Study Information

Title	An Observational Study of Xeljanz® (tofacitinib citrate) and Biologic Rheumatoid Arthritis Treatments to Characterize their General Treatment Patterns, Effectiveness and Safety in a Real-World Taiwanese Population
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Medicinal Product	Tofacitinib
Research Question and Objectives	The objective of this study is to understand general treatment patterns, effectiveness, and safety of tofacitinib in a non-restricted population of rheumatoid arthritis patients in the real-world setting.
Author	Redacted [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Term
	Definition
CIOMS	Council for International Organizations of Medical Sciences
CRP	C-reactive protein
DAS	disease activity score
DAS28	Disease Activity Score in 28 joints
DMARD	disease-modifying antirheumatic drug
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
HAQ DI	health assessment questionnaire disability index
HCV	hepatitis C virus
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mg	milligram
NA	Not applicable
NIS	non-interventional study
NSAIDs	nonsteroidal anti-inflammatory drugs
PRO	patient reported outcome
PS	performance status
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
SRSD	single reference safety document
TB	tuberculosis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
USA	United States of America

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Redacted	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Standalone document, see Annex 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	16 March 2022	Title Page	Added PASS information	Administrative
		Section 2. Abbreviations	Updated Table	Administrative
		Section 5. Abstract	Made into a Standalone document see Annex 1	Administrative
		Section 6 Milestones	Updated to align with Study Report	Administrative
		Section 9.1 Study Design .Table 1, footnote e	Updated to align with Study Report	Administrative
		Section 9.2.1 Inclusion Criteria	Align with Study Report, moved footnote to bottom of page	Administrative

6. .MILESTONES

Milestone	Planned date
Start of data collection	12 August 2016
End of data collection	31 May 2021
Final study report	25 March 2022

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disorder that mainly affects the diarthrodial joint, often causing pain and deformity in affected persons.[1] It is the most common form of inflammatory arthritis and has a substantial societal effect in terms of cost, disability, and lost productivity.[2] The global estimated prevalence of RA varies between 0.3% and 1% with a prevalence of 0.4% in South-East Asia.[3,4] It is more common in developed countries, and is highly prevalent in women compared to men.[3] While the specific etiology of the disease is unknown, risk factors such as gender, age, carrier of specific human leukocyte antigen alleles, bacterial infection, cigarette smoking, and stress are considered to increase one's likelihood of developing RA.[1]

Given that there is no cure for RA, currently available treatments target prevention of disease progression, reduction of symptomatic ailments and joint deformities, and improvement of quality-of-life. The medications used in the management of RA symptoms include nonsteroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic disease-modifying antirheumatic drugs (DMARDs), and corticosteroids. The choice of therapeutic agent(s) is influenced by the severity of disease, medication risk for a particular patient, and patient preference. The available literature supports early aggressive treatment with DMARDs (methotrexate, sulfasalazine or leflunomide) which are relatively well-tolerated, used alone or in combination with low-dose glucocorticoids, to induce and maintain tight control of disease.[5-12] When treatment goals are not achieved with this treatment approach, a biologic DMARD (bDMARD) as second line are often added. bDMARDs include tumor necrosis factor inhibitors [(TNFi) such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab)], abatacept, tocilizumab and under certain circumstances rituximab.[13]

There are limitations associated with bDMARDs which include the mode of administration (parenteral), high costs, and side-effects as well as the potential for antidrug anti-bodies.[14, 15] Tofacitinib, an orally administered non-biologic and potent, selective inhibitor of the Janus kinase family of kinases with a high degree of selectivity against other kinases in the human genome, can be considered as a good alternative if traditional DMARDs fail. It was approved in Taiwan for patients with moderate to severe RA in December 2013 and nationally reimbursed as of December 2014.

Currently there is limited data describing the characteristics of patients who receive tofacitinib in Taiwan as well as the long-term clinical effectiveness, and safety in the real-word setting. In the context of the treatment of RA patients in Taiwan and the current reimbursement guidelines, it is also important to study clinical outcomes, and patient-reported outcomes (PRO) associated with current treatment practice. Pfizer is therefore conducting a real-world study of Xeljanz® (tofacitinib) and bDMARDs within the context of a registry of tofacitinib users in Taiwan.

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

8. RESEARCH QUESTION AND OBJECTIVES

The main objectives of this multicenter, prospective, observational comparative study in Taiwan are to understand effectiveness, general treatment patterns, and safety of tofacitinib in a non-restricted population of RA patients in the real-world setting.

The primary objectives of this study are to describe and compare the baseline characteristics and effectiveness of the treatment group (ie, newly initiated patients on tofacitinib) and the comparison group [ie, newly initiated patients on commonly used treatments either Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)].

1. Describe the baseline characteristics of RA patients prescribed tofacitinib or TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)] and evaluate whether baseline characteristics of patients treated with tofacitinib are comparable to patients prescribed TNFi within line of therapy.

