | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** |
| Total Number of AEs (Serious and Nonserious) | 137476 | | 43.97 | 82153 | | 64.82 | 219629 | | 49.99 |
| Blood and Lymphatic System Disorders | 274 | 0.20 | 0.09 | 87 | 0.11 | 0.07 | 361 | 0.16 | 0.08 |

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| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Cardiac Disorders | 778 | 0.57 | 0.25 | 397 | 0.48 | 0.31 | 1175 | 0.53 | 0.27 |
| Congenital, Familial, and Genetic Disorders | 25 | 0.02 | 0.01 | 20 | 0.02 | 0.02 | 45 | 0.02 | 0.01 |
| Ear and Labyrinth Disorders | 121 | 0.09 | 0.04 | 81 | 0.10 | 0.06 | 202 | 0.09 | 0.05 |
| Endocrine Disorders | 62 | 0.05 | 0.02 | 45 | 0.05 | 0.04 | 107 | 0.05 | 0.02 |
| Eye Disorders | 594 | 0.43 | 0.19 | 354 | 0.43 | 0.28 | 948 | 0.43 | 0.22 |
| Gastrointestinal Disorders | 1396 | 1.02 | 0.45 | 668 | 0.81 | 0.53 | 2064 | 0.94 | 0.47 |
| General Disorders and Administration Site Conditions | 3567 | 2.59 | 1.14 | 1232 | 1.50 | 0.97 | 4799 | 2.19 | 1.09 |
| Hepatobiliary Disorders | 256 | 0.19 | 0.08 | 133 | 0.16 | 0.10 | 389 | 0.18 | 0.09 |
| Immune System Disorders | 248 | 0.18 | 0.08 | 138 | 0.17 | 0.11 | 386 | 0.18 | 0.09 |
| Infections and Infestations | 4943 | 3.60 | 1.58 | 2466 | 3.00 | 1.95 | 7409 | 3.37 | 1.69 |
| Injury, Poisoning, and Procedural Complications | 2409 | 1.75 | 0.77 | 1332 | 1.62 | 1.05 | 3741 | 1.70 | 0.85 |
| Investigations | 793 | 0.58 | 0.25 | 397 | 0.48 | 0.31 | 1190 | 0.54 | 0.27 |
| Metabolism and Nutrition Disorders | 326 | 0.24 | 0.10 | 181 | 0.22 | 0.14 | 507 | 0.23 | 0.12 |
| Musculoskeletal and Connective Tissue Disorders | 3061 | 2.23 | 0.98 | 1363 | 1.66 | 1.08 | 4424 | 2.01 | 1.01 |
| Neoplasms Benign, Malignant and Unspecified | 1137 | 0.83 | 0.36 | 536 | 0.65 | 0.42 | 1673 | 0.76 | 0.38 |

| PsA | Tofacitinib IR 14,000 PY | | | Tofacitinib XR 6706 PY | | | All Tofacitinib 20,706 PY | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Nervous System Disorders | 1357 | 0.99 | 0.43 | 772 | 0.94 | 0.61 | 2129 | 0.97 | 0.48 |
| Pregnancy, Puerperium and Perinatal Conditions | 17 | 0.01 | 0.01 | 3 | 0.00 | 0.00 | 20 | 0.01 | 0.00 |
| Product Issues | 22 | 0.02 | 0.01 | 8 | 0.01 | 0.01 | 30 | 0.01 | 0.01 |
| Psychiatric Disorders | 358 | 0.26 | 0.11 | 174 | 0.21 | 0.14 | 532 | 0.24 | 0.12 |
| Renal and Urinary Disorders | 513 | 0.37 | 0.16 | 266 | 0.32 | 0.21 | 779 | 0.35 | 0.18 |
| Reproductive System and Breast Disorders | 87 | 0.06 | 0.03 | 44 | 0.05 | 0.03 | 131 | 0.06 | 0.03 |
| Respiratory, Thoracic and Mediastinal Disorders | 1306 | 0.95 | 0.42 | 555 | 0.68 | 0.44 | 1861 | 0.85 | 0.42 |
| Skin and Subcutaneous Tissue Disorders | 375 | 0.27 | 0.12 | 134 | 0.16 | 0.11 | 509 | 0.23 | 0.12 |
| Social Circumstances | 119 | 0.09 | 0.04 | 35 | 0.04 | 0.03 | 154 | 0.07 | 0.04 |
| Surgical and Medical Procedures | 131 | 0.10 | 0.04 | 181 | 0.22 | 0.14 | 312 | 0.14 | 0.07 |
| Vascular Disorders | 691 | 0.50 | 0.22 | 376 | 0.46 | 0.30 | 1067 | 0.49 | 0.24 |

*AE* adverse event, *IR* immediate release, *PsA* psoriatic arthritis, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *SOC* system organ class, *XR* extended release.

a. Percentages are based on total AEs by formulation
b. Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)

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**Table 9. Serious Adverse Events by SOC Among Patients with PsA and RA (tofacitinib formulation not reported)**

| PsA | Tofacitinib NR PsA | | Tofacitinib NR RA | |
|---|---|---|---|---|
| | N | %[a] | N | %[a] |
| Total Number of AEs (Serious and Non serious) | 905 | | 12216 | |
| Blood and Lymphatic System Disorders | 1 | 0.11 | 55 | 0.45 |
| Cardiac Disorders | 1 | 0.11 | 86 | 0.70 |
| Congenital, Familial, and Genetic Disorders | | 0.00 | 5 | 0.04 |
| Ear and Labyrinth Disorders | 1 | 0.11 | 14 | 0.11 |
| Endocrine Disorders | | 0.00 | 5 | 0.04 |
| Eye Disorders | 1 | 0.11 | 52 | 0.43 |
| Gastrointestinal Disorders | 10 | 1.10 | 190 | 1.56 |
| General Disorders and Administration Site Conditions | 14 | 1.55 | 459 | 3.76 |
| Hepatobiliary Disorders | 5 | 0.55 | 36 | 0.29 |
| Immune System Disorders | 4 | 0.44 | 47 | 0.38 |
| Infections and Infestations | 29 | 3.20 | 582 | 4.76 |
| Injury, Poisoning, and Procedural Complications | 5 | 0.55 | 248 | 2.03 |
| Investigations | 1 | 0.11 | 148 | 1.21 |
| Metabolism and Nutrition Disorders | 2 | 0.22 | 28 | 0.23 |
| Musculoskeletal and Connective Tissue Disorders | 17 | 1.88 | 347 | 2.84 |
| Neoplasms Benign, Malignant | 4 | 0.44 | 213 | 1.74 |

| PsA | Tofacitinib NR PsA | | Tofacitinib NR RA | |
|---|---|---|---|---|
| | N | %[a] | N | %[a] |
| and Unspecified | | | | |
| Nervous System Disorders | 14 | 1.55 | 131 | 1.07 |
| Pregnancy, Puerperium and Perinatal Conditions | | 0.00 | 0 | 0.00 |
| Product Issues | | 0.00 | 1 | 0.01 |
| Psychiatric Disorders | | 0.00 | 50 | 0.41 |
| Renal and Urinary Disorders | 3 | 0.33 | 61 | 0.50 |
| Reproductive System and Breast Disorders | | 0.00 | 7 | 0.06 |
| Respiratory, Thoracic and Mediastinal Disorders | 8 | 0.88 | 190 | 1.56 |
| Skin and Subcutaneous Tissue Disorders | 5 | 0.55 | 81 | 0.66 |
| Social Circumstances | | 0.00 | 15 | 0.12 |
| Surgical and Medical Procedures | 2 | 0.22 | 15 | 0.12 |
| Vascular Disorders | 7 | 0.77 | 97 | 0.79 |

*AE* adverse event, *BID* twice daily, *NR* not reported, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SAE* serious adverse event, *SOC* system Organ Class
a. Percentages are based on total AEs by indication.

