NON-INTERVENTIONAL STUDY PROTOCOL

Study Information

Title	A Non-Interventional Multinational Study of Tofacitinib in Patients Treated for Psoriatic Arthritis
Protocol number	A3921332
Protocol version identifier	2.0
Date	14 February 2023
Active substance	L04AA29 tofacitinib citrate
Medicinal product	Tofacitinib (Xeljanz®)
Research question and objectives	The aim of this study is to evaluate the effectiveness of treatment with tofacitinib on disease activity, remission, and quality of life (QoL) in patients with Psoriatic Arthritis (PsA) over a 12-month observation period. **Primary Objective** To evaluate the proportion of patients achieving low disease activity (LDA) after 6 months of follow-up. **Secondary Objectives** 1. To evaluate the proportion of patients achieving LDA after 3 and 12 months of follow-up. 2. To evaluate the proportion of patients achieving minimum disease activity (MDA) after 3, 6, and 12 months of follow-up. 3. To evaluate the proportion of patients achieving remission after 3, 6, and 12 months of follow-up. 4. To evaluate change from baseline in Psoriatic Arthritis Impact of Disease 12 Questions (PsAID12) score after 3, 6, and 12 months of follow-up. 5. To evaluate change from baseline in Spondylarthritis Research Consortium of Canada Enthesitis Index

	(SPARCC-EI) score after 3, 6, and 12 months of follow-up. 6. To identify prognostic indicators for achieving LDA after 3, 6, and 12 months of follow-up. 7. To evaluate change from baseline in QoL scores after 3, 6, and 12 months of follow-up. **Exploratory objectives** To evaluate changes in measures of disease activity (Psoriatic Arthritis Disease Activity Score [PASDAS] and Disease Activity in Psoriatic Arthritis [DAPSA]) from baseline after 3, 6, and 12 months of follow-up.
Author	**Main Author**: Prof. PPD Tel Aviv Medical Center, Israel **Co-Author**: PPD, Pfizer Israel

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR20	American College of Rheumatology (Criteria) 20%
AE	adverse event
AEM	adverse event monitoring
ALK PH	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
bDMARD	biologic Disease-Modifying Antirheumatic Drug
BSA	Body Surface Area
CBC	complete blood count
CI	confidence interval
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
csDMARD	conventional synthetic Disease-Modifying Antirheumatic Drug
DAPSA	Disease Activity in Psoriatic Arthritis
DMARD	Disease-Modifying Antirheumatic Drug
DMP	data management plan
eCRF	electronic case report form
EDC	electronic data capture
EDP	exposure during pregnancy

Abbreviation	Definition
EMA	European Medicines Agency
ENR	all enrolled set
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS	full analysis set
GPP	good pharmacoepidemiology practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HbA1C	hemoglobin A1C
HDL	high-density lipoprotein
IBM-CD	International Business Machines Clinical Development
ICF	informed consent form
IEC	Independent Ethics Committee
IFN	interferon gamma
IL	interleukin
ISPE	International Society for Pharmacoepidemiology
IRB	Institutional Review Board
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
LDA	low disease activity
LDI	Leeds Dactylitis Index
LDL	low-density lipoprotein

Abbreviation	Definition
LEI	Leeds Enthesitis Index
MDA	minimum disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NIS	non-interventional study
NRS	Numerical Rating Scale
NSTEMI	non-ST-elevation myocardial infarction
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PDE4	phosphodiesterase 4
PRO	patient reported outcome
PsA	psoriatic arthritis
PsAID12	Psoriatic Arthritis Impact of Disease 12 Questions
PV	pharmacovigilance
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SF-36	Short Form 36
SJC	swollen joints count
SmPC	summary of product characteristics

Abbreviation	Definition
SPARCC-EI	Spondyloarthritis Research Consortium of Canada Enthesitis Index
SSZ	salazopyrine
STEMI	ST-elevation myocardial infarction
Th	T-helper (cell)
TJC	tender joints count
TNFi	tumor necrosis factor inhibitors
tsDMARD	targeted synthetic Disease-Modifying Antirheumatic Drug
UA	uric acid
VAS	Visual Analogue Scale
VTE	venous thromboembolism
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Prof. Ori Elkayam	Head, Rheumatology Institute	Tel Aviv Sourasky Medical Center	Weisman 6, Tel Aviv, Israel
Dr. Meriem Kessouri	Non-Interventional Study Lead	Pfizer France	23-25 Avenue du Docteur Lannelongue Paris, France

4. ABSTRACT

Stand Alone Document

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendments(s)	Reason
1	14 February 2023	Section 4. Abstract	Aligned with changes to main text.	Consistency.
		Section 6. Milestones	Changed dates of end of data collection and final study report. Added actual start of data collection.	Enrolment period extended by 8 months.
		Section 7. Rationale and Background	Added new formulation of 11 mg extended release.	Updated SmPC and recommended dose.
		Section 9.1. Study Design	Changed the patient number from '500' to '200' in Figure 1.	To reflect change in sample size.
		Section 9.2. Setting	Changed planned enrollment to 200 patients, updated country list, changed enrolment period to 25 months, and total study duration to 37 months.	Changed enrolment projections and extended enrolment period.
		Section 9.4. Data Sources	Clarified that IQVIA will enter PROs into the EDC rather than the sites.	Change in procedure.
			Corrected non-observational to non-interventional	Typo.