2. Describe measures of short-term and long-term effectiveness for tofacitinib and TNFi.

    a. Clinical effectiveness after one week of treatment from the incident dose as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) which is a patient-administered questionnaire, and the Clinical Disease Activity Index (CDAI).

    b. Clinical effectiveness over the long term as measured by the HAQ-DI, CDAI, and the Disease Activity Score 28 (DAS28) - Erythrocyte Sedimentation Rate (ESR).

3. Compare the long-term effectiveness of tofacitinib and TNFi if baseline characteristics of patients treated with tofacitinib and TNFi are comparable.

The secondary objectives of this study are to:

1. Describe safety outcomes in patients receiving tofacitinib and TNFi. The safety outcomes of interest [Targeted Adverse Events (TAE)] include cardiovascular events, hepatitis B and C reactivation, tuberculosis (TB), serious infections, herpes zoster, malignancy, and liver enzyme abnormalities.

2. Describe the treatment patterns of RA patients prescribed tofacitinib and TNFi in the study.
3. Describe adherence and persistence to tofacitinib and TNFi in RA patients in the study.
4. Describe clinical outcomes and patient-reported outcomes following mandated reduction of dose/weaning off tofacitinib or TNFi after 24 months per national insurance requirements.

9. RESEARCH METHODS

9.1. Study Design

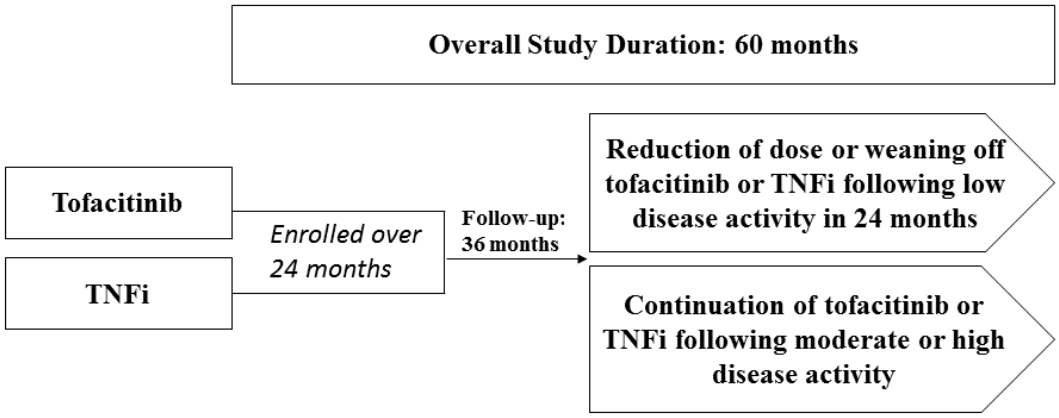
This is a prospective, observational, multicenter, comparative effectiveness study of tofacitinib and TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)] in Taiwanese patients with RA. The treatment group consists of patients newly initiated on tofacitinib for RA as prescribed by the physician in Taiwan. Tofacitinib is labelled for treatment as a 5 mg tablet twice daily and was approved to be used in combination with methotrexate or other non-biologic DMARDs for moderately to severely active RA patients who have had inadequate response or intolerant to methotrexate. The comparison group consists of patients newly prescribed either Enbrel®, Humira®, or Simponi® for RA at a given dose per label instructions and as directed by the physician in Taiwan.

The study will collect data on the short and long-term effectiveness, safety, treatment patterns and adherence for patients who are newly prescribed tofacitinib or a TNFi in routine practice by physicians in Taiwan. As this is an observational study, patients will receive care based on the standard of care for RA patients in Taiwan and per the judgment of the patient's treating physician. No drug will be supplied for this study but patients will receive treatment through standard local practice. The evaluation of study outcomes during follow-up will be at the discretion of the treating physician. The study data collection and assessment schedule is described in Table 1.

Written informed consent will be provided by the patients prior to being enrolled into the study. Patients who meet all the inclusion and exclusion criteria will be followed-up for at least 36 months or death, withdrawal from study, or loss of follow-up, whichever occurs first. Reimbursement guidelines in Taiwan dictate that patients be tapered from the dose of tofacitinib or TNFi when achieving low disease activity after 24 months of treatment and discontinued from tofacitinib or TNFi in the following 12 months. More detail is provided in Section 9.4.2.2.

The patients will continue to be followed-up in the study even if they discontinue treatment at any point during the study duration. This will be described in more detail in the Statistical Analysis Plan (SAP). Figure 1 shows a description of the study design.

Figure 1. Study Design



*Dose changes not mandated by the NHI at 24 months can occur at any time during follow-up.