In patients with PsA, the most frequently reported PTs overall were drug ineffective, off-label use, condition aggravated, pain and headache (Figure 1). In patients with RA, the most frequently reported PTs overall were drug ineffective, pain, condition aggravated and headache (Figure 2). For both PsA and RA, the most frequently reported PTs were similar across IR and XR formulations (Figure 1 and Figure 2). Results for reports with no formulation specified are shown in Figure 3.

**Figure 1. Most Frequent AEs occurring in ≥2% of Patients with PsA (by PT). Percentages were calculated from the total case reports per formulation. AE adverse event, HZ herpes zoster, IR immediate release, PsA psoriatic arthritis, PT Preferred Term, XR extended release.**

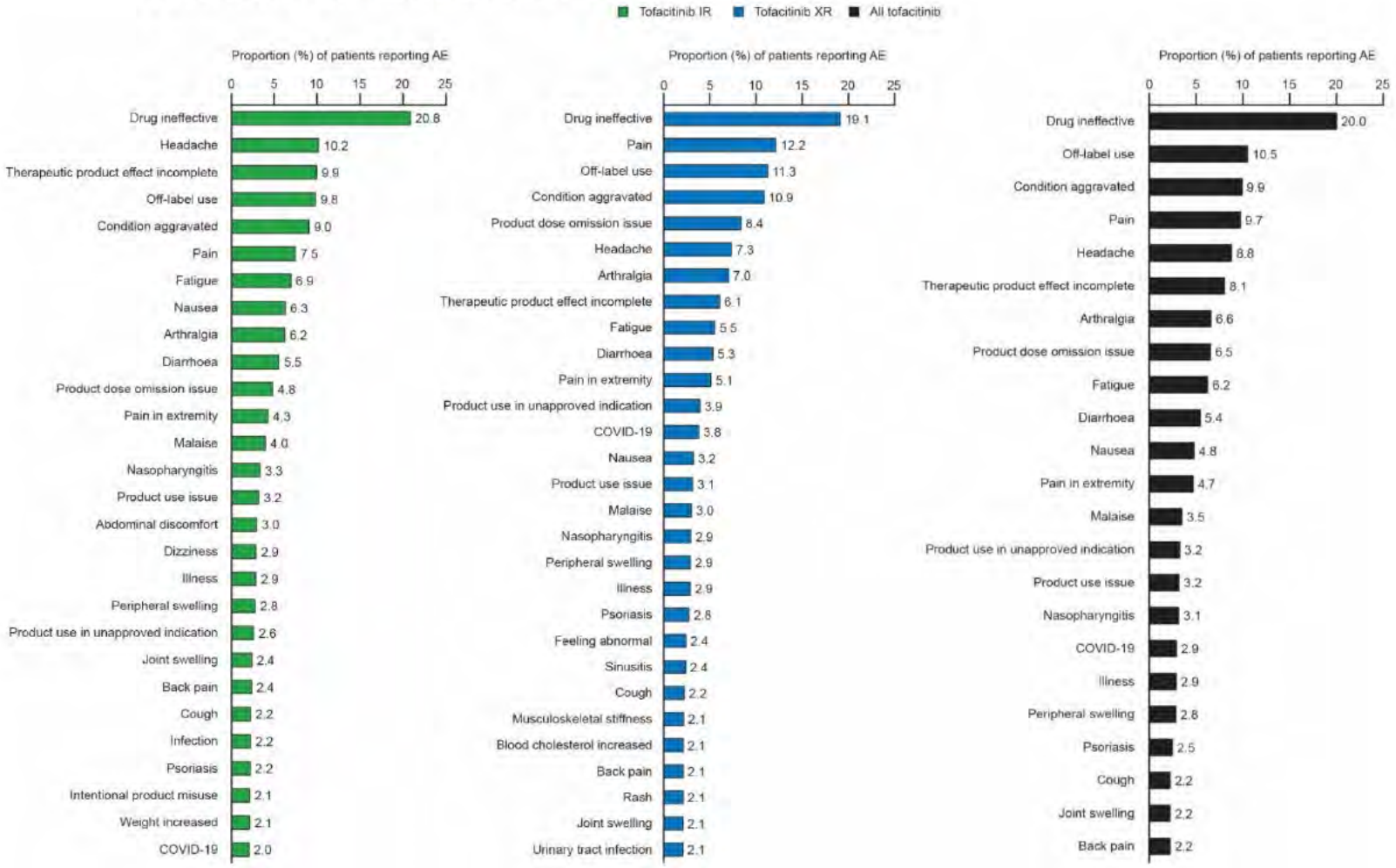


**Figure 2. Most frequent AEs occurring in ≥2% of patients with RA (by PT). Percentages were calculated from the total case reports per formulation. AEs adverse events, HZ herpes zoster, IR immediate release, PT Preferred Term, RA rheumatoid arthritis, XR extended release.**