Amendment number	Date	Protocol section(s) changed	Summary of amendments(s)	Reason
		Section 9.4.2. PROs	Added text describing the Psoriatic Arthritis Impact of Disease 12 questionnaire.	To align with the list of variables in section 9.3
		Section 9.5. Study Size	Updated enrolment to 200 patients, expected evaluable patients to 154 patients, and precision estimate to 6.3%.	To reflect changes in enrolment projections.
		Section 10.4	Adding that due to the observational nature of this study, IRB/IEC approval is not required in Denmark	Clarification.
		Section 11	Updating the non-serious Adverse Event to be reported to Pfizer safety. New text added regarding exposure during pregnancy	The previous list is not representative of AESI, but the risk category. Clarifying what events are reportable during pregnancy
		Annex 2	ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS	Removed annex as ENCePP checklist not required.

6. MILESTONES

Milestone	Planned date
Planned start of data collection	31 August 2020
Actual start of data collection	17 May 2021
End of data collection	22 July 2024
Final study report	22 November 2024

7. RATIONALE AND BACKGROUND

Psoriatic arthritis (PsA) is a chronic progressive inflammatory disease involving skin (psoriasis), nails, and joints (peripheral as well as sometimes spinal). Involvement of the musculoskeletal system in PsA may cause inflammation of joints, periarticular tissues (enthesitis, tenosynovitis, dactylitis), and spine (sacroiliitis and/or spondylitis) and irreversible articular and periarticular structural damage. PsA has a significant negative impact on the patient's general condition, mood, and quality of life (QoL) with progressive disability if untreated. The prevalence of PsA is estimated to be up to 1% of the general population, and it is more prevalent among patients with psoriasis, ranging from 6% to 42%.[1-6]

PsA is often accompanied with multiple co-morbidities such as diabetes mellitus, obesity, nonalcoholic fatty liver disease, metabolic syndrome, gout, hypertension, mood disorders, and fibromyalgia.[7-11] PsA presents significant health and socioeconomic burdens for the individual and society. There is currently no cure for PsA. The purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize QoL, and, if possible, induce complete remission.[12]

Currently, there are no widely agreed upon definitions of disease severity in PsA and it is judged on a case-by-case basis by patients and health care providers. However, severity is assessed using both level of disease activity at a given time point, and the presence or absence of poor prognostic factors and long-term damage. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score of ≥12 and a Body Surface Area (BSA) score of ≥10.[13]

There is relatively little existing evidence to support the effectiveness of conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) in PsA (eg, methotrexate [MTX], salazopyrine [SSZ]). The csDMARDs do not appear to consistently slow or prevent progressive joint damage, and drug intolerance and safety issues are often present.[14-16]

Use of biological Disease-Modifying Antirheumatic Drugs (bDMARDs) remains limited with the inconvenience of the required routes of parenteral administration (intravenous infusions or subcutaneous injections) and apparent loss of initial effectiveness with continued use in a significant proportion of patients.[14-16] In published studies, tumor necrosis factor

inhibitors (TNFi) have demonstrated both effectiveness (reduction of joint disease activity, psoriasis skin improvement, and retardation of joint damage) and acceptable safety.[14-16] New bDMARDs have been introduced, such as anti-interleukin (IL)-12/IL-23 p40 common subunit ustekinumab, anti-IL-17A secukinumab and ixekizumab, and selective T-cell co-stimulation modulator abatacept.[17] Recently, effectiveness of IL-23/12 and IL-17 inflammatory axis drugs was demonstrated in PsA. Treatment failure with these drugs can represent a significant clinical problem and treatment with these agents can be hindered in daily clinical practice by the presence of co-morbidities, such as nonalcoholic steatohepatitis.[18]

Therefore, there is a potential unmet medical need for new Disease-Modifying Antirheumatic Drugs (DMARDs) in the PsA patient population.[14-16] The discovery of pro-inflammatory intracellular pathways involved in PsA pathogenesis, such as transcription factors Janus kinase (JAK) has led to the development of different targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs). Apremilast (Otesla®, PDE4 [phosphodiesterase 4] inhibitor) and tofacitinib (Xeljanz®, JAK inhibitor) are the only tsDMARDs approved in the treatment of PsA.

Tofacitinib (CP-690,550) is an oral JAK inhibitor that targets inflammation by reducing pro- inflammatory cytokine signaling and production.[19] Tofacitinib is indicated for the treatment of inflammatory diseases including rheumatoid arthritis (RA), PsA, and ulcerative colitis.

Tofacitinib in combination with MTX is indicated for the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy, the recommended dose is 5 mg administered twice daily or 11 mg prolonged release tablets administered once daily (summary of product characteristics [SmPC] dated 14 December 2021[EMA/103898/2017]).[20] The use of tofacitinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, active tuberculosis, serious infections such as sepsis or opportunistic infections, severe hepatic impairment, pregnancy, and lactation.[20]

Tofacitinib acts inside the cell by preferentially inhibiting signaling by cytokine receptors associated with JAK1 or JAK3.[21] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including
IL -2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in the modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon gamma (IFNγ).[22,23] In addition to interfering with T-helper (Th)1 and Th2 cell differentiation, tofacitinib has been shown to interfere with the production of inflammatory Th17 cells.[24] These effects provide the basis for use in diseases in which the immune response plays a pathogenic role such as RA and PsA.[25,26]