Data will be collected at baseline and at six-month intervals (24 weeks) thereafter reflecting treatment outcomes over the previous six months, even if patient switches therapy according to routine clinical practice. Data from visits that occur prior to a six-month data collection point will be documented in the medical charts. Baseline data will include patient sociodemographic, clinical and treatment characteristics, which have been summarized in more detail in Section 9.3 and Section 9.4. During follow-up, data will be collected on clinical and treatment-related outcomes, and PRO, using physician and patient questionnaires and patient medical records which will be used to evaluate effectiveness and safety outcomes. The measurements of effectiveness and safety outcomes have been described in more detail in Section 9.4. Safety outcomes include Adverse Events (AEs), Serious Adverse Events (SAEs), and TAEs. TAEs are AEs of special interest for tofacitinib and TNFi, and they include cardiovascular events, hepatitis B and C reactivation, TB, serious infections (defined in the study as those requiring hospitalization or parenteral antibiotics), herpes zoster, and malignancy where additional information on these events will be captured.

Visits occurring outside of the six-month (24 weeks) schedule will include a one-week visit to assess short-term clinical effectiveness of tofacitinib and TNFi, and one-month (four- week) and three-month (12-week) visits to assess the clinical effectiveness of tofacitinib and TNFi following a mandatory dose reduction in patients with low disease activity in compliance with the National Health Insurance (NHI) reimbursement guidelines. According to Taiwan NHI reimbursement guidelines, a reduction in dose is mandated when a patient has been treated with tofacitinib or a TNFi for 24 months and has low disease activity measured using the DAS28-ESR as (1) DAS28 ≤3.2 and (2) ESR≤25MM/h and C-reactive Protein (CRP) ≤1mg/dL.[16] However, the mandatory dose reduction due to low disease activity can occur at any time during the study. At the one-week visit, the HAQ-DI which is a patient-administered questionnaire, and CDAI which involves a combination of physician assessments, and patient and physician administered global assessment of symptoms, will be

used to assess short-term effectiveness of the treatment and comparison groups. The HAQ-DI and CDAI are described in more detail in Section 9.4.1. Obtaining the assessments one week after treatment will also establish a post-treatment baseline for long-term clinical effectiveness measurements. The four-week and 12-week visits after mandatory dose reduction will include the assessments made at the regular six-month (24 weeks) visits.

Enrollment of patients at the sites will continue systematically until approximately 250 incident users of tofacitinib and 250 incident users of TNFi are enrolled or 24 months have passed from the date the first patient enrolls, whichever occurs first. In order to ensure the enrollment of patients is uniform in both the treatment and comparator arms, consecutive users of Enbrel®, Humira®, or Simponi® will be enrolled. Enrollment targets may be implemented depending on pace of enrollment. The enrollment of patients at the sites is described in more detail in Section 9.2.

Table 1. Study Data Collection and Assessment Schedule

Data Collection Schedule:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Visit after Dose Down (Per NHI requirements)[a]**	
Title	Enrollment/Baseline	Wk1	Wk24	Wk48	Wk72	Wk96	Wk120	Wk144	Wk168	Wk192	Wk216	Wk240	Wk4	Wk12
Visit Window (in days)[b]	0	+3	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographic Characteristics	X													
Medical History	X													
Smoking History	X													
Height	X													
Weight	X													
AEs/TAE/SAEs[c]	----------X----------													
Previous RA Treatment	X													
Concomitant Medication(s)	----------X----------													
RA Treatment during Study[d,e,f]	----------X----------													
Laboratory Data[g]	X		X	X	X	X	X	X	X	X	X	X	X	X
CDAI[h,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAS28-ESR[h,j]	X		X	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-RA[h]	X		X	X	X	X	X	X	X	X	X	X	X	X

Data Collection Schedule:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Visit after Dose Down (Per NHI requirements)[a]**	
Title	Enrollment/Baseline	Wk1	Wk24	Wk48	Wk72	Wk96	Wk120	Wk144	Wk168	Wk192	Wk216	Wk240	Wk4	Wk12
Visit Window (in days)[b]	0	+3	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28

a. Visits will occur 4 weeks and 12 weeks after mandatory dose reduction due to low disease activity.

b. If patient could not be followed within the window period due to personal/special situation, data of the closest visiting date for that visit could be collected.

c. AEs/TAE/SAEs will be collected throughout the study starting from the incident dose of the medication until 28 days following the last administration of a drug under study.

d. Patients discontinuing from the initial study drug treatment will be followed-up through the end of the study.

e. Patients could have dose modifications at any time during the study. Reasons for dose change/interruption were collected as AE, per NHI requirements, lack of efficacy, and other.

f. Patients with low disease activity will have mandatory dose reductions any time during the study.

g. Laboratory data includes but is not limited to blood collection for ESR, CRP, AST, ALT, Total Bilirubin, Serum Creatinine, Lipid profile, CBC/Differential count. Collect laboratory data from the closest visit to data collection.

h. For patients changing treatment during follow-up, ideally baseline information will be collected assuming they are conducted as routine practice.

i. The CDAI consists of patient global assessment, physician global assessment, 28-swollen joint count and 28-tender joint count.

j. The DAS28-ESR consists of patient global assessment, 28-swollen joint count, 28-tender joint count, and the Erythrocyte Sedimentation Rate (ESR).