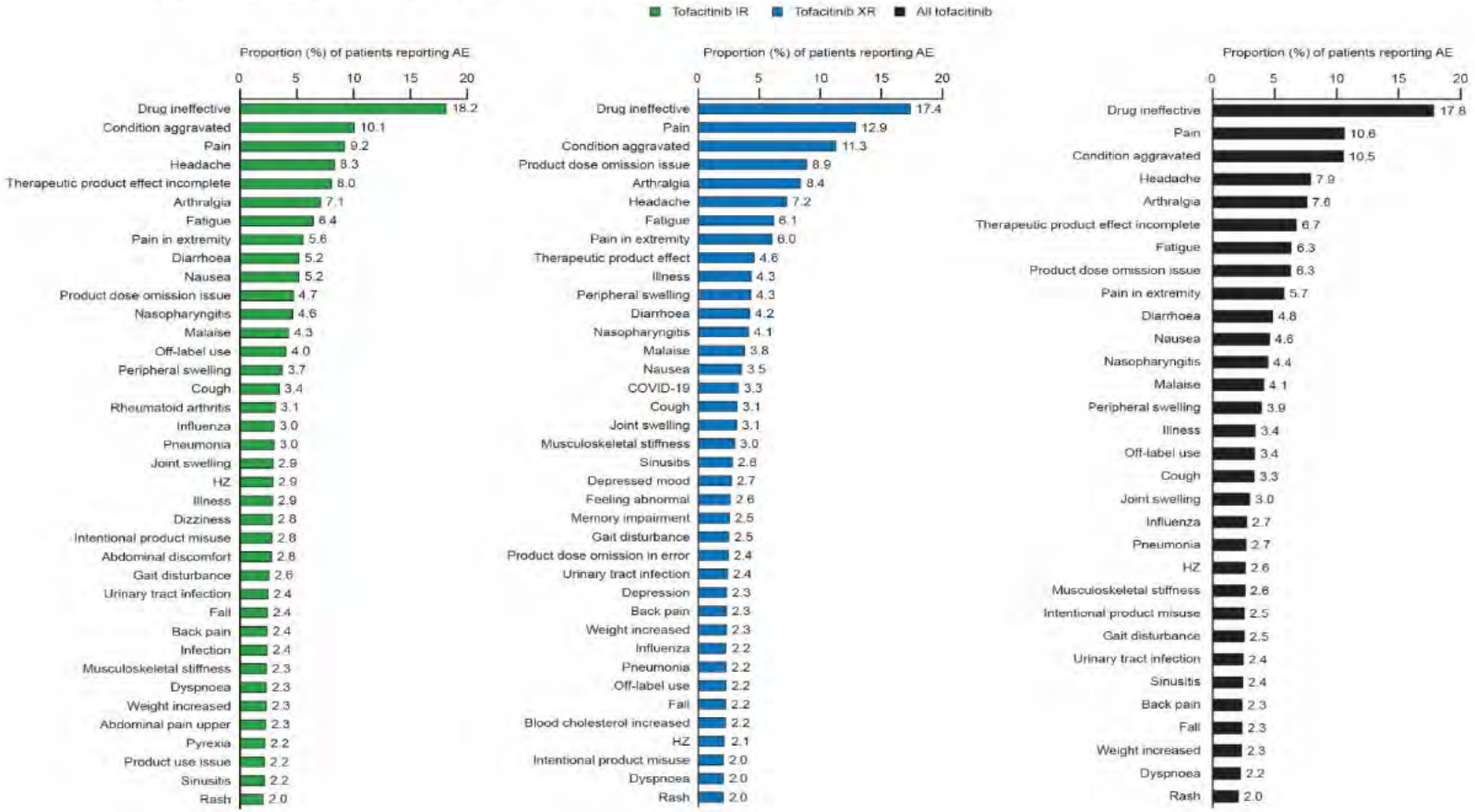
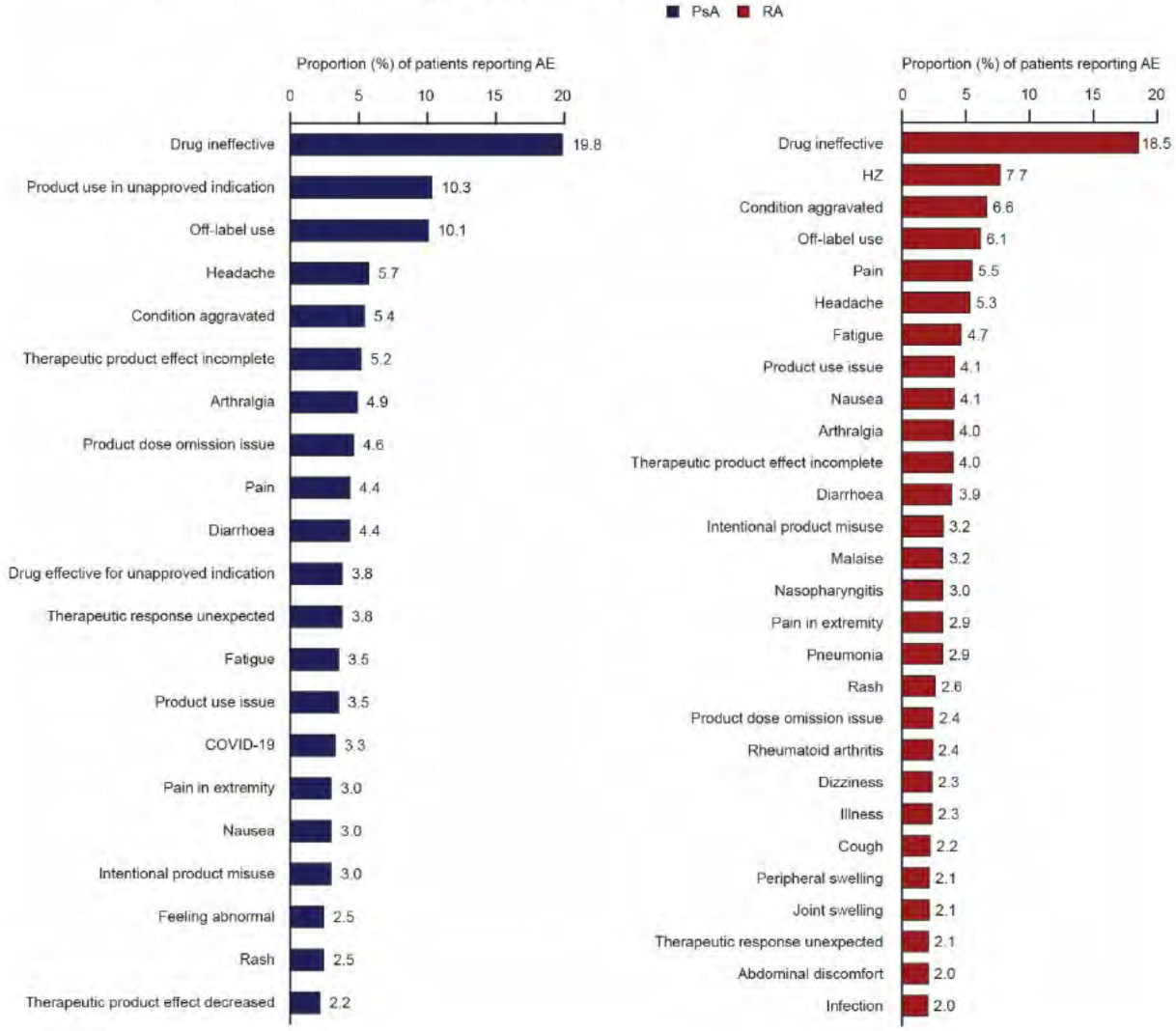


**Figure 3. Most frequent AEs occurring in ≥2% of patients with PsA and RA (tofacitinib formulation not reported). Percentages were calculated from the total case reports with no tofacitinib formulation reported. AE adverse event, HZ herpes zoster, IR immediate release, PsA psoriatic arthritis, RA rheumatoid arthritis, XR extended release.**




## AESIs

Across indications and formulations, the most reported AESI was serious infection, followed by HZ (Table 5). Within the AESI category of serious infections, the most reported PTs were pneumonia, lower respiratory tract infection and COVID-19 or COVID-19 pneumonia (Table 10). The frequency and RR for serious and non-serious COVID-19 infections in RA was 0.6% and 0.3, with 39% (494/1263) of these infections having been reported as serious. The frequency and RR for serious and non-serious COVID-19 infections in PsA was 0.9% and 0.7, with 10% (15/147) of these infections reported as serious. The most reported PTs in the HZ AESI category were HZ, ophthalmic HZ, and HZ disseminated (Table 10). Of

the total HZ AEs reported, 10.2% (IR) and 8.6% (XR) for PsA and 24.1% (IR) and 9.8% (XR) for RA were considered serious. The most reported PT meeting cardiovascular event AESI criteria was cerebrovascular accident, followed by myocardial infarction and pulmonary embolism (Table 10). Excluding the non-specific PT of 'neoplasm malignant', breast cancer or breast cancer female was the most reported PT meeting AESI criteria for malignancies excluding NMSC, followed by lung neoplasm malignant and colon cancer (Table 10). The most reported NMSC PT was skin cancer, followed by basal cell carcinoma and squamous cell carcinoma (Table 10). The majority of VTEs reported were pulmonary embolism, followed by deep vein thrombosis and pulmonary thrombosis (Table 10).