The effectiveness of tofacitinib was demonstrated in 2 Phase 3 randomized, double-blind, placebo-controlled clinical trials (NCT01877668 [OPAL BROADEN: 422 patients enrolled] and NCT01882439 [OPAL BEYOND: 395 patients enrolled]) that enrolled adult patients with active PsA at screening and baseline, and with inadequate response to prior csDMARDs. NCT01877668 enrolled 422 PsA patients naïve to TNFi but allowing concurrent treatment with MTX, leflunomide, or sulfasalazine, and had 12 months of total follow-up; and NCT01882439 enrolled 395 PsA patients with inadequate response or lack of toleration to previously administered TNFi and had 6 months of total follow-up. Both studies had change in American College of Rheumatology (Criteria) 20% (ACR20) and Health Assessment Questionnaire -Disability Index (HAQ-DI) at Month 3 as primary endpoints, and showed superior efficacy over placebo at 3 months of treatment.[27,28] In both studies, adverse events (AEs) were comparable to those observed in RA studies. To date, tofacitinib is the only JAK inhibitor that has been approved for the treatment of PsA by the United States Food and Drug Administration (approved 14 December 2017) and the European Commission (approved 28 June 2018).[17]

Clinical trial results reflect responses in selected populations, often excluding patients with significant co-morbidities. Evaluation of RA patients enrolled in a disease registry and who were treated with a TNFi estimated that only 21-33% of patients would have met the eligibility criteria of major trials. Registry patients that were considered ineligible for the clinical trials had lower baseline disease activity, more comorbidity, and lower functional status.[29] This study will evaluate the effectiveness of tofacitinib in PsA patients in a real-world setting over a 12-month period.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

The aim of this study is to evaluate the effectiveness of treatment with tofacitinib on disease activity, remission, and QoL in patients with PsA, over a 12-month observation period.

8.2. Objectives

Primary Objective

- To evaluate the proportion of patients achieving low disease activity (LDA) after 6 months of follow-up.

Secondary Objectives

- To evaluate the proportion of patients achieving LDA after 3 and 12 months of follow-up.
- To evaluate the proportion of patients achieving minimum disease activity (MDA) after 3, 6, and 12 months of follow-up.
- To evaluate the proportion of patients achieving remission after 3, 6, and 12 months of follow-up.

- To evaluate change from baseline in Psoriatic Arthritis Impact of Disease 12 Questions (PsAID12) score after 3, 6, and 12 months of follow-up.
- To evaluate change from baseline in Spondylarthritis Research Consortium of Canada Enthesitis Index (SPARCC-EI) score after 3, 6, and 12 months of follow-up.
- To identify prognostic indicators for achieving LDA after 3, 6, and 12 months of follow-up.
- To evaluate change from baseline in QoL scores after 3, 6, and 12 months of follow-up.

Exploratory Objectives

To evaluate changes in measures of disease activity (Psoriatic Arthritis Disease Activity Score [PASDAS] and Disease Activity in Psoriatic Arthritis [DAPSA]) from baseline after 3, 6, and 12 months of follow-up.

9. RESEARCH METHODS

9.1. Study Design

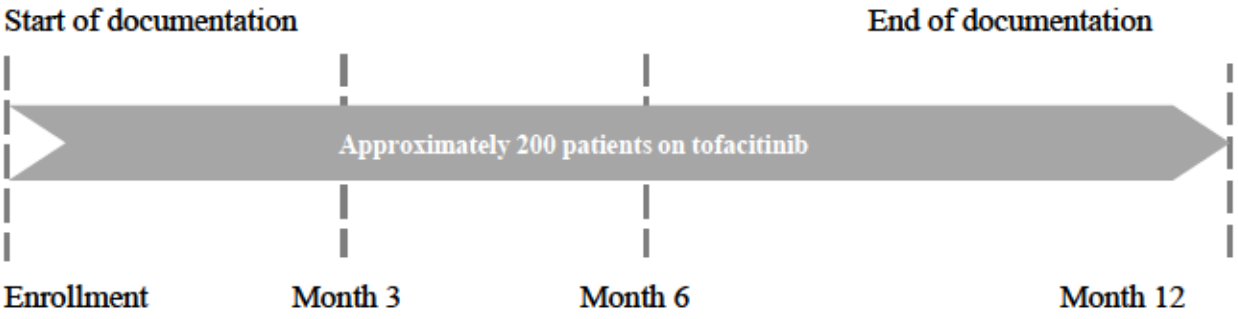
This is a prospective, non-interventional, multinational, multi-center study to evaluate the effectiveness of tofacitinib in patients with PsA in routine clinical practice with up to 12 months of follow-up. Patients must be treatment naïve for tofacitinib at the time of enrollment.

All assessments described in this protocol are performed as part of routine clinical practice or following standard practice guidelines, for the patient population and healthcare provider specialty in the countries where this non-interventional study is being conducted. The medicinal product(s) will be prescribed in routine clinical care in accordance with the terms of local country reimbursement guidelines. No study drug will be provided as a part of this study, and this protocol does not recommend the use of any specific treatments. The assignment of the patients to a particular therapeutic strategy is not decided by this protocol but falls within current practice and the clinical decision for the prescription of tofacitinib should be clearly separated from the decision to include the patient in the study. Dose and duration of treatment should be based on clinical and individual needs and are determined by the treating physician.

No additional diagnostic or monitoring procedures are mandated, and follow-up visits are captured as part of normal medical practice. Epidemiological methods will be used for the analysis of collected data. Patients will be followed up during routine clinic visits consistent with the European League Against Rheumatism (EULAR) guidelines for follow-up of patients with PsA (Figure 1). Documented visits for the purpose of this study will be at enrollment, then at approximately Months 3 (visit 2), 6 (visit 3), and 12 (visit 4, end of study visit) following initiation of treatment with tofacitinib. Patients that permanently discontinue

treatment with tofacitinib will be discontinued from the study. Study follow-up will stop at Month 12 unless a patient has already discontinued.

Figure 1. Study Design



Approximate schedule of planned visits

9.1.1. Endpoints

Primary endpoint

- Proportion of patients achieving LDA defined as PASDAS score ≤3.2 at Month 6.