Abbreviations: AE: Adverse Event; CDAI: Clinical Disease Activity Index; DAS28-ESR: Disease Activity Score 28 - Erythrocyte Sedimentation Rate; HAQ-DI: Health Assessment Questionnaire Disability Index; RA: Rheumatoid Arthritis; SAE: Serious Adverse Event; TAE: Targeted Adverse Event; WPAI-RA: Work Productivity and Activity Impairment in RA; CRP: C-Reactive Protein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CBC: Complete Blood Count.

9.2. Setting

Patients will be recruited from approximately six sites in Taiwan with a specialty in rheumatology treatment. Participating study sites are required to enroll consecutive eligible patients who are newly initiating tofacitinib based on physician prescribing into this study. For Enbrel®, Humira®, or Simponi® initiators, the invitation to join will be extended systematically, eg, every consecutive patient at such frequency as to approximate the rate of enrollment for tofacitinib patients. If an eligible patient was approached and does not participate in the study, the reason for nonparticipation will be documented in the enrollment log. Enrollment caps will be placed on the sites to ensure that enrollment is uniform across sites and the two arms. Given that tofacitinib is a newly approved medication with slower anticipated enrollment rates compared to TNFi, it is important to monitor enrollment rates throughout the enrollment period to ensure that a 1:1 ratio of tofacitinib to TNFi is achieved. If for example the ratio of tofacitinib to TNFi patients is 1:3 at Month 9 (36 weeks), then a temporary cap will be placed on the enrollment into the TNFi arm at the site until the 1:1 ratio is achieved. There are no initial restrictions however on the enrollment of specific numbers of patients on a given drug within the comparison group (ie, no ratio has been defined for patients on Enbrel®, Humira®, or Simponi®). These measures are to help minimize timing as a potential bias.

Patients who are newly initiating tofacitinib, Enbrel®, Humira®, or Simponi® for RA under routine clinical practice are eligible to participate in this study and will be enrolled at the time of presentation of a routine clinic visit. Aside from the one-week visit for the completion of HAQ-DI and CDAI, and the one-month (4-week) and three month (12-week) visits following mandatory dose reduction, no other clinic visits are required as part of participation in this study. All clinical assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record. PROs will be completed by patients on paper at the time of a routine clinic visit and responses will be entered into the Electronic Data Capture by the site. For patients missing the one-week visit, data will be reported as missing. Eligibility in the study has been summarized below in Section 9.2.1 and Section 8.2.2. Eligible patients in the treatment group must be naïve to tofacitinib, and in the comparison group to Enbrel®, Humira®, or Simponi® at the time of enrollment but need not be naïve to other RA treatments. They must not currently be enrolled in any other clinical trial of an investigational product. Prevalent users of these products will not be eligible for enrollment because they may be more or less likely to experience AEs, may fail to report AEs that occurred before study enrollment, or may have discontinued treatment due to an AE. Additionally, patients participating in other clinical studies are excluded due to protocol driven activities outside of normal practice and potential confounding in safety assessments. Patients in the treatment group (tofacitinib) will be evaluated separately from patients in the comparison group (TNFi).

9.2.1. Inclusion Criteria

To be eligible to participate in this study, patients must meet all of the following inclusion criteria at the time of enrollment:

1. Adults over 20 years of age[1]
2. The patient had a clinical diagnosis of RA.
3. The patient is newly prescribed tofacitinib or a TNFi (ie, Enbrel®, Humira® or Simponi®) for RA at the time of enrollment. Patients switching from one TNFi to another or from one TNFi to tofacitinib will be included as long as they are incident users of a given TNFi or of tofacitinib.
4. The patient must have 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.
5. The patient is able to read, write and reply the study questionnaires.

9.2.2. Exclusion Criteria

1. The patient is enrolled in any other clinical trial of an investigational product.

9.3. Variables

Table 2 below shows the list of exposures, outcomes, and other variables to be collected including risk factors, comorbidities and concomitant medications. Detailed definitions of the variables are described in Section 9.7.

[1] As patients between 18 and 20 will require to co-sign the consent from along with their legal guardian according to the local law.

Table 2. List of Variables and Definitions (non-exhaustive)

