NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title:

Retrospective Post-Marketing Safety Surveillance Study of Tofacitinib in Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA)

Date:

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Name and Affiliation of The Main Author:

Redacted

Keywords:

tofacitinib citrate/Xeljanz; post-marketing surveillance; safety; spontaneous adverse event reporting; psoriatic arthritis; rheumatoid arthritis

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. 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. 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.

International treatment guidelines for PsA recommend initial therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate. 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 possibly due to control of systemic inflammation similar rates malignancies and increased risk of infection compared to patient populations not receiving bDMARDs. However, results across studies are varied, 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).

Tofacitinib is an oral Janus Kinase inhibitor for the treatment of PsA, RA, ulcerative colitis (UC), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis. 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 studies19,20 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.

The 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]). 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 UC24 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 was voluntarily conducted by Pfizer.

Research Question and Objectives:

What are the types and reporting rates (RR) of adverse events (AE) in patients receiving tofacitinib for PsA or RA reported in the Pfizer safety database?

Objectives:

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

- *To characterize the types and reporting rates of adverse events in patients receiving tofacitinib for PsA or RA captured within the Pfizer Safety database.*

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 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 adverse events reported in the PMS database by formulation (tofacitinib immediate release [IR], tofacitinib extended release [XR], unknown, tofacitinib all [tofacitinib IR and tofacitinib XR]) for PsA or RA:*
    - *Age (median range);*
    - *Age ≥65 years/<65 years;*
    - *Sex (male/female/Unk);*
    - *Race (Black or African American/White/Asian/Other/Native Hawaiian or other Pacific Islander/American Indian or Alaska Native) and Ethnicity (Hispanic or Latino/Not Hispanic or Latino/Unknown);*
    - *Region (North America[1] [NA]/Europe[2]/Rest of World [ROW][3]).*
2. *Types and Reporting Rate (RR) of treatment emergent AEs in the Pfizer Safety database[4] by formulation (tofacitinib IR, tofacitinib XR, unknown, tofacitinib All) for PsA or RA:*

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[1] *North America includes United States, Canada, and Puerto Rico.*

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

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

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

- *AEs;*
- *Serious adverse events (SAEs) as defined by MedDRA SOC;*
- *Most commonly reported AEs (occurring ≥2%) by MedDRA preferred term (PT);*
- *Fatal Cases;*
- *Select Adverse Events of Special Interest (AESIs) as categorically defined by SOC/PT in Periodic Benefit Risk Evaluation Reports (PBRER*):
  - *Serious Infections;*
  - *Herpes Zoster (serious and non-serious);*
  - *Cardiovascular risk*[5]
  - *Malignancies (excluding Non-Melanoma Skin Cancer [NMSC]); NMSC;*
  - *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:*[6] *For PSA, December 2017 – November 2019, December 2019 – November 2021; for RA, November 2015 – November 2017,*[7] *December 2017 – November 2019), December 2019 – November 2021.* [8]

2. *Types and RR for treatment emergent AEs reported in the Pfizer Safety database by formulation (tofacitinib IR, tofacitinib XR, tofacitinib all) for PsA or RA during the first four years of approval for the respective indication. For PsA, the timeframe 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.

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

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

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

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

Setting:

Data were extracted from the Pfizer Safety database and IQVIA Health's MIDAS (Sales) database and prescription data from IQVIA Health's Prescriber Insights database.

Inclusion Criteria:

All AEs reported in the Pfizer safety database in patients residing in countries/regions with available IQVIA Health MIDAS data[9] who were ≥18 years of age receiving tofacitinib for RA.

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

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 is defined using ICD-10 codes M06 Other Rheumatoid Arthritis and M05 Seropositive Rheumatoid Arthritis. PsA indication is defined using ICD-10 code L405 Arthropathic psoriasis was used to define PsA indication.[10]*
- *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.

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[9] United States, Canada, Puerto Rico, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, 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.

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

Population:

Included above under Inclusion Criteria.

Variables:

All variables/Endpoints are defined in the Analysis Plan including query/code lists and data location.