**Table 10. Most Reported PTs for AESI Categories[a] by Tofacitinib Formulation Among Patients with PsA and RA**

| | PsA | | RA | |
|---|---|---|---|---|
| **N** | **Tofacitinib IR** | **Tofacitinib XR** | **Tofacitinib IR** | **Tofacitinib XR** |
| Serious Infections | | | | |
| Pneumonia (SAE) | 43 | 29 | 1183 | 549 |
| Lower Respiratory Tract Infection (SAE) | 30 | 6 | 354 | 52 |
| COVID-19 or COVID-19 Pneumonia (SAE) | 15 | 30 | 196 | 298 |
| COVID-19 (Serious and Non-serious)[b] | 54 | 93 | 451 | 812 |
| HZ[c] | | | | |
| HZ | 47 | 32 | 1143 | 512 |
| Ophthalmic HZ | 0 | 2 | 28 | 12 |
| HZ Disseminated | 0 | 0 | 6 | 2 |
| Cardiovascular Events[d] | | | | |
| Cerebrovascular Accident | 7 | 3 | 187 | 117 |
| Myocardial Infarction | 8 | 8 | 178 | 95 |
| Pulmonary Embolism | 16 | 6 | 137 | 66 |
| Malignancies (excluding NMSC)[e] | | | | |
| Breast Cancer or Breast Cancer Female | 4 | 4 | 97 | 48 |
| Lung Neoplasm Malignant | 1 | 1 | 72 | 44 |

| N | PsA | | RA | |
|---|---|---|---|---|
| | Tofacitinib IR | Tofacitinib XR | Tofacitinib IR | Tofacitinib XR |
| Colon Cancer | 0 | 2 | 35 | 12 |
| NMSC | | | | |
| Skin Cancer | 2 | 2 | 90 | 62 |
| Basal Cell Carcinoma | 1 | 2 | 38 | 18 |
| Squamous Cell Carcinoma | 1 | 2 | 20 | 13 |
| VTE[f] | | | | |
| Pulmonary Embolism | 16 | 6 | 137 | 66 |
| Deep Vein Thrombosis | 5 | 5 | 88 | 44 |
| Pulmonary Thrombosis | 2 | 1 | 50 | 31 |

*AESI* adverse event of special interest, *COVID-19* Coronavirus disease 2019, *HZ* herpes zoster, *IR* immediate release, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* non-melanoma skin cancer, *PT* Preferred Term, *PsA* psoriatic arthritis, *SAE* serious adverse event; *VTE* venous thromboembolism, *XR* extended release.

a. Data represent event counts for the top 3 PTs reported in each AESI category. Search criteria for AESI categories are described in Supplementary Methods.
b Includes the following PTs: asymptomatic COVID, COVID-19, COVID-19 pneumonia. The following MedDRA terms were excluded as they could apply to non-COVID-19 coronavirus: coronavirus infection, coronavirus pneumonia.
c. Total serious HZ (PTs: HZ, HZ cutaneous disseminated, HZ disseminated, HZ infection neurological, HZ meningitis, HZ meningoencephalitis, HZ oticus, HZ reactivation, ophthalmic HZ): RA tofacitinib IR n=170; RA tofacitinib XR n=52; PsA tofacitinib IR n=5; PsA tofacitinib XR n=3.
d. Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
e. Excluding the non-specific PT of 'neoplasm malignant'
f. Pulmonary embolism events are captured in the cardiovascular events and VTE categories.

**Exploratory Analyses**

When evaluating only the first 4 years post-approval, AE RRs higher for RA (Table 8) than in the 4-year data for PsA (Table 11) for both formulations and higher for XR vs IR in both indications. There was limited exposure to the XR formulation in the first 4 years for RA (November 2012–November 2016) as it was approved in February 2016 (2000 PY, vs 49,439 PY for IR). When AE reporting was evaluated by 2-year time intervals, the number of case reports, AEs, and PY of exposure increased over time for both indications (Table 12). For PsA, RRs of AEs, SAEs, AESIs, and fatal cases were similar across the two-time intervals examined, as were the frequencies of SAEs, AESIs, and fatal cases. For RA, RRs of AEs, SAEs, most AESIs, and fatal cases were highest in the first-time interval (November 2015 to November 2017) and lower thereafter; frequencies of SAEs, AESIs, and fatal cases were comparable across time intervals (Table 12).

**Table 11. Safety Outcomes by Tofacitinib Formulation in the First 4 Years Post Approval Among Patients with RA**

| | **Nov 2012 to Nov 2016** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Tofacitinib IR** | | | **Tofacitinib XR** | | | **All Tofacitinib** | | |
| | 49,439 PY | | | 2000 PY | | | 51,439 PY | | |
| | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** |
| Case reports | 12,298 | | | 757 | | | 13,055 | | |
| AEs | 47,389 | | 95.85 | 2940 | | 147.00 | 50,329 | | 97.84 |
| SAEs | 9449 | 19.94 | 19.11 | 489 | 16.63 | 24.45 | 9938 | 19.75 | 19.32 |
| AESI[c] | | | | | | | | | |
| Serious Infections | 1745 | 3.68 | 3.53 | 82 | 2.79 | 4.10 | 1827 | 3.63 | 3.55 |
| HZ (Serious and | 324 | 0.68 | 0.66 | 24 | 0.82 | 1.20 | 348 | 0.69 | 0.68 |

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| | Nov 2012 to Nov 2016 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Tofacitinib IR** | | | **Tofacitinib XR** | | | **All Tofacitinib** | | |
| | 49,439 PY | | | 2000 PY | | | 51,439 PY | | |
| | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** | **N** | **%[a]** | **RR[b]** |
| Non-serious) | | | | | | | | | |
| Cardiovascular Events[d] | 212 | 0.45 | 0.43 | 20 | 0.68 | 1.00 | 232 | 0.46 | 0.45 |
| Malignancies (excluding NMSC) | 252 | 0.53 | 0.51 | 10 | 0.34 | 0.50 | 262 | 0.52 | 0.51 |
| NMSC | 69 | 0.15 | 0.14 | 2 | 0.07 | 0.10 | 71 | 0.14 | 0.14 |
| VTE[e] | 44 | 0.09 | 0.09 | 5 | 0.17 | 0.25 | 49 | 0.10 | 0.10 |
| Fatal Cases | 196 | 1.59[f] | 0.40 | 7 | 0.92[f] | 0.35 | 203 | 1.55[f] | 0.39 |

*AE* adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *IR* immediate release, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* non-melanoma skin cancer, *PT* Preferred Term, *PY* patient-years, *RA* rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *VTE* venous thromboembolism, *XR* extended release.

a. Percentages are based on total AEs by formulation except where otherwise indicated.
b. Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases).
c. Search criteria for AESI categories are described in Supplementary Methods.
d. Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
e. Pulmonary embolism events are captured in the cardiovascular events and VTE categories.
f. Percentages based on total case reports by formulation.

