Study information

Title	Canadian Non-Interventional Study of Xeljanz in Rheumatoid Arthritis
Protocol number	A3921280
Protocol version identifier	1.1
Date of last version of protocol	N/A
EU Post Authorisation Safety Study (PAS) register number	EU PAS Registration pending
Active substance	Tofacitinib citrate ATC code: L04AA29
Medicinal product	Xeljanz
Research question and objectives	The study will describe the baseline, characteristics of Canadian RA patients initiating tofacitinib in clinical practice and subsequently assessing disease activity, patient reported outcomes, and persistence of response.
Author	John Woolcott, PhD, Director Outcomes and Evidence, Inflammation and Immunology

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ACR	American College of Rheumatology
ANA	Antinuclear antibody
CDAI	Clinical Disease Activity Index
CRA	Canadian Rheumatology Association
CRF	Case Report Form
CRP	C-Reactive Protein
DAS-28	28-Joint Disease Activity Score
DBP	Diastolic Blood Pressure
DMARD	Disease Modifying Antirheumatic Drug
EDC	Electronic Data Capture
EQ-5D	EuroQol-5 Dimension
ESR	Erythrocyte Sedimentation Rate
FACTIT	Fatigue Questionnaire
FDA	U.S. Food and Drug Administration
HAD-DI	Health Assessment Questionnaire Disability Index
HCRU	Health Care Resource Utilization
HZ	Herpes Zoster
HCV	Hepatitis C
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDA	Low Disease Activity
MDGA	Physician Global Assessment of Disease Activity
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
PACES	Post Approval Clinical Epidemiology Studies
PRO	Patient-Reported Outcome
PtGA	Patient Global Assessment of Disease Activity
QA	Quality Assurance
QoL	Quality of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RAPID-3	Routine assessment of patient index data
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SJC	Swollen Joint Count

Abbreviation	Definition
SOP	Standard Operation Procedures
TEAE	Treatment-Emergent Adverse Event
TB	Tuberculosis
TJC	Tender Joint Count
VAS	Visual Analogue Scale
WPAI:RA	Work Productivity and Activity Impairment Questionnaire

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Corina Galos, MD	Medical Advisor	Pfizer Canada Inc	17300 Trans Canada, Kirkland, Qc, H9J 2M5
John Woolcott, PhD	Director Outcomes and Evidence	Pfizer Inc	500 Arcola Drive, Collegeville, PA 19426
Claire Bombardier, MD	Professor	University of Toronto	University Health Network, 200 Elizabeth St. Toronto, Ontario M5G2C4
Boulos Haraoui, MD	Professor	University of Montreal	Institut de Rhumatologie de Montreal, 15512 rue Ontario Est, Montreal, QC H2L 1S6

3. ABSTRACT

<table>
<tr><td colspan="6">Study title:</td></tr>
<tr><td>Protocol Number</td><td>A3921280</td><td>Phase</td><td>4</td><td>Type</td><td>Observational</td></tr>
<tr><td>Condition/Disease</td><td colspan="5">People with Rheumatoid Arthritis</td></tr>
<tr><td>Number of subjects</td><td colspan="2">800</td><td colspan="2">Permanence of subjects in the study</td><td>36 months</td></tr>
<tr><td>Participant countries (number of sites)</td><td colspan="2">Canada (50 proposed sites)</td><td colspan="2">Duration of study</td><td>54 Months</td></tr>
<tr><td colspan="6">Rational

Biological therapies are drugs that emerged almost a decade ago for preventing or reducing the swelling caused by Rheumatoid Arthritis (RA) after failure from a conventional drug such as methotrexate.

Furthermore, there are also chemically synthesized molecules produced from chemical precursors for the treatment of arthritis; tofacitinib is a chemically synthesized drug targeted to block the pathway of an enzyme called Janus kinase (JAK), involved in body’s immune response, and fighting swelling from inside the cell.

Although there are several studies for the assessment of efficacy (including patient reported outcomes) and safety of tofacitinib compared with placebo or methotrexate in the treatment of RA, there is limited information on its use in current practice in Canada. Specific questions still exist around the patients treated with tofacitinib, the clinical effectiveness of tofacitinib, and the persistence of tofacitinib. Studies focusing on these areas using real world data without interventions, are of great importance for payers, physicians, and patients in Canada.</td></tr>
<tr><td colspan="6">Objectives
Primary objectives:
• To describe the profile of RA patients initiating treatment with tofacitinib in the Canadian real – world/clinical setting.
• To describe the clinical effectiveness of tofacitinib over time in patients with moderate to severe RA in the real-world/clinical setting.
Secondary objectives:
In patients with moderate to severe RA that are initiated on treatment with tofacitinib to:
• Describe treatment patterns and treatment trajectory.
• Describe adherence to treatment and its association with clinical effectiveness.
• Identify determinants of therapeutic response.
• Describe durability of response, persistence of treatment and reasons for discontinuation.
• Describe the change in patient-reported pain, fatigue, quality of life and health care resource utilization.
• Describe the incidence of adverse events (including serious adverse events) and AEs of special interest for tofacitinib* (Cardiovascular events/MACE, opportunistic infections (including tuberculosis), malignancy, serious infections (ie, infections requiring hospitalization), and herpes zoster).</td></tr>
<tr><td colspan="6">Study design
This will be an observational (non – interventional), multi-centre study using a prospective cohort design. Patients with moderate to severe RA that are newly treated with tofacitinib as per the decision of their physician, in accordance with the Canadian label.</td></tr>
</table>