Variable	Role	Data Source(s)[b]	Operational Definition
Xeljanz (tofacitinib)	Exposure	Medical chart	Newly prescribed
bDMARD	Exposure	Medical chart	Newly prescribed
cDMARD	Exposure	Medical chart	Newly prescribed/Current use
Previous drug/smoking history	Exposure	Medical chart	Completed by patient
Concomitant Therapies (NSAID, steroids, others)	Exposure	Medical chart	Current use
HBV/HCV reactivation	Outcome	Medical chart and TAE Form	Reported by Physician
Total serious infections[a]	Outcome	Medical chart and TAE Form	Reported by Physician
Pneumonia	Outcome	Medical chart and TAE Form	Reported by Physician
Septicemia	Outcome	Medical chart and TAE Form	Reported by Physician
Bone/Joint infection	Outcome	Medical chart and TAE Form	Reported by Physician
Cellulitis	Outcome	Medical chart and TAE Form	Reported by Physician
Diverticulitis	Outcome	Medical chart and TAE Form	Reported by Physician
Bronchitis	Outcome	Medical chart and TAE Form	Reported by Physician
Gastroenteritis	Outcome	Medical chart and TAE Form	Reported by Physician
Other serious infection	Outcome	Medical chart and TAE Form	Reported by Physician
Opportunistic infection	Outcome	Medical chart and TAE Form	Reported by Physician
Herpes Zoster infection (serious and non-serious)	Outcome	Medical chart and TAE Form	Reported by Physician
TB	Outcome	Medical chart and TAE Form	Reported by Physician
Total Nonserious infection	Outcome	Medical chart	Reported by Physician
MACE[c]	Outcome	Medical chart and TAE Form	Reported by Physician
GI perforation	Outcome	Medical chart and TAE Form	Reported by Physician
Total malignant events	Outcome	Medical chart and TAE Form	Reported by Physician
All Malignancies excluding NMSC	Outcome	Medical chart and TAE Form	Reported by Physician
Lymphoma	Outcome	Medical chart and TAE Form	Reported by Physician
Lung cancer	Outcome	Medical chart and TAE Form	Reported by Physician
Breast cancer	Outcome	Medical chart and TAE Form	Reported by Physician
Skin cancers NMSC	Outcome	Medical chart and TAE Form	Reported by Physician
Melanoma	Outcome	Medical chart and TAE Form	Reported by Physician

Variable	Role	Data Source(s)[b]	Operational Definition
Other cancer	Outcome	Medical chart and TAE Form	Reported by Physician
Death	Outcome	Medical chart and TAE and Exit Forms	Reported by Physician
Pregnancy	Outcome	Medical chart	Reported by Patient
Years since diagnosis	Baseline Characteristic	Medical chart	Reported by Physician
Age	Baseline Characteristic	Medical chart	Reported by Physician
Sex	Baseline Characteristic	Medical chart	Reported by Physician
Body Weight	Baseline characteristic	Medical chart	Reported by Physician
Body Height	Baseline characteristic	Medical chart	Reported by Physician
History of Hyperlipidemia	Baseline characteristic	Medical chart	Reported by Physician
History of Hypertension	Baseline characteristic	Medical chart	Reported by Physician
History of Diabetes Mellitus	Baseline characteristic	Medical chart	Reported by Physician
History of HBV/HCV	Baseline Characteristic	Medical chart	Reported by Physician
History of Herpes Zoster vaccination/varicella exposure	Baseline characteristic	Medical chart	Reported by Physician
History of Herpes Zoster	Baseline Characteristic	Medical chart	Reported by Patient
History of Malignancy	Baseline Characteristic	Medical chart	Reported by Physician
History of TB	Baseline Characteristic	Medical chart	Reported by Physician
History of diverticulitis	Baseline Characteristic	Medical chart	Reported by Physician
HAQ-DI	Baseline Characteristic/Outcome	Patient Questionnaire	Completed by Patient
CDAI	Baseline Characteristic/Outcome	Physician Questionnaire and Medical chart	Calculated variable
DAS28-ESR	Baseline Characteristic/Outcome	Medical chart	Calculated variable
Tender Joint Count	Baseline Characteristic/Outcome	Physician Questionnaire	Reported by Physician
Swollen Joint Count	Baseline Characteristic/Outcome	Physician Questionnaire	Reported by Physician
ESR (or CRP if collected)	Baseline Characteristic/Outcome	Lab Form	Lab data
AST/ALT/bilirubin	Baseline Characteristic/Outcome	Lab Form	Lab data
Serum Creatinine	Baseline Characteristic/Outcome	Lab Form	Lab data
Lipid profile	Baseline Characteristic/Outcome	Lab Form	Lab data
CBC/Differential Count	Baseline Characteristic/Outcome	Lab Form	Lab data
WPAI-RA	Baseline/ Outcome	Patient Questionnaire	Completed by Patient

a. Serious infections are defined as infections requiring hospitalization or use of parenteral antibiotics;
b. The data sources can vary by site and availability of information.

c. Major Adverse Cardiovascular Event including: Nonfatal events of myocardial infarction (MI), Stroke and Transient Ischemic Attack (TIA) in addition to Cardiovascular-related deaths from MI, Congestive Heart Failure, arrhythmia, sudden cardiac death, Pulmonary Embolism, stroke/cerebrovascular accident, and other CV-related deaths

Abbreviations: bDMARD, biologic disease modifying antirheumatic drug; CDAI, clinical disease activity index; ESR, erythrocyte sedimentation rate; cDMARD, conventional disease modifying antirheumatic drug GI, gastrointestinal; HAQ DI, health assessment questionnaire disability index; HBV: Hepatitis B virus; HCV: Hepatitis C virus MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; NSAIDS, non- steroidal anti-inflammatory drugs; TAE: Targeted Adverse Event; TB, tuberculosis; WPAI-RA, work productivity and activity impairment – rheumatoid arthritis.