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**Table 12. Summary of Safety Outcomes Across Time Intervals Among Patients with PsA and RA (all tofacitinib)**

| Time interval | PsA | | | | | | RA | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dec 2017–Nov 2019 | | | Dec 2019–Nov 2021 | | | Nov 2015–Nov 2017 | | | Dec 2017–Nov 2019 | | | Dec 2019–Nov 2021 | | |
| | 7276 PY | | | 13,430 PY | | | 60,035 PY | | | 135,013 PY | | | 215,155 PY | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Case Reports | 1515 | | | 3351 | | | 15,938 | | | 18,371 | | | 22,725 | | |
| AEs | 4977 | | 68.40 | 10,280 | | 76.55 | 59,714 | | 99.47 | 61,282 | | 45.39 | 72,453 | | 33.67 |
| SAEs | 646 | 12.98 | 8.88 | 1276 | 12.41 | 9.50 | 10,388 | 17.40 | 17.30 | 10,098 | 16.48 | 7.48 | 11,001 | 15.18 | 5.11 |
| AESIs[c] | | | | | | | | | | | | | | | |
| Serious Infections | 158 | 3.17 | 2.17 | 272 | 2.65 | 2.03 | 2241 | 3.75 | 3.73 | 2191 | 3.58 | 1.62 | 2023 | 2.79 | 0.94 |
| HZ (serious and nonserious) | 28 | 0.56 | 0.38 | 51 | 0.50 | 0.38 | 482 | 0.81 | 0.80 | 577 | 0.94 | 0.43 | 498 | 0.69 | 0.23 |
| Cardiovascular events[d] | 20 | 0.40 | 0.27 | 44 | 0.43 | 0.33 | 289 | 0.48 | 0.48 | 385 | 0.63 | 0.29 | 371 | 0.51 | 0.17 |
| Malignancies (excluding NMSC) | 19 | 0.38 | 0.26 | 33 | 0.32 | 0.25 | 377 | 0.63 | 0.63 | 424 | 0.69 | 0.31 | 463 | 0.64 | 0.22 |
| NMSC | 2 | 0.04 | 0.03 | 8 | 0.08 | 0.06 | 81 | 0.14 | 0.13 | 89 | 0.15 | 0.07 | 95 | 0.13 | 0.04 |

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| Time interval | PsA | | | | | | RA | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dec 2017–Nov 2019 | | | Dec 2019–Nov 2021 | | | Nov 2015–Nov 2017 | | | Dec 2017–Nov 2019 | | | Dec 2019–Nov 2021 | | |
| | 7276 PY | | | 13,430 PY | | | 60,035 PY | | | 135,013 PY | | | 215,155 PY | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| VTE[e] | 8 | 0.16 | 0.11 | 30 | 0.29 | 0.22 | 58 | 0.10 | 0.10 | 165 | 0.27 | 0.12 | 209 | 0.29 | 0.10 |
| Fatal Cases | 12 | 0.79[f] | 0.16 | 22 | 0.66[f] | 0.16 | 335 | 2.10[f] | 0.56 | 359 | 1.95[f] | 0.27 | 335 | 1.47[f] | 0.16 |

Case reports and their associated AEs were categorized by time interval according to the date when the case report was first received. Therefore, additional AEs reported subsequently under existing case reports may have actually occurred in later time intervals. Regulatory approval for tofacitinib was attained in December 2017 for PsA and November 2012 for RA. RR for AEs, SAEs, fatal cases and SAEs by SOC from 2012 to 2015 have been reported previously for RA
*AE* adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* non-melanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *RA*, rheumatoid arthritis, *RR* reporting rate, *SAE* serious adverse event, *SOC* system organ class, *VTE* venous thromboembolism

a. Percentages are based on total AEs by formulation except where otherwise indicated.
b. Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)
c. Search criteria for AESI categories are described in Supplementary Methods
d. Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
e. Pulmonary embolism events are captured in the cardiovascular events and VTE categories.
f. Percentages based on total case reports by formulation.

Across PsA and RA, AEs were more likely to be reported for female patients than for male patients, although RRs for SAEs, AESIs and fatal cases were generally consistent (Table 5). Similarly, in both PsA and RA, AEs were more likely to be reported in patients <65 years of age than in patients ≥65 years of age, with RRs for SAEs, AESIs and fatal cases remaining comparable across the age categories.

**Table 13. Safety Outcomes by Sex and Age <65 and ≥65 Years Among Patients with PsA and RA (all tofacitinib)**

| PsA | Age <65 years | | | Age ≥65 years | | | Female Sex | | | Male Sex | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13,453 PY | | | 7253 PY | | | 14,331 PY | | | 6375 PY | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| Case Reports | 3299 | | | 965 | | | 3468 | | | 1338 | | |
| AEs | 10,198 | | 75.80 | 3505 | | 48.32 | 11,455 | | 79.93 | 3770 | | 59.14 |
| SAEs | 1130 | 11.08 | 8.40 | 555 | 15.83 | 7.65 | 1402 | 12.24 | 9.78 | 530 | 14.06 | 8.31 |
| AESIs[c] | | | | | | | | | | | | |
| Serious Infections | 284 | 2.78 | 2.11 | 114 | 3.25 | 1.57 | 312 | 2.72 | 2.18 | 113 | 3.00 | 1.77 |
| HZ (Serious and Non-serious) | 46 | 0.45 | 0.34 | 25 | 0.71 | 0.34 | 59 | 0.52 | 0.41 | 21 | 0.56 | 0.33 |
| Cardiovascular Events[d] | 31 | 0.30 | 0.23 | 23 | 0.66 | 0.32 | 38 | 0.33 | 0.27 | 27 | 0.72 | 0.42 |
| Malignancies (excluding NMSC) | 32 | 0.31 | 0.24 | 19 | 0.54 | 0.26 | 38 | 0.33 | 0.27 | 17 | 0.45 | 0.27 |
| NMSC | 6 | 0.06 | 0.04 | 5 | 0.14 | 0.07 | 10 | 0.09 | 0.07 | 1 | 0.03 | 0.02 |
| VTEe | 21 | 0.21 | 0.16 | 11 | 0.31 | 0.15 | 22 | 0.19 | 0.15 | 16 | 0.42 | 0.25 |
| Fatal Cases | 10 | 0.30 | 0.07 | 26 | 2.69 | 0.36 | 24 | 0.69 | 0.17 | 14 | 1.05 | 0.22 |

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| PsA | Age <65 years | | | Age ≥65 years | | | Female Sex | | | Male Sex | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13,453 PY | | | 7253 PY | | | 14,331 PY | | | 6375 PY | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| **RA** | **Age <65 years** | | | **Age ≥65 years** | | | **Female Sex** | | | **Male Sex** | | |
| | 247,644 PY | | | 191,726 PY | | | 336,013 PY | | | 103,357 PY | | |
| | **N** | **%** | **RR** | **N** | **%** | **RR** | **N** | **%** | **RR** | **N** | **%** | **RR** |
| Case Reports | 42,923 | | | 22,076 | | | 49,300 | | | 10,757 | | |
| AEs | 142,559 | | 57.57 | 80,419 | | 41.94 | 176,244 | | 52.45 | 33,014 | | 31.94 |
| SAEs | 20,472 | 14.36 | 8.27 | 17,104 | 21.27 | 8.92 | 29,088 | 16.5 | 8.66 | 6292 | 19.06 | 6.09 |
| AESIs[c] | | | | | | | | | | | | |
| Serious Infections | 4326 | 3.03 | 1.75 | 3238 | 4.03 | 1.69 | 5904 | 3.35 | 1.76 | 1253 | 3.80 | 1.21 |
| HZ (Serious and Non-serious) | 1013 | 0.71 | 0.41 | 769 | 0.96 | 0.40 | 1389 | 0.79 | 0.41 | 229 | 0.69 | 0.22 |
| Cardiovascular eEventsd | 519 | 0.36 | 0.21 | 655 | 0.81 | 0.34 | 831 | 0.47 | 0.25 | 303 | 0.92 | 0.29 |
| Malignancies (excluding NMSC) | 615 | 0.43 | 0.25 | 791 | 0.98 | 0.41 | 979 | 0.56 | 0.29 | 331 | 1.00 | 0.32 |
| NMSC | 117 | 0.08 | 0.05 | 181 | 0.23 | 0.09 | 211 | 0.12 | 0.06 | 78 | 0.24 | 0.08 |