Secondary endpoints

- Proportion of patients achieving LDA defined as PASDAS score ≤3.2 at Months 3 and 12.
- Proportion of patients achieving MDA defined as at least 5 of 7 criteria (see Table 3) met at Months 3, 6, and 12.
- Proportion of patients achieving remission defined as PASDAS score ≤1.9 at Months 3, 6, and 12.
- Proportion of patients achieving remission defined as DAPSA score ≤4.0 at Months 3, 6, and 12.
- Change from baseline in PsAID12 score at Months 3, 6, and 12.
- Change from baseline in SPARCC-EI score at Months 3, 6, and 12.
- Proportion of patients achieving LDA at Months 3, 6, and 12 based on presence of prognostic factors listed in Section 9.4.3.
- Change from baseline in QoL using patient reported outcome (PRO) scores at Months 3, 6, and 12.

Exploratory endpoints

- Change from baseline in PASDAS scores at Months 3, 6, and 12.
- Change from baseline in DAPSA scores at Months 3, 6, and 12.

9.2. Setting

This study will enroll approximately 200 patients from rheumatologists and/or PsA specialist centers in 8 countries (Belgium, Denmark, Finland, France, Israel, Netherlands, Spain, and Sweden) over an enrollment period of 25 months. The countries listed above are anticipated to participate in this study, however additional countries may be included at a later time. Each patient will have up to 12 months of follow-up for a total study duration of 37 months.

Consecutive patients attending a routine clinical visit will be invited to participate if they meet the eligibility criteria for the study and are to start on treatment with tofacitinib for active PsA. An enrollment/screening log will be maintained by the sites to record basic demographics and reasons for non-enrollment for patients that choose not to enroll.

All visits shall be scheduled according to local clinical practice. Within this study, a total of 4 visits are included: at enrollment, then at approximately Month 3, Month 6, and Month 12 following initiation of treatment with tofacitinib. All patients will be followed from enrollment until the end of follow-up (including discontinuations), death, loss to follow-up, or withdrawal of consent (whichever occurs first).

9.2.1. Inclusion Criteria

Patient eligibility should be reviewed by an Investigator before patients are included in the study. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients aged ≥18 years.
2. Moderate to severe PsA disease activity diagnosed.
3. Patients for whom the physician's decision has been made to initiate treatment with tofacitinib, in usual clinical practice conditions and in compliance with the local label.
4. Patients are treatment naïve to tofacitinib on the date of providing informed consent.
5. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
6. Patients on DMARDs must have not had a treatment change in the past 3 months.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Contraindications according to the Xeljanz® (tofacitinib) prescribing information.
2. Receipt of any investigational drug within 3 months before study inclusion.
3. Patient is pregnant or breastfeeding.
4. Recent herpes zoster infection (within past 6 months) or history of severe disseminated herpes zoster infection.
5. Active treatment for a malignancy.
6. Concomitant treatment with biological Disease-Modifying Antirheumatic Drugs (bDMARD).

9.3. Variables

The Schedule of Activities (Table 1) provides an overview of the requested data to be collected at each visit, with further details described below.

Table 1. Schedule of Activities

	Approximate schedule of planned visits			
	Enrollment (Visit 1)	Month 3 (Visit 2)	Month 6 (Visit 3)	Month 12 (Visit 4)
Informed consent	X			
Eligibility	X			
Demographics	X			
PsA disease history	X			
Medical history	X			
Previous PsA treatments	X			
Co-morbidities	X		X	
Concomitant PsA treatments	X	X	X	X
Tofacitinib treatment	X	X	X	X
Physical examination[1]	X	X	X	X
Blood biochemistry/hematology[2]	X	X	X	X
Inflammatory markers[3]	X	X	X	X
Disease activity measures[4]	X	X	X	X
Patient reported outcomes[5]	X	X	X	X
End of study				X
Adverse events	Continuous			

Abbreviations: PsA = Psoriatic Arthritis.

1. Height (only collected at enrollment), weight, calculated body mass index, waist circumference, smoking status (current/quit<1yr/former/never/unknown).
2. Complete blood count (CBC), creatinine, uric acid (UA), alkaline phosphatase (ALK PH), aspartate transaminase (AST), alanine transaminase (ALT), glucose, hemoglobin A1C (HbA1C), total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL).

3. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).
4. Swollen joint count (SJC66), tender joint count (TJC68), Patient Global Assessment, Physician Global Assessment, Patient Pain Assessment, Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI), tender enthesial points, Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC-EI), and radiological reports scored using Sharpe-Van de Heijde modified scoring for PsA.
5. Short Form 36 (SF-36), Health Assessment Questionnaire – Disability Index (HAQ-DI), Psoriatic Arthritis Impact of Disease 12 Questions (PsAID12).

9.3.1. Enrollment Visit (Visit 1)

- Informed Consent.
- Inclusion/Exclusion criteria.
- Demography (date of birth, sex).
- PsA disease history (date of diagnosis).
  - Duration of symptoms prior to enrollment (ie, current episode of symptoms [if applicable]).
  - Presence of rheumatoid nodules [present/absent/not available].
  - Arthritis of hand joints [present/absent/not available].
  - Counts of joints affected by arthritis at enrollment (specified by: small joints, medium joints, large joints, hand joints).
  - Unequivocal radiological erosion [present/absent/not available].
  - Unequivocal bony decalcification in hand and wrist joints [present/absent/not available].
- Tofacitinib dosing (dosage, start date).
- Concomitant PsA treatment (generic name, dosage, start/stop dates, reason for discontinuation [if applicable]).
- Prior treatment history of PsA (generic name, dosage, start/stop dates, reason for discontinuation [if applicable]).
- Other relevant medical history and co-morbidities (specify, date of diagnosis, end date [if applicable]), including:
  - History of venous thromboembolism (VTE) (date of event, type of event [deep venous thrombosis, pulmonary embolism]);