9.4. Data Sources

Data will be collected from baseline physician and patient questionnaires completed at enrollment and during follow-up at approximately six-month (24-week) intervals. Questionnaires will not contain personal identifiers. In the event of a switch to a new therapy during follow-up, baseline questionnaires will be captured.

Clinical effectiveness will be measured using the HAQ-DI, CDAI, and the DAS28-ESR at baseline and every six months. Additionally, the HAQ-DI and CDAI scores will be collected at one-week since the initiation of treatment. Additional clinical effectiveness assessment will be conducted to determine the impact of mandatory dose reduction or treatment discontinuation on the patient. This will include an opportunity to collect clinical effectiveness and HAQ-DI questionnaires results one month (four-week) and three months (12-week) after the mandatory dose reduction or discontinuation event and then continuing at the standard six-month intervals.

AEs will be collected and any report of a TAE (events of special interest will trigger the completion of a more detailed TAE form by the physician (as described in Table 2). When physician questionnaires indicate the occurrence of a TAE, this will be flagged and it will trigger the completion of TAE questionnaires. More information regarding the reporting of AEs is described in Section 11.

The Work Productivity and Activity Impairment-rheumatoid arthritis (WPAI-RA) questionnaire will be used to assess work productivity, activity impairment, presenteeism and absenteeism at work during study follow-up.

Prescriptions will be used to calculate adherence and persistence to both the newly initiated treatment and comparison drugs during follow-up. Details on the calculation of adherence and persistence are provided in Section 9.7.2.

9.4.1. Patient-Reported Outcome (PRO) Measures

9.4.1.1. The Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI is a commonly used self-assessment instrument used in rheumatoid arthritis to measure functional disability in patients.[17] This validated tool is a generic instrument that contains questions related to eight functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The responses range from a scale of 0 (no functional disability) to three (severe functional disability).

9.4.1.2. Work Productivity and Activity Index-Rheumatoid Arthritis (WPAI-RA)

The WPAI-RA, a self-administered tool to measure work productivity, was validated in patients with RA.[18] It consists of six questions on work productivity and activity impairment over the previous seven days, and four main outcomes can be generated from the six questions: work productivity, activity impairment, absenteeism and presenteeism.

9.4.2. Physician-Reported Measures

9.4.2.1. Clinical Disease Activity Index (CDAI)

The CDAI is a composite measure of disease activity in RA patients which consists of patient global assessment, physician global assessment, 28-swollen joint count and 28-tender joint count with some minimum input provided by patients.[19] CDAI scores less than 2.8 are targeted for remission according to the American College of Rheumatology (ACR).[20]

9.4.2.2. Disease Activity Score 28 (DAS28-ESR)

The DAS28-ESR is a composite measure of disease activity in RA patients that consists of patient global assessment, 28-swollen joint count, 28-tender joint count, and the Erythrocyte Sedimentation Rate (ESR).[19] DAS28-ESR scores less than 2.6 are targeted for remission according to the ACR.

9.5. Study Size

To establish the registry of patients for this prospective study, patients will be recruited from approximately six sites with a specialty in rheumatology treatment in Taiwan. Approximately 250 patients initiated on tofacitinib and 250 patients initiated on TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)] will be enrolled into the study. Patients will be enrolled over the course of 24 months and followed for at least 36 months after enrollment.

9.6. Data Management

Data collection methods and tools are fully described in Section 9.2, Section 8.3, and Section 8.4.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a detailed SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol. Effectiveness and patient-reported outcomes will be described for tofacitinib patients and for Enbrel®, Humira®, or Simponi® separately and combined. The visit intervals will be every six months unless indicated.

Statistical analysis and generation of all tables, listings and figures will be performed by using SAS® (SAS Institute, North Carolina), version 9.2 or higher.

The Full Analysis Set (FAS) will be comprised of all enrolled patients providing informed consent in writing to participate in the study, where required by local regulation. If a patient withdraws consent, the patient's data collected before the consent withdrawal will remain in the dataset. All analyses will be performed on the FAS unless otherwise specified in the SAP.

Unless otherwise specified in the SAP, missing data will not be imputed and data will be analyzed and presented as they are recorded in the database. If considered necessary, sensitivity analysis could be performed as stated in the SAP thorough Maximum Likelihood approach to missing data.

9.7.1. Primary Analysis

Baseline characteristics will be summarized for RA patients separately by drug type and line of therapy as appropriate based on available sample size. Variables collected at baseline will include patient sociodemographic, clinical, and treatment characteristics. Continuous variables will be summarized as mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized as proportions with 95% confidence intervals. P-values will be used to compare baseline characteristics of tofacitinib with TNFi.