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Adult patients, at least 18 years of age or older at the time of recruitment.
- Diagnosis with RA as per the revised 1987 ACR or 2010 ACR/EULAR criteria.
- Patients for whom the treating physician has made the decision to commence tofacitinib treatment in accordance with the Canadian Product Monograph.
- Initiation of treatment with tofacitinib within 28 days from study enrolment.
- Acceptance for patients to participate in the study and the signing of the informed consent.

Exclusion criteria:

- Patients meeting any of the following criteria will not be included in the study:
- Patients who do not have the ability answer the questionnaires by themselves or who have any kind of disorder that may affect their answers.
- Patients diagnosed with autoimmune rheumatic diseases other than RA.
- Cannot or will not sign informed consent.
- Active participation or enrollment in an interventional trial.
- Previous experience with tofacitinib through either a clinical trial or previous treatment.
- Is not expected to be available for follow up assessments as required for adequate management.
- According to the judgment of the physician will not be able to participate in the study including the presence of any condition that, in the opinion of the treating physician, prohibits the patient from participating in the study or obscures the assessment of the treatment of RA.
- Pregnant and breastfeeding women.
- Patients with lymphoproliferative disorders (e.g. Epstein Barr Virus (EBV) related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

Recruitment mode: Patients to be recruited by participating sites and will be enrolled in the study based on meeting the inclusion/exclusion criteria.

Data collection:

The information may only be collected once the protocol has been approved by Pfizer and the Ethics Committee of the sites, training on adverse events (AE) reporting has been provided, and the informed consent form has been signed by the patients. After the potential patients to be included in the study are identified, the treating physician (rheumatologist) will verify the inclusion/exclusion criteria for determining the patient eligibility and will complete the baseline information.

The investigator will apply the case report forms at the beginning of recruitment (month zero) and throughout the proposed follow-up period. Before sending the information to Pfizer in a standard form for subsequent analysis, data from patients must be codified and verified by the CRO to assure that we will receive complete information and that patients would not be identified by Pfizer.

Outcomes

- Information reported by patients (*Patient Reported Outcomes* [PRO]) and physicians on disease activity, functional status, quality of life and work productivity.
- Frequency of adverse events of special interest.

Data sources:

- Patients, through application of PROs:
  - Patient global assessment.
  - *Routine Assessment of Patients Index Data* (RAPID3): Disease activity.
  - *Health Assessment Questionnaire* (HAQ): Functional status.
  - *EuroQol Questionnaire* (EQ-5D): Quality of life.
  - *Work Productivity and Activity Impairment* (WPAI): Work productivity.
  - Spontaneously reported safety information.
- Medical records

<table>
<tr><td colspan="4">

- Clinical and demographic information of patients: age, sex, comorbidities, concomitant medications, risk factors.
- Characteristics of the disease: duration of the disease, laboratory test data, disease activity.
- Treatment: previous and current treatment alongside reason for discontinuation of previous treatment.

</td></tr>
<tr><td colspan="4">Data analysis:
The information collected by the Clinical Research Organization (CRO) will be analyzed by Pfizer through a statistical management plan. Initially, the sample will be matched using propensity score calculated from baseline variables. For effectiveness outcomes, a descriptive analysis will be performed for all variables. For persistence assessments Kaplan-Meier assessments will be completed. For safety outcomes, all the safety data will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation.</td></tr>
<tr><td>First Patient First Visit</td><td>October 2017</td><td>Last Patient Last Visit</td><td>February 2022</td></tr>
<tr><td>Last Patient First Visit</td><td>February 2019</td><td>Estimated duration of recruitment</td><td>18 months</td></tr>
</table>

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	October 2, 2017	Substantial	Section 3 Abstract Section 8.4 Data Source Section 8.6 Data Management Section 10 Management and Reporting of Adverse Events/Adverse Reaction	Section 3- Update to start date and clarifications aligned with changes in subsequent sections. Section 8.4- Clarity on data to be collected and sources of data and clarity on safety data collected for analysis. Section 8.6- Removal of information which is not relevant to the management of data. Section 10.1- 1) Additional guidance regarding safety information volunteered by patients in responses to patient reported outcome case report forms. Section 10.2 -) Addition of safety language and guidance for Secondary Data Collection- includes protocol required Human Review of Unstructured data (collection of previous medical history, baseline data and patient characteristics from patient charts) .	Updates requested after secondary, post Pfizer protocol approval review of safety language and protocol version 1.