Redacted

| PsA | Age <65 years | | | Age ≥65 years | | | Female Sex | | | Male Sex | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13,453 PY | | | 7253 PY | | | 14,331 PY | | | 6375 PY | | |
| | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] | N | %[a] | RR[b] |
| VTE[e] | 222 | 0.16 | 0.09 | 222 | 0.28 | 0.12 | 332 | 0.19 | 0.10 | 117 | 0.35 | 0.11 |
| Fatal cases | 312 | 0.73[f] | 0.13 | 825 | 3.74[f] | 0.43 | 744 | 1.51[f] | 0.22 | 332 | 3.09[f] | 0.32 |

*AE* adverse event, *AESI* adverse event of special interest, *HZ* herpes zoster, *MedDRA* Medical Dictionary for Regulatory Activities, *NMSC* non-melanoma skin cancer, *PsA* psoriatic arthritis, *PT* Preferred Term, *RR* reporting rate, *SAE* serious adverse event, *VTE* venous thromboembolism

a. Percentages are based on total AEs by formulation except where otherwise indicated.
b. Events/100 PY (exposure estimated from IQVIA's Multinational Integrated Data Analysis System and Prescriber Insights databases)
c. Search criteria for AESI categories are described in Supplementary Methods.
d. Includes Standardised MedDRA Queries central nervous system vascular disorders, myocardial infarction and associated terms, ischaemic heart disease and associated terms; and PTs cardiac death, cardiac failure congestive, sudden cardiac death and pulmonary embolism.
e. Pulmonary embolism events are captured in the cardiovascular events and VTE categories.
f. Percentages based on total case reports by formulation.

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### 11.4. Other Analyses

None.

### 11.5. Adverse Events/Adverse Reactions

This study involved a combination of existing structured data and unstructured data, which were converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods.

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

## 12. DISCUSSION

### 12.1. Limitations of the Research Methods

Limitations of this analysis included the potential for reporting bias (eg, favouring female and/or younger patients), varied reporter identity/training (eg, consumer vs physician; specialists may be more likely to report than general practitioners) and exposure estimation from commercial sales data (covering only 61 countries and one region, with indication share derived from even fewer countries [n=18] where prescription data were available). When interpreting the AE data, the use of mixed data sources should be noted; the RRs in this analysis were calculated using the estimated exposure data, while the n and frequency (%) are solely based on case report or AE numbers. Also, more data were available for RA than for PsA and for IR than for XR tofacitinib, which should be considered when interpreting differences across indications and formulations. Furthermore, causality of AEs, considering tofacitinib compared with other concomitant medications, was not robustly collected. Most patients would have received concomitant methotrexate or other csDMARDs per regulatory labelling, so the role of these medications in contributing to AE risk cannot be ruled out. Other limitations of PMS data in general include under-reporting of non-serious AEs, difficulty identifying events with low frequency and difficulty quantifying risks (owing to the lack of a reliable denominator).

### 12.2. Interpretation

In this analysis, the post-marketing safety of tofacitinib in PsA and RA ascertained from AE reports submitted to the Pfizer safety database was aligned with the known safety profile of tofacitinib. This analysis with 4 years of data is the first PMS report for tofacitinib in PsA and extends the RA PMS data across a longer timeframe (9 years) than previously published data. Trends in reporting of overall AEs, including types and seriousness, were comparable across the PsA and RA indications. PMS data for AESIs and the most reported AEs provide complementary information to the safety results of previous clinical and observational trials.

Prior post-marketing data in RA and UC generally showed safety reporting trends similar to those of the present study. For example, the most frequently reported AEs (by PT) were mostly consistent with those reported in the earlier RA PMS study and the UC PMS study. In all three studies, drug ineffective, condition aggravated, headache, diarrhea and fatigue were among the top ten most frequently reported AEs. In contrast to these findings for the PMS reports, data from the tofacitinib clinical development program found that nasopharyngitis and upper respiratory tract infections were the most common AEs experienced by patients receiving tofacitinib for PsA or RA. These differences may relate to methodology; in clinical trials, all potential AEs are captured in a tightly controlled setting (including non-severe respiratory illnesses), whereas for spontaneous reporting, AEs that are suspected to be treatment-related may be prioritized.

In this analysis, off-label use was coded as an AE in line with its inclusion as a MedDRA PT. Off-label use was the second most frequently reported AE for PsA, which might be attributable to use as monotherapy (tofacitinib is approved for PsA in combination with methotrexate or nonbiologic DMARDs, depending on the country). A recent analysis of US claims data found that 62.6% of patients treated with tofacitinib for PsA were receiving monotherapy. Alternatively, off-label use may represent utilisation of a higher dose, such as 10 mg BID, which is not approved for PsA, and is approved for RA in Russia and Botswana (and formerly Switzerland, until 2020).

Our study provides important insight into the safety profile of tofacitinib in PsA, which was similar overall to the safety profile in RA. Higher RRs for AEs were observed for PsA than for RA in the present study over the full period of data collection, which covered 9 years for RA and 4 years for PsA. However, when restricting the analysis to the first 4 years post-approval for each indication, to align the duration of data collection, the RRs were higher for RA vs PsA. RRs are typically highest in the first 2 years post approval (a phenomenon referred to as the Weber effect), so these results were not unexpected, given that tofacitinib was approved for RA before PsA, and had a novel mechanism of action at the time of its first approval. Also, RA has been associated with a generally higher comorbidity burden than PsA, which may increase patients' likelihood of experiencing AEs. In pooled analyses of the tofacitinib clinical trial program, incidence rates of SAEs and AEs leading to discontinuation were higher in RA than in PsA, while rates of AESIs were generally comparable, except for numerically lower rates of serious infections and HZ in PsA vs RA. These differences were suggested to relate to patient characteristics including older age and higher corticosteroid use in the RA cohort vs the PsA cohort. In these PMS data, we did not observe noticeable differences in frequency or RR of AESI between PsA and RA. Previous registry studies have found higher exposure-adjusted incidence rates and/or risk ratios of infections,[9] MACE[13,14] malignancies,[10] and VTE [11] in RA vs PsA. In this analysis, the most frequent AEs reported by PT were similar between PsA and RA, except for differences in off-label use, as discussed above. To our knowledge, no other PMS data are available comparing rates of AESI in PsA vs RA.

Overall, the AESIs observed in this study were aligned with those observed in other PMS studies of bDMARDs in PsA and RA, but differences in geographical regions, patient and disease characteristics, and data-collection methodology make it difficult to compare AE rates across studies. In previous real-world safety studies, rates of AESIs were generally comparable between tofacitinib and bDMARDs in overall populations of patients with RA except for HZ, which occurred more frequently with tofacitinib than with bDMARDs. No comparable large studies have been published in PsA, but an analysis comparing tofacitinib clinical data with US Truven MarketScan registry data for bDMARDs (with patient exclusion criteria similar to those of the tofacitinib clinical trials applied) showed generally similar incidence rates for most AESI in PsA, except for rates of HZ which, as expected, were higher in the tofacitinib clinical data than in the bDMARD observational data. In patients with RA and elevated CV risk, differences in AESI rates between tofacitinib and bDMARDs have been noted in the ORAL Surveillance and STAR-RA studies.