- Myocardial infarction within previous 3 months (date of event, type of event [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), unknown]);
- Diagnosis of heart failure (date of diagnosis);
- Diabetes (date of diagnosis, specify [type 2/type 1]);
- Hypertension (date of diagnosis, treated [Yes/No/unknown], treatment resistant [Yes/No/unknown]);
- Inherited coagulation disorder (date of diagnosis, specify);
- Malignancy (date of diagnosis, specify);
- Use of combined hormonal contraceptives or hormone replacement therapy (generic name, start/end date, reason for discontinuation [if applicable]);
- Any other relevant medical history.

- Physical examination (height, weight, calculated body mass index, waist circumference, smoking status [current/quit <1yr/former/never/unknown]).
- Blood biochemistry & hematology (result, unit, reference range [when applicable], clinically significant [Yes/No]).
- Complete blood count (CBC).
- Creatinine, uric acid (UA), alkaline phosphatase (ALK PH), aspartate transaminase (AST), alanine transaminase (ALT), glucose, hemoglobin A1C (HbA1C), total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL).
- Inflammatory markers (result, unit, reference range, clinically significant [Yes/No]).
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Disease activity measures.
- Number of swollen and tender joints (swollen joint count [SJC66]/tender joint count [TJC68]).
- Patient Global Assessment.

- Physician Global Assessment.
- Patient Pain Assessment.
- Leeds Enthesitis Index (LEI).
- Leeds Dactylitis Index (LDI).
- Tender enthesial points.
- PASI.
  - BSA.
  - Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC-EI).
  - Radiological reports scored using Sharpe-Van der Heijde modified scoring for PsA.[30]
- PROs.
  - Short Form 36 (SF-36).
  - HAQ-DI.
  - PsAID12.

9.3.2. Follow-up Visits 2, 3, 4 (at approximately Months 3, 6, and 12)

- Tofacitinib dosing (dosage, start/stop dates, reason for discontinuation [if applicable]).
- Concomitant PsA treatment (generic name, dose, start/stop dates, reason for discontinuation [if applicable]).
- Relevant co-morbidities (specify, date of diagnosis, end date [if applicable]) at Month 6 only.
- Physical examination (weight, calculated body mass index, waist circumference, smoking status [current/quit <1yr/former/never/unknown]).
- Blood biochemistry & hematology (result, unit, reference range [if applicable], clinically significant [Yes/No]).
  - CBC.

- Creatinine, UA, ALK PH, AST, ALT, glucose, HbA1C, total cholesterol, triglycerides, LDL, HDL.

- Inflammatory markers (result, unit, reference range, clinically significant [Yes/No]).
  - ESR.
  - CRP.
- Disease activity measures.
  - Number of swollen and tender joints (SJC66/TJC68).
  - Patient Global Assessment.
  - Physician Global Assessment.
  - Patient Pain Assessment.
  - LEI.
  - LDI.
  - Tender enthesial points.
  - PASI.
  - BSA.
  - SPARCC-EI.
  - Radiological reports scored using Sharpe-Van der Heijde modified scoring for PsA.
- PROs.
  - SF-36.
  - HAQ-DI.
  - PsAID12.
- AEs.

9.3.3. End of Study

The following additional parameters will be requested at the end of study visit:

- Study discontinuation (date of discontinuation, reason for study discontinuation);
- Tofacitinib treatment status at discontinuation;
- Alternative DMARD treatment (generic name, dose, start date).

9.3.4. Derived Variables

The study endpoints are PsA disease assessments, which are derived global scores from different disease indicators. Table 2 shows the disease indicators used to prepare the disease assessment scores.

Table 2. Assessments Required for Derivation of Study Endpoints

		Endpoints				
	Method	**PASDAS**	**DAPSA**	**MDA**	**LDA**	**remission**
Physician global assessment	VAS	x				
Patient global assessment	VAS	x	x	x		
Patient pain assessment	VAS		x			
Swollen joints count	exam	x	x	x		
Tender joints count	exam	x	x	x		
Tender enthesial points	exam			x		
Leeds enthesitis index	exam	x				
Leeds dactylitis index	exam	x				
PASI (calculated)	exam			x		
BSA	exam			x		
CRP	blood	x	x			
SF-36 (physical component)	PRO	x				
HAQ-DI	PRO			x		
PASDAS score					x (≤3.2)	x (≤1.9)

Abbreviations: BSA= Body Surface Area, CRP= C-reactive protein, DAPSA= Disease Activity in Psoriatic Arthritis, HAQ-DI= Health Assessment Questionnaire - Disability Index, LDA= low disease activity, MDA= minimum disease activity, PASDAS= Psoriatic Arthritis Disease Activity Score, PASI= Psoriasis Area and Severity Index, PRO= patient reported outcome, SF-36= Short Form 36, VAS= Visual Analogue Scale.