The measure of effectiveness used after one week of treatment from the incident dose is the HAQ-DI. CDAI scores will also be collected. The prevalence of disability using the HAQ-DI will be summarized as the proportion of patients with an increase in the score from baseline to the one-week visit and at subsequent follow-up visits. The cutoff value for the HAQ-DI score will be further described in the SAP. Effectiveness will be measured over a longer period of time by using patient-reported HAQ-DI, CDAI, DAS28-ESR, and WPAI-RA. The CDAI is a composite measure of disease activity and will be summarized as the proportion of patients with scores <2.8, ie, with remission at a given visit. The DAS28-ESR will summarized as the proportion of patients with scores <2.6, ie, with remission at a given visit. Additionally, descriptive comparisons will be made at six months and 12 months.

The effectiveness of tofacitinib will be descriptively compared to TNFi by using mixed logistic regression models with dichotomous outcome variables for HAQ-DI, CDAI and DAS-ESR. Three separate longitudinal models will be built for each outcome variable, and will each include a dichotomous variable for treatment exposure, adjusted for confounders

(baseline sociodemographic, clinical and treatment characteristics). Given the non-random assignment of treatment in this observational study setting, propensity scores (PS) may be used to adjust for confounding by indication. The PS will be defined as the probability of being exposed to tofacitinib conditioning on factors impacting the prescription of tofacitinib (baseline sociodemographic, clinical and treatment characteristics). The PS will either be included in the model described above as a covariate or a matching of the PS between the two exposure groups will be performed to balance the baseline covariates between the two groups.

The mean and standard deviation of WPAI-RA scores will be summarized at a given time point for each patient.

9.7.2. Secondary Analysis

AEs, TAEs and SAEs will be recorded at each occurrence and summarized as the proportion of patients with each safety event at a given point in time and descriptive in nature.

Treatment patterns will be captured as the proportion of patients using a given treatment over a 12-month period including switching. Dose changes will be summarized as appropriate for each treatment at every study visit.

Adherence to the treatment and comparison drugs will be calculated from prescriptions over a 12-month period using the proportion of days covered (PDC) method. This 12-month time frame accounts for gaps in treatment and a relatively longer time period also accounts for the administration of TNFi not being as frequent as tofacitinib. Adherence will be calculated for both treatment and comparison groups using information obtained from prescriptions including medication name, dosage, unit, route, refill date and duration. Adherence values will be calculated at the individual level and a 12-month period will be defined as the time between 01 January 1 and 31 December 31 of a given year. Details regarding the computation of PDC will be provided in the SAP.[22,23] Persistence will be calculated as a continuous measure from prescriptions over the follow-up duration as total number of days between the first refill date and the last refill date (plus the days' supply of the last refill).[21,23] Persistence will also be calculated as the proportion of patients who remain on therapy following 36 to 60 months of treatment.

Clinical and patient-reported outcomes will be summarized following mandated reduction of dose or weaning off tofacitinib or TNFi in patients with low disease activity after 24 months per NHI requirements. The clinical and patient-reported outcomes of interest include effectiveness measured by using the HAQ-DI, CDAI, DAS28-ESR, and WPAI-RA, and they will be summarized as described in Section 9.7.1.

Safety and effectiveness analysis will be performed in particular subgroups of interest such as Hepatitis patients, and other clinically relevant populations.

9.8. Quality Control

Site training regarding data collection is important to ensure that the staff collects the data in an organized and complete manner. Well-designed questionnaires which are easy to use with a clear definition of data elements will help to minimize errors. Reducing the amount of data elements by prioritizing on data necessary to achieve study objectives will decrease burden and improve the focus of the data collected. Given that this is a non-interventional study, the data elements must be aligned to information collected as part of routine care. Edit checks must be performed and ongoing data review must be conducted. Although it is optimal to prevent missing data altogether, strategies for handling missing data will be used at the data analysis stage.

9.9. Limitations of the Research Methods

Given that this study is comparing effectiveness for patients on different treatments, patient characteristics directly related to the treatment are likely to influence physician prescribing behaviors. As a result there will be confounding by indication when comparing effectiveness outcomes between the two treatment groups. PS will be used to control for this bias to the extent possible.

Other possible sources of bias may be linked to patient selection and recall error due to patient self-report. Potential selection bias arising from the lack of complete enrollment of potential eligible patients will be reduced by maintaining screening logs at sites. A relatively small sample size of 250 patients will be used for the treatment and comparison groups each, given that tofacitinib is a new drug and will require a longer time for enrollment. The measurement error associated with self-report of treatment outcomes and disease severity will be addressed by using shorter recall periods.

9.10. Other Aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study and any changes made during the course of the study must be prospectively approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. 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 form.

10.2. 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 subject outcome, if possible. The investigator should 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.

10.3. 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 in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

Table 3 below summarizes the requirements for recording safety events on the medical charts and AE/TAE forms 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) SAEs; (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy (EDP), exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the Section 10.3.

Table 3. Types of Adverse Events

Safety Event	**Recorded on the Medical Charts and AE/TAE Forms**	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to the drug under study, including EDP, 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)

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 (see Section 10.3.2 below).

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 the drug under study**. 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 Table 3 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 physician questionnaire. 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.

11.1. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of or at the time of the patient's informed consent if s/he is already exposed to *either* Xeljanz® (tofacitinib), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) 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 Table 3 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 (eg, 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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab), the SAE also must be reported to Pfizer Safety.