A trend towards higher reporting of AEs and SAEs with the XR formulation than with the IR formulation was observed across indications, although RRs for acute events of interest (AESIs) and fatal cases were similar. However, types of AEs and frequency (% of total AEs) are generally similar for XR and IR formulations.

There are several factors that might explain the higher volume of reports, and resulting RR, for XR relative to IR. Notably, SAEs occurred with similar frequency (in terms of percentage) between the XR and IR formulations, possibly indicating that the difference could be due to reporting trends rather than a reflection of differing safety profiles. The total exposure time for the XR formulation was lower than for the IR formulation, which may have impacted the resulting RR. Almost all of the case reports received for the XR formulation originated from North America, potentially indicating a regional trend in reporting frequency. The XR formulation was first approved in North America, and the US contributes the highest number of AE reports globally to large Individual Case Safety Reports databases such as VigiBase and the FDA Event Reporting System (FAERS). In addition, specialists may be more likely to report AEs than general practitioners, and the US has a higher density of rheumatologists than other countries with large populations.

Furthermore, the XR once daily formulation might be preferred by patients receiving multiple treatments per day, who may have comorbidities and potentially experience a greater number of AEs. Notably, approximately twice as many patients receiving the XR formulation reported multiple indications as those receiving the IR formulation. In a randomized clinical trial setting, the safety profile of the IR and XR formulations was comparable. The two formulations have been shown to have equivalent pharmacokinetic profiles based on areas under the curve and similar effectiveness in the real-world CorEvitas (formerly Corrona) RA registry.

External factors such as regulatory safety alerts or changes to a drug's approval status have been shown to lead to increases in AE reporting, which is termed notoriety bias. In 2019, an ad hoc safety analysis of the ORAL Surveillance study revealed increases in rates of pulmonary embolism with tofacitinib 10 mg BID vs TNFi and all-cause mortality with tofacitinib 10 mg BID vs tofacitinib 5 mg BID and TNFi. Final results additionally showed an increased risk of MACE, malignancy excluding NMSC, HZ, and adjudicated NMSC with both tofacitinib doses (5 and 10 mg BID) vs TNFi. Serious infections and VTE occurred more frequently with tofacitinib (10 mg BID >5 mg BID) than with TNFi. After the results of ORAL Surveillance, signal detection studies of JAK inhibitors using FAERS and VigiBase have revealed increased reporting odds ratios for VTE or thromboembolic events and a disproportionality signal for skin cancers.

In another analysis of VigiBase directly comparing JAK inhibitors and TNFi, no increased reporting odds ratio was found for MACE, although an increased risk of VTE was observed. In our analysis of PMS data collected from the Pfizer safety database, an increase in event reporting over time was not consistently observed across AEs, which might suggest that differences in reporter identity or training can influence post-marketing data collection.

There was a higher proportion of reports received for females than for males; this trend is expected for RA, given the epidemiological rates of disease prevalence (approximately 2-5 times higher in females than males, depending on age); however, this was unexpected for PsA (approximately 1:1 female: male ratio,[2]), suggesting a bias for reporting AEs in females compared with males. It is not surprising that a higher RR is observed in female patients vs male patients, given the higher volume of reports for females. It will be important to further explore whether these trends are based on a higher likelihood of the attending HCP, or the consumer, to report an event occurring in a female, or if the rate of AEs occurring is truly higher in females. When considering SAEs, AESIs, and fatal cases, the RRs were similar between the sexes. Higher RRs were also observed in patients <65 vs ≥65 years. In this case, it is possible that AEs in patients ≥65 years are more likely to be attributed to an older age than to the treatment and are therefore less likely to be reported. Alternatively, these trends in RRs could point to differences in clinical care between subgroups. In the VigiBase analysis of MACE and VTE comparing JAK inhibitors and TNFi, age, and sex did not significantly influence RRs.

In addition, frequencies of SAEs, AESIs and fatal cases (as a proportion of total AEs or total cases) were generally similar between tofacitinib formulations with numerical differences noted for certain AESIs observed more frequently in IR than XR formulation (VTE and CV events for PsA, and fatal cases for RA). AE reports found that safety findings for overall AEs and AESIs with tofacitinib were consistent between PsA and RA indications and were aligned with the known safety profile of tofacitinib.

### 12.3. Generalizability

Not Applicable.

## 13. OTHER INFORMATION

Not Applicable.

## 14. CONCLUSIONS

This PMS study using data ascertained from submitted AE reports found that safety findings for overall AEs and AESIs with tofacitinib were consistent between PsA and RA and were aligned with the known safety profile of tofacitinib. Frequencies of SAEs, AESIs, and fatal cases (as a proportion of total AEs or total cases for fatal events) were similar between tofacitinib formulations, while RRs were higher with the XR formulation vs the IR formulation. This difference in RRs may relate to differences in cumulative exposure, regional reporting trends, or different patient populations. Potential trends in reporting by sex and age require further assessment, with higher RRs observed in females than in males and in younger than in older patients. Conclusions based on RRs are problematic, since RRs are more like an instant rate, considering that the exposure data in the denominator comes from sales data, whilst numerator data is based on case reports from another data base (Argus).

While these results should be interpreted in the context of the above limitations of PMS studies and spontaneous AE reporting, this study provides important insight into regarding the global real-world safety profile of tofacitinib, examined here for the first time in PsA.

## 15. REFERENCES

1. Ritchlin C, Colbert R, and Gladman D. The New England Journal of Medicine (2017) 376:957-70.

2. Scottia L, Franchia M, Marchesonib A, et al. Prevalence and incidence of psoriatic arthritis: As systematic review and meta-analysis *Seminars in Arthritis and Rheumatism* 48 (2018): 28-34.

3. Wilcox Hagberg K, Li L, Peng M, et al. Rates of Cancers and Opportunistic Infections in Patients with Psoriatic Arthritis Compared with Patients Without Psoriatic Arthritis *JCR: Journal of Clinical Rheumatology* Volume 22, Number 5, 2016.

4. Singh J, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis. Foundation Guideline for the Treatment of Psoriatic Arthritis, *Arthritis Care & Research* Vol. 71, No. 1, January 2019, pp 2–29 DOI 10.1002/acr.23789 © 2018, American College of Rheumatology.

5. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies:2019 update *Ann Rheum Dis:* first published as 10.1136/annrheumdis-2020-217159 on 20 May 2020.

6. Coates L, Soriano E, Corp N, et al. The group for research and assessment of psoriasis and psoriatic arthritis (grappa) treatment recommendations 2021Scientific Abstracts.

7. Ogdie A, Yu YD, Haynes K, et al. Risk of Major Cardiovascular Events in Patients with Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis: A population-based cohort study Published in final edited form as: *Ann Rheum Dis.* 2015 February; 74(2): 326–332. doi:10.1136/annrheumdis-2014-205675.

8. Roubille C, Richer V, Starnino T, et al. Evidence-based Recommendations for the Management of Comorbidities in Rheumatoid *The Journal of Rheumatology* 2015; 42:10; doi:10.3899/jrheum.141112.