Table 3. Calculation of Disease Activity Indicators

Disease activity indicators	Definition/Calculation
Psoriatic Arthritis Disease Activity Score (PASDAS)[31-33]	(0.18 × √physician global assessment [VAS, 0-100) + (0.159 × √patient global assessment [VAS, 0-100]) – (0.253 × √SF-36 – Physical component summary [PRO]) + (0.101 × ln [Swollen joint count [SJC66] + 1]) + (0.048 × ln [Tender joint count [TJC68] + 1]) + (0.23 × ln [Leeds enthesitis count [LEI] + 1]) + (0.377 × ln[Leeds dactylitis count [LDI] + 1]) + (0.102 × ln [CRP (mg/L) + 1)] + 2) × 1.5 *PASDAS score range: 1-10* *Note: PASDAS VAS are based on a 100mm scale*
Disease Activity in Psoriatic Arthritis (DAPSA)[32-34]	Swollen joint count (SJC66) + Tender joint count (TJC68) + Patient global assessment [VAS, 0-10] + Patient pain assessment [VAS, 0-10] + CRP (mg/dL) *DAPSA score range: 0-164* *Note: DAPSA VAS are based on a 10cm scale*
Minimum Disease Activity (MDA)[33,35]	A patient is classified as in MDA when they meet 5 of 7 of the following criteria: • Tender joint count [TJC66] ≤1 • Swollen joint count [SJC68] ≤1 • PASI ≤1 or BSA ≤3 • Patient pain assessment [VAS, 0-100] ≤15 • Patient global assessment [VAS, 0-100] ≤20 • HAQ- DI ≤0.5 • Tender enthesial points ≤1 *Note: MDA VAS are based on a 100mm scale*
Psoriasis Area and Severity Index (PASI)	For each region: head, upper limb, trunk, lower limbs 1. BSA 2. Plaque characteristics: erythema + induration/thickness + scaling 0 = None 1 = Slight 2 = Moderate

Disease activity indicators	Definition/Calculation
	3 = Severe 4 = Very severe 3. Percentage area affected: 0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100% Score calculation: For each region: (sum of plaque scores) × (body region BSA) × (percent of area affected [0-6]) PASI score = sum of results over all 4 body regions. *PASI score range: 0-72*
Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC-EI)[36]	Clinical evaluation of 16 sites: Greater trochanter (R/L) Quadriceps tendon insertion into the patella (R/L) Patellar ligament insertion into the patella and tibial tuberosity (R/L) Achilles tendon insertion (R/L) Plantar fascia insertion (R/L) Medial epicondyles (R/L) Lateral epicondyles (R/L) Supraspinatus insertion (R/L) Tenderness at each site is quantified as: 0= non-tender and 1= tender. *SPARCC-EI score range: 0–16*
Psoriatic Arthritis Impact of Disease 12 Questions (PsAID12)[37]	The PsAID12 calculation is based on Numeric Rating Scale (NRS) questions. Each NRS is assessed as a number between 0 and 10. The range of the final PsAID12 value is 0–10 where higher numbers indicate worse status. (PsAID12.Q1 [pain] NRS value ×3) +(PsAID12.Q 2 [fatigue] NRS value ×2) +(PsAID12.Q 3 [skin] NRS value ×2) +(PsAID12.Q 4 [Work and/or leisure activities] NRS value ×2) +(PsAID12.Q 5 [function] NRS value ×2) +(PsAID12.Q 6 [discomfort] NRS value x2) +(PsAID12.Q 7 [sleep] NRS value ×2)

Disease activity indicators	Definition/Calculation
	+(PsAID12.Q 8 [coping] NRS value ×1)
	+(PsAID12.Q 9 [anxiety] NRS value ×1)
	+(PsAID12.Q 10 [embarrassment] NRS value ×1)
	+(PsAID12.Q 11 [social life] NRS value ×1)
	+(PsAID12.Q 12 [depression] NRS value ×1)
	The total is divided by 20 for the final score.
	PsAID12 score range: 0-10

Abbreviations: BSA= Body Surface Area, CRP= C-reactive protein, DAPSA= Disease Activity in Psoriatic Arthritis, HAQ-DI= Health Assessment Questionnaire - Disability Index, LDI= Leeds Dactylitis Index, LEI= Leeds Enthesitis Index, MDA= minimum disease activity, NRS= Numeric Rating Scale, PASDAS= Psoriatic Arthritis Disease Activity Score, PASI= Psoriasis Area and Severity Index, PRO= patient reported outcome, PsAID12= Psoriatic Arthritis Impact of Disease 12 Questions, SPARCC-EI= Spondyloarthritis Research Consortium of Canada Enthesitis Index, SF-36= Short Form 36, SJC66= swollen joint count (66), TJC= tender joint count (68), VAS= Visual Analogue Scale

9.4. Data Sources

No visits or examinations, laboratory tests, or procedures are mandated as part of this study, data will be collected from patient records and during routine clinical care. Investigators will be requested to perform commonly used PsA disease assessments. Patients will be requested to complete validated PROs at each study visit, which will be completed in paper form in local language .

This is a prospective non-interventional study where patient data will be entered into an electronic case report form (eCRF) located on a secure web-based electronic data entry (EDC) system. The use of a standardized eCRF will ensure that data is captured consistently across sites. All sites will be trained on use of the eCRF, and data entry guidelines will be provided. The eCRF is to be completed based on data that has been collected in the patient file. The PRO completed by patients will be entered into the EDC system by IQVIA.

9.4.1. Physical Assessments

Physician Global Assessment

The physicians' global opinion of the skin and joints recorded on a 0 - 100 mm scale.

Patient Global Assessment

The patients' global opinion of the skin and joints recorded on a 0 - 100 mm scale.[33]

Patient Pain Assessment

Patients will assess the severity of their arthritis pain using a 100 mm VAS by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponds to the

magnitude of their pain. The minimum clinically important difference of pain VAS is considered to be 10 mm.

Swollen Joint Count (SJC66)

The joint assessor will also assess 66 joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable (for artificial joints).[38] Artificial joints will not be assessed.

Tender/Painful Joint Count (TJC68)

Sixty-eight (68) joints will be assessed to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable (for artificial joints).[38] Artificial joints will not be assessed.