Variable/Endpoint	Role	Operational Definition
Adverse Event (AE)	Endpoint	A Report of AE during study timeframe
Adverse Event, most frequent	Endpoint	Report of AE (by PT) during study timeframe with frequency ≥2%
Age Categories	Baseline Characteristic/Stratifying Variable	Age at time of event ((≥65/<65)
Age (Age (Median, Range)	Baseline Characteristic/Stratifying Variable	Age at time of event
Blood and Lymphatic System Disorders	Endpoint	System Organ Class MedDRA Classification
Cardiac Disorders	Endpoint	System Organ Class MedDRA Classification
Cardiovascular Risk /Cardiovascular Events	Endpoint	AESI; Report of Events Meeting Cardiovascular Risk Criteria[11]
Congenital, Familial and Genetic Disorders	Endpoint	System Organ Class MedDRA Classification
Cumulative Exposure	Endpoint	Estimated Cumulative Drug Exposure based on 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	Endpoint	System Organ Class MedDRA Classification

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

Variable/Endpoint	Role	Operational Definition
Tissue 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
Psychiatric Disorders	Endpoint	System Organ Class MedDRA Classification
Pulmonary Embolism (PE)	Endpoint	AESI; Report of PE
Race	Baseline Characteristic	Patient Race (Asian/Black or African American /Native Hawaiian or other Pacific Islander /American Indian or Alaska Native/White /Unknown/Other [specify])
Region	Baseline Characteristic	Regional location of patient (NA/Europe/ ROW
Renal and Urinary Disorders	Endpoint	System Organ Class MedDRA Classification
Reproductive System and Breast Disorders	Endpoint	System Organ Class MedDRA Classification
Respiratory, Thoracic and Mediastinal Disorders	Endpoint	System Organ Class MedDRA Classification
Rheumatoid Arthritis (RA)	Baseline Characteristic/Stratifying Variable	Diagnosis of RA
Serious Adverse Event (SAE)	Endpoint	Report of Serious AE
Serious Infection	Endpoint	AESI; Report of Serious Infection
Sex/Gender	Baseline Characteristic/Stratifying Variable	Patient Sex (Male/Female)
Skin and Subcutaneous Tissue Disorders	Endpoint	System Organ Class MedDRA Classification
Social Circumstances	Endpoint	System Organ Class MedDRA Classification
Surgical and Medical Procedures	Endpoint	System Organ Class MedDRA Classification
Time Interval	Stratifying Variable	Discrete period of time within the overall study Timeframe
Vascular Disorders	Endpoint	System Organ Class MedDRA Classification
Venous Thromboembolism (VTE)	Endpoint	AESI; Report of venous thromboembolism

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.[12]

[12] 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.

Cumulative exposure during this timeframe was calculated as 20,706 patient years for PsA (Includes psoriasis)[13] 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.

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

Select AESI category data was 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).

Results:

73,525 case reports were reviewed (PsA=5394/RA=68,131), with 20,706/439,370 PY (PsA/RA) exposure. More AEs were reported for IR versus XR (IR/MR: PsA=8349/7602; RA=137,476/82,153). RRs for AEs (IR/MR: PsA=59.6/113.4; RA=44.0/64.8) and SAEs (PsA=8.1/13.6; RA=8.0/9.5) were higher with XR versus IR. Frequency of SAEs, AESIs, and fatal cases was mostly similar across formulations and indications. AE RRs (RA) in the first 4 years after IR approval were 95.9 (IR; 49,439 PY) and 147.0 (MR; 2000 PY). Case reports, AEs and PY of exposure increased over time (2-year time intervals) for both indications. 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 and lower

[13] Includes Psoriasis indication.

thereafter; frequencies of SAEs, AESIs, and fatal cases were comparable across time intervals. The most frequently reported AE Preferred Terms (PsA/RA) included drug ineffective (20.0%/17.8%), pain (9.7%/10.6%), 52 condition aggravated (9.9%/10.5%), headache (8.8%/7.9%) and, for PsA, off-label use (10.5%/3.4%).

Conclusion:

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.

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	13November 2023	

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 2021 Scientific 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.