9. Haynes K, Beukelman T, Curtis JR, et al. Risk of Major Cardiovascular Events in Patients with Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis: A population based cohort study.

10. Vaengebjerg S, Skov L, Egeberg A, et al. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis, A Systematic Review and Meta-analysis *JAMA Dermatol.* 2020;156(4):421-429. doi:10.1001/jamadermatol.2020.0024 Published online February 19, 2020.

11. Baumrin E, Van Voorhees A, Garg A, et al. A systematic review of herpes zoster incidence and consensus recommendations on vaccination in adult patients on systemic therapy for psoriasis or psoriatic arthritis: From the Medical Board of the National Psoriasis Foundation. Published online March 15, 2019. American Academy of Dermatology, Inc. https://doi.org/10.1016/j.jaad.2019.03.017.

12. Zisman D, Bitterman H, Shalom G, et al. *Ann Rheum Dis:* first published as 10.1136/annrheumdis-2013-205148 on 26 September 2014. D Psoriatic arthritis treatment and the risk of herpes zoster Zisman D, et al. *Ann Rheum Dis* 2016;75:131–135. doi:10.1136/annrheumdis-2013-205148.

13. Haddad A, Li S, Thavaneswaran A, et al. The Incidence and Predictors of Infection in Psoriasis and Psoriatic Arthritis: Results from Longitudinal Observational Cohorts *The Journal of Rheumatology* 2016; 43:2; doi:10.3899/jrheum.140067.

14. Patel S, Kumthekar A. Psoriatic Arthritis: The Influence of Co-morbidities on Drug Choice *Rheumatol Ther* (2022) 9:49–71 https://doi.org/10.1007/s40744-021-00397-7.

15. Wu J, Poom K. Tumor Necrosis Factor Inhibitor Therapy and Myocadianl Infarction Risk in Patients with Psoriasis, Psoratic Arthritis of Both, *Journal of Drug in Dermatology* August 2014 932(13)8.

16. Stovall R, Peloquin C, Felson D, Relation of therapies for ankylosing spondylitis and psoriatic arthritis to risk of myocardial infarction: a nested case control study *BMC Rheumatology* (2021) 5:36 https://doi.org/10.1186/s41927-021-00207-1.

17. Xeljanz/Xeljanz XR/Xeljanz Oral Solution [prescribing information]. New York, NY: Pfizer Inc. December 2021.

18. Xeljanz [summary of product characteristics]. October 2021.

19. Gladman D, Rigby W, Azevedo V, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors *n engl j med* 377;16.

20. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis *n engl j med* 2017 2017;377:1537-50.

21. Nash P, Coates L, Fleishaker D, et al. Safety and efficacy of tofacitinib up to 48 months in patients with active psoriatic arthritis: final analysis of the OPAL Balance long-term extension study *Lancet Rheumatol* 2021; 3: e270–83.

22. Burmester GR, Nash P, Sands BE, et al. Adverse events of special interest in clinical trials of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and psoriasis with 37066 patient-years of tofacitinib exposure *RMD Open* 2021;7e001595.

23. Ytterberg S, Bhatt D, Mikuls TR, et al. ORAL Surveillance Investigators Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis *n engl j med* 386;4.

24. Rubin D, Modesto I, Vermeire S, et al. Worldwide post-marketing safety surveillance experience with tofacitinib in ulcerative colitis *Alimentary Pharmacology & Therapeutics* (2021) 00:1-9.

25. Cohen S, Curtis J, DeMasi R, et al. Worldwide, 3-Year, Post-Marketing Surveillance Experience with Tofacitinib in Rheumatoid Arthritis *Rheumatol Ther* (2018) 5:283–291.

26. Galíndez-Agirregoikoa E, Prieto-Peña D, Martín-Varillas JL, et al. Treatment with tofacitinib in refractory psoriatic arthritis. national multicenter study of the first 87 patients of clinical practice *Rheumatol Ther* (2018) 5:283–291.

## 16. LIST OF SOURCE TABLES AND FIGURES

Figure 2. Most frequent AEs occurring in ≥2% of patients with RA (by PT). Percentages were calculated from the total case reports per formulation. AEs adverse events, HZ herpes zoster, IR immediate release, PT Preferred Term, RA rheumatoid arthritis, XR extended release.

Figure 3. Most frequent AEs occurring in ≥2% of patients with PsA and RA (tofacitinib formulation not reported). Percentages were calculated from the total case reports with no tofacitinib formulation reported. AE adverse event, HZ herpes zoster, IR immediate release, PsA psoriatic arthritis, RA rheumatoid arthritis, XR extended release

# 17. SUPPLEMENTARY INFORMATION

## 17.1. Supplementary Methods

### 17.1.1. Search Criteria for AESIs

| AESI | MedDRA/SMQ level \| MedDRA Term(s)/SMQ (MedDRA Version 24.1) |
|---|---|
| Venous Thromboembolism (Deep Vein Thrombosis/Pulmonary Embolism) | SMQ Narrow \| Embolic and Thrombotic Events, Venous |
| Serious and Other Important Infections | (Adverse Events that met serious criteria only)<br>SOC \| Infections and Infestations [Primary Path]<br>PT \| Febrile Neutropenia |
| Herpes Zoster Reactivation | PT \| Disseminated Varicella Zoster Virus infection<br>PT \| Genital Herpes Zoster<br>PT \| Herpes Zoster<br>PT \| Herpes Zoster Cutaneous Disseminated<br>PT \| Herpes Zoster Disseminated<br>PT \| Herpes Zoster Infection Neurological<br>PT \| Herpes Zoster Meningitis<br>PT \| Herpes Zoster Meningoencephalitis<br>PT \| Herpes Zoster Meningomyelitis<br>PT \| Herpes Zoster Meningoradiculitis<br>PT \| Herpes Zoster Necrotizing Retinopathy<br>PT \| Herpes Zoster Oticus<br>PT \| Herpes Zoster Pharyngitis |

| AESI | MedDRA/SMQ level \| MedDRA Term(s)/SMQ (MedDRA Version 24.1) |
|---|---|
| | PT \| Herpes Zoster Reactivation<br><br>PT \| Ophthalmic Herpes Zoster |
| Non-Melanoma Skin Cancer | HLT \| Skin Neoplasms Malignant and Unspecified (excluding Melanoma) (Primary Path)<br><br>PT \| Squamous Cell Carcinoma |
| Malignancy (terms covered under non-melanoma skin cancer are not included here) | SMQ Narrow \| Malignancy-related Conditions<br><br>SMQ Narrow \| Malignancy-related Therapeutic and Diagnostic Procedures<br><br>SMQ Narrow \| Malignant or Unspecified Tumors<br><br>SMQ Narrow \| Tumor Markers |
| Cardiovascular Events | SMQ Narrow \| Central Nervous System Vascular Disorders<br><br>SMQ Narrow \| Myocardial Infarction<br><br>SMQ Narrow \| Other Ischaemic Heart Disease<br><br>PT \| Cardiac Death<br><br>PT \| Cardiac Failure Congestive<br><br>PT \| Sudden Cardiac Death<br><br>PT \| Pulmonary Embolism |
| All-Cause Mortality | Clinical Outcome = Fatal |

*AESI* adverse event of special interest, *HLT* high level term, *MedDRA* Medical Dictionary for Regulatory Activities, *PT* Preferred Term, *SMQ* standardized MedDRA query, *SOC* system organ class.

# Document Approval Record

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