Leeds Enthesitis Index (LEI)

Evaluate pain/tenderness on pressure at 6 sites: achilles tendon insertions (right/left), medial femoral condyles (right/left), lateral epicondyles of the humerus (right/left). Tenderness on examination is recorded as either 1= present or 0= absent for each of the 6 sites.[39]

Leeds Dactylitis Index (LDI)

The clinician squeezes the affected fingers with moderate pressure and documents the patient's response: 0= no tenderness, 1= tender, 2= tender and winces, and 3= tender and withdraws.[40]

Body Surface Area (BSA)

The number of a patient's hand areas affected, on the assumption that one "handprint" reflects approximately 1% of BSA.

9.4.2. PROs

Short Form 36 (SF-36)

The SF-36 measures a patient's functional health and well-being based on 36 questions about physical and mental health concepts that are relevant across age, disease, and treatment.

These questions are combined into groupings to form 2 summary measures and 8 scales: the Physical Component Summary and its 4 scales (physical functioning, role-physical, bodily pain, and general health); and the Mental Component Summary and its 4 scales (vitality, social functioning, role-emotional, and mental health). The raw scores are recoded to a 100-point scale using a scoring key, and summary measure scores are calculated. Higher scores indicate a better QoL.

Health Assessment Questionnaire - Disability Index (HAQ-DI)

The HAQ-DI[41] assesses the degree of difficulty a patient has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do". Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status. The form should then be checked by the site staff for completeness.

Psoriatic Arthritis Impact of Disease 12 Questions (PsAID12)

The PsAID12 is a PsA specific questionnaire designed to measure impact of the disease. It is composed of 12 numeric rating scales (ranging 0-10), each assessing a different domain of health (pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, anxiety, embarrassment and/or shame, social participation, depression). The formula to calculate the overall score uses weights on each domain to rebalance the contribution of each domain to the final score (Table 3). The weights were derived from a survey of 474 patients with PsA from 13 countries.[37]

9.4.3. Prognostic Factors

The following PsA prognostic factors will be considered based on information collected at enrollment and may be used to stratify results.

- BMI at enrollment (<18.5, 18.5 to <25, 25 to <30, ≥30).
- Treatment line (tofacitinib as monotherapy or combination therapy with MTX).
- Duration of symptoms of at least 6 weeks prior to enrollment.
- Abnormal (above the normal range) CRP or ESR.
- The following will be derived based on counts of joints affected by arthritis at enrollment, specified by: small joints, medium joints, large joints, hand joints:
  - Arthritis ≥3 joint areas;
  - Arthritis of the hand joints;
  - Symmetric arthritis;
  - Arthritis of only 1 medium-large joint;
  - Arthritis of 2-10 medium-large joints and/or 1-3 small joints;

- Arthritis of 4-10 small joints with or without involvement of large joints;
- Arthritis of >10 joints (with at least one small joint).

The following will be requested from radiological reports at enrollment:

- Rheumatoid nodules;
- Unequivocal radiological erosion;
- Unequivocal bony decalcification localized to the joints of the hands and wrists.

9.5. Study Size

Based on feasibility this non-interventional study will include approximately 200 patients.

For a sample size of 154 evaluable patients (assuming a 23% drop-out rate), a 2-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation will extend 0.063 from the observed proportion for an expected proportion of 0.2.

There are no plans to conduct any hypothesis testing or comparisons between groups therefore no formal sample size calculation has been performed.

9.6. Data Management

A data management plan (DMP) will be created before the start of data collection and will describe all functions, processes, and specifications for data collection, cleaning and validation to ensure that the data are as clean and as accurate as possible when presented for analysis. Data collection and validation procedures will be detailed in appropriate operational documents. The eCRFs will include programmable edit checks to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the DMP. Queries will be generated within the EDC system and followed up for resolution. Confirmation of the data collected is required by the physician's electronic signature.

All study data will be recorded by the study sites in the EDC system International Business Machines Clinical Development (IBM-CD) which fulfills all requirements of 21 Code of Federal Regulations Part 11 and the central server is backed up once a day. Access to the system takes place via a secure website. Access is only given to registered users who log in with a unique username and password. Depending on their function in the study, individual users are assigned defined access rights. Access rights to the EDC system are monitored by authorized contract research organization (CRO) employees.

9.6.1. Case Report Forms (CRFs)

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The Investigator shall ensure that the CRFs are securely stored at the study site in an encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

The Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, will be used to classify (system organ class and preferred term) verbatim terms collected for safety events, medical history, and co-morbidities. The most updated version of MedDRA at the time of conducting the data analysis will be used. All concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version valid at study start.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the Investigator according to local regulations or as specified in the clinical study agreement, whichever is longer. The Investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another Investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Handling of missing data will be described in the SAP, unless otherwise specified in the SAP no imputation will be performed, and if considered necessary sensitivity analysis could be performed and will be described in the SAP. Variables to be used in the analyses will be derived as described in Table 3.

Statistical Analysis Software (SAS®, Version 9.1 or above) will be used for all statistical analyses described.

9.7.1. Analysis Populations

All enrolled set (ENR) will contain all subjects who provide informed consent and met all eligibility criteria to participate in this study.

Full analysis set (FAS) will contain all enrolled patients who have received at least one dose (including partial dose) of study medication.

9.7.2. Effectiveness Analyses

Descriptive statistics will be used to present the results of this study for the endpoints described in Section 9.1.1. Continuous variables will be presented as the number of observations, mean, median, standard deviation, interquartile range, and range. Categorical variables will be presented as number of observations, frequency, and percentage, 2-sided 95% CIs will be included as appropriate. Graphical summaries may also be presented.