11.2. 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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab), 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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Xeljanz® (tofacitinib), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) 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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) did not cause the event, this should be clearly documented on the physician questionnaire and the NIS AEM Report Form.

11.3. Definitions of Safety Events

11.3.1. 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 symptoms and signs;
- 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;
- EDP;
- 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.

11.3.2. Serious Adverse Events (SAE)

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 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 (eg, 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 (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, 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 (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

11.3.3. Scenarios Necessitating Reporting to Pfizer Safety Within 24 Hours

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

Exposure during pregnancy (EDP)

An EDP occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) Xeljanz® (tofacitinib), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Xeljanz® (tofacitinib), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) (maternal exposure).

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

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

As a general rule, prospective and retrospective EDP reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) 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), Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) in a pregnant woman (eg, 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 (eg, 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 a SAE (eg, 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 one month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after one 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 EDP may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, 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.

<u>Exposure during breastfeeding</u>

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 (eg, 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 (eg, 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 (eg, 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 (eg, 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.

11.4. Single Reference Safety Document

The local Product Label will serve as the single reference safety document (SRSD) 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 SRSD should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the 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 NIS protocol that the investigator becomes aware of.

13. REFERENCES

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001; 358(9285):903-11.

2. Sullivan PW, Ghushchyan V, Huang XY, et al. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. *J Rheumatol*. 2010; 37(3):544-9.

3. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001; 27(2):269-81.

4. Rudan I, Sidhu S, Papana A, Meng S, Xin–Wei Y, Wang W. Global Health Epidemiology Reference Group (GHERG). (n.d.). Prevalence of rheumatoid arthritis in low– and middle–income countries: A systematic review and analysis. *Journal of Global Health*, *5*(1), 010409.

5. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. 2010;69(4):638-43.

6. Goekoop-ruiterman YP, De vries-bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2007;146(6):406-15.

7. Puolakka K, Kautiainen H, Möttönen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis Rheum*. 2004;50(1):55-62.

8. Goekoop-ruiterman YP, De vries-bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52(11):3381-90.

9. Möttönen T, Hannonen P, Leirisalo-repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet*. 1999;353(9164):1568-73.

10. Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum*. 2009;60(5):1222-31.

11. Verstappen SM, Jacobs JW, Van der veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis*. 2007;66(11):1443-9.

12. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet*. 2004;364(9430):263-9.

13. Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum*. 2000;43(1):22-9.

14. Lundquist LM, Cole SW, et al. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. *World J Orthop*. 2014;5(4):504–511.

15. Benucci M, Li Gobbi F, Meacci F, et al. Antidrug antibodies against TNF-blocking agents: correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. *Biologics : Targets & Therapy*. 2015; 9: 7–12.

16. Xeljanz Film-Coated Tablets. Center for Drug Evaluation. Available at: http://www.nhi.gov.tw/Resource/webdata/26686_1_Xeljanz%20Film-Coated%20Tablets%E8%A9%95%E4%BC%B0%E5%A0%B1%E5%91%8A.pdf. Accessed: November 2015. (Article in Chinese).

17. Krishnan E, Sokka T, Häkkinen A, et al. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. *Arthritis Rheum*. 2004;50(3):953-960.

18. Zhang W, Bansback N, Boonen A, et al. Validity of the work productivity and activity impairment questionnaire-general health version in patients with rheumatoid arthritis. *Arthritis Research and Therapy.* 2010; 12(5):s R177.

19. Salaffi F, Cimmino MA, Leardini G, et al. Disease activity assessment of rheumatoid arthritis in daily practice: validity, internal consistency, reliability and congruency of the Disease Activity Score including 28 joints (DAS28) compared with the Clinical Disease Activity Index (CDAI). *Clin Exp Rheumatol*. 2009;*27*(4):552-9.

20. van der Helm-van Mil AH, Breedveld FC, Huizinga TW. Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res Ther*. 2006;8:216–22.

21. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997; 50(1): 105-116.

22. Nau DP. Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence. Available at: http://pqaalliance.org/resources/adherence.asp Accessed: January 2016.

23. Leslie RS. Calculating Medication Compliance, Adherence, and Persistence in Administrative Pharmacy Claims Databases. Available at: http://www.wuss.org/proceedings08/08WUSS%20Proceedings/papers/anl/anl09.pdf. Accessed: November 2015.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	ID4435 / HAQ-DI_AU1.0-chi-TW	05 May 08	The Health Assessment Questionnaire – Disability Index (HAQ-DI) in Chinese
2	V2.0	NA	Work Productivity and Activity Impairment – Rheumatoid Arthritis (WPAI-RA) in Chinese
3	Section 4	16 March 2022	An Observational Study of Xeljanz® (tofacitinib citrate) and Biologic Rheumatoid Arthritis Treatments to Characterize their General Treatment Patterns, Effectiveness and Safety in a Real-World Taiwanese Population.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not Applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

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