Details of any statistical modeling and suitable sub-group analyses, if applicable, will be defined in the SAP.

Proportions will be calculated using all patients with the required measurements as the denominator, and the number of patients achieving the specified endpoint as the numerator, as appropriate.

Changes from baseline will use mixed effects models for repeat measures when appropriate, with timepoint as a fixed effect, and baseline values included as covariates. Additional potential confounding variables will be evaluated and included as covariates when appropriate (eg, age, disease severity at enrollment, prognostic factors in Section 9.4.1).

9.7.3. Safety Analyses

Safety data will be presented in tabular and/or listing format and summarized descriptively, where appropriate. Event count and AE frequency will be reported. Number (% of subjects) with AEs, SAEs, and discontinuations due to an AE will be reported.

9.7.4. Interim Analysis

No interim analysis is planned as part of this study.

9.8. Quality Control

During the site initiation visit, the monitor will provide training on the conduct of the study to the Investigator, co-Investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Site monitoring will be performed by IQVIA to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution. All corrections of entries on the eCRFs must be explained (reason for change) and signed off (electronic signatures).

Corrections of entries are automatically recorded by the system (including date of change, user changing data, old and new value, reason for change).

High data quality standards will be maintained and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for

analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

9.9. Limitations of the Research Methods

Observational studies are used to evaluate the effectiveness and safety of pharmacological treatments in a real-world setting.

Selection bias

Patients who enroll in the study may differ from patients who choose not to enroll, likewise PsA patients who are treated with tofacitinib may differ from PsA patients who are not. The eligibility criteria are not restrictive in order to allow enrollment of all PsA patients indicated for treatment with tofacitinib. A screening log has been included to collect de-identified information on patients who choose not to be enrolled, including their reason for non-enrollment; this will allow for a comparison to determine if the 2 populations are different.

Information bias

At the Investigator level, information bias can be mitigated by careful CRF design, ensuring that all requested data is properly collected. The data collected from medical records reflect real-world medical practice and inherently includes missing data.

At a patient level, misclassification of drug exposure should be considered. Medical records provide detailed information on prescribed medication but may not contain information on the actual use of the medication by the patient. It is also possible that other concomitant medications will not be reported by the patient and will be missing from the database.

Confounding

Stratified analysis and/or adjusted analyses might be used to assess the impact of potential confounding variables. Further details will be given in the SAP. Though efforts have been made to identify and collect potential confounding factors, it is possible that others exist.

Patients selected for study inclusion represent a population who are initiated on tofacitinib as part of routine clinical care. The sample of patients will be obtained from physicians who are willing to participate in the study and there is a possibility that certain types of patients will be selected to be prescribed tofacitinib (selection bias) and join the study and this could potentially have an impact on generalizability of results (if the 'type' is expected to impact the effectiveness). Therefore, study findings may not be generalizable to all PsA patients.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure the protection of patient personal data.

Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in an encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.

The Investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The Investigator must ensure that each study patient or his or her legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The Investigator further must ensure that each study patient or his or her legally acceptable representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the Investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the Investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The Investigator will retain the original of each patient's signed consent document.

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The Investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the Investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer. Due to the observational nature of this study, IRB/IEC approval is not required in Denmark.

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (eg, informed consent form [ICF]) to the responsible IRB/IEC for its review. Patient enrollment will not start at any site before the Client has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of

the date of the meeting at which the favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations.

Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, and ICF, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to Pfizer. All correspondence with the IRB/IEC should be retained in the Investigator file.

Should the study be terminated early for any unanticipated reason, the Investigator will be responsible for informing the IRB/IEC of the early termination.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the guidelines of good pharmacoepidemiology practices (GPP)[42] issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki[43] and its amendments, and any applicable national guidelines.

Prior to the enrollment of any patients in the study, the following documents must be provided by the site to the Client (or their designee):

- Copy of the IRB/IEC approval letter for the protocol and informed consent (all written information provided to the patient must be approved by the IRB/IEC);
- Copy of the IRB/IEC-approved informed consent document to be used;
- Copy of the protocol sign-off page signed by the Investigator;
- Fully executed site agreement.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

SINGLE REFERENCE SAFETY DOCUMENT

The Xeljanz (tofacitinib) prescribing information will serve as the single reference safety document during the course of the study, which will be used by Pfizer Safety to assess any safety events reported to Pfizer Safety by the Investigator during the course of this study.

The single reference safety document should be used by the Investigator for prescribing purposes and guidance.

Patients experiencing events as listed in the Xeljanz (tofacitinib) prescribing information [with particular attention paid to Sections 4 (Contraindications), 5 (Special Warnings) and 6 (Precautions)] should be monitored and if indicated, treatment should be withdrawn according to the provision of the respective prescribing information.

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	•

Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to Xeljanz® (tofacitinib)**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Xeljanz® (tofacitinib) or the time of the patient's informed consent if s/he is being treated with Xeljanz® (tofacitinib) at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days

following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Xeljanz® (tofacitinib), the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to Xeljanz® (tofacitinib), follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Xeljanz® (tofacitinib) caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Xeljanz® (tofacitinib) caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Xeljanz® (tofacitinib) did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases

by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep).
- Administrative admission (e.g., for yearly exam).
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Xeljanz® (tofacitinib) or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Xeljanz® (tofacitinib) (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to Xeljanz® (tofacitinib) prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to drug/vaccine of interest during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Xeljanz® (tofacitinib) this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Xeljanz® (tofacitinib) in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Contact details and the list of all Investigators available upon request.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.