5. MILESTONES

Milestone	Planned date
Start of data collection	October 2017
End of data collection	February 1 2022
Study progress report 1	1 February 2018
Interim report 1	1 February 2018
Final study report	1 August 2022

6. RATIONALE AND BACKGROUND

Rheumatoid Arthritis (RA) is a chronic, auto-immune, inflammatory disease that affects approximately 1.0% of the adult Canadian population[1] The syndrome is characterised by progressive inflammatory synovitis of the joints that can lead to erosion of the cartilage and subchondral bone.[1] As a result of these joint abnormalities patients experience functional impairment and pain that has a negative impact on quality of life, productivity with increased morbidity and health care utilization.[2]

Management of patients with RA is focused on reducing pain and inhibition of disease progression. Early use of Disease Modifying Anti-Rheumatic Drugs (DMARDS) has been recommended in order to control disease progression.[3,4] The advent of biologic DMARDS for the management of RA has provided significant benefits to patients, and in particular those that have suboptimal or non- sustained response to traditional DMARDS.[5]

However, the increased risk for serious infections and malignancy and uncertainty regarding the long term sustained therapeutic response for biologic DMARDS remains a concern.[6,7] In addition, the intravenous method of administration of biological DMARDS is a potential obstacle for use by patients, who tend to prefer treatment regimens that allow for at-home administration.[8] Furthermore, there is a need for an alternative treatment for patients that do not respond or lose the response with biologic DMARDS. It follows that molecules with a different mechanism of action may address this need.

Tofacitinib is an oral Janus kinase (JAK) inhibitor approved in Canada in April 2014. It is indicated in combination with methotrexate (MTX) for reducing the severity of symptoms in patients with moderately to severely active RA who have had an inadequate response to MTX.[9] In cases of intolerance to methotrexate (MTX) physicians may consider use of tofacitinib as monotherapy.[9]

The mechanism of action of tofacitinib involves blocking of the immune response by inhibition of intra-cellular JAK signaling pathways.[10] This is different from that of currently available biologic DMARDS acting on the extracellular inflammatory pathways which involve pro inflammatory cytokine such as Tumor Necrosis Factor (TNF-alpha) and Interleukin (IL-6).

The results of randomized controlled trials have demonstrated the efficacy and safety of tofacitinib comparable to the biologic DMARDs.[11-16] Data from long term observational extensions of controlled trials have shown that the real world use of tofacitinib has a safety profile that is comparable to that observed in registrational studies and comparable to that of the currently approved biologic DMARDs.

Randomized controlled trials conducted under ideal conditions using highly selected patients allow the assessment of safety and efficacy and support decisions regarding marketing approval of treatments by regulatory agencies. The efficacy results reported in controlled clinical trials most often are not corroborated by the effectiveness observed in the real world setting. In addition, safety signals that can be undetected in controlled clinical trials often emerge in the real – life setting. This leads to a treatment and safety gap between the results expected on the basis of controlled clinical trials and the real – world experience with marketed interventions. The causes of this discrepancy are first the difference between patients included in controlled clinical trials and those treated in the real – life setting with respect to demographics, disease severity and profile, comorbidities and concomitant medication use. Sub – optimal adherence to treatment in the real – life setting is another major contributor to the treatment gap. In addition access to care, physician decision making and treatment patterns are additional important factors contributing to this phenomenon.

Post Approval Clinical Epidemiological Studies (PACES) which include among others, phase IV trials, Post Marketing Non-Interventional Observational Studies and Patient Registries are the only means by which the treatment and safety gaps in real life setting can be assessed. In addition PACES allow the evaluation of interventions at the patient, physician and health care system levels aimed at minimizing the treatment and safety gaps and optimizing patient management.

Regional specificity is an important element of PACES. Although PACES can be conducted on a multinational and even global scale with many objectives being, contextually similar across regions, regional idiosyncrasies with respect to disease epidemiology, patient profile and behavior, physician practice patterns and access to care prohibit the generalization of the results from one country or even region to another. Therefore PACES must be conducted at regional levels in order to address the needs of the population. Currently there is limited data describing the characteristics of patients receiving tofacitinib in Canada as well as the long-term effectiveness and safety in Canadian clinical practice.

The purpose of the current study is to assess the patterns of use tofacitinib in the management of moderate to severe RA in the real world setting in Canada. The study will also describe the real –life effectiveness and safety of RA patients initiating treatment with tofacitinib in Canada. The study will also evaluate determinants of optimal therapeutic response. By enrolling patients from a representative sample of academic and community rheumatologists the results are generalizable to the Canadian RA population. The non-interventional nature of the study will be protected by enrolling only patient for whom the treating physician has decided to initiate treatment with tofacitinib independently of the study. The long term duration of patient observation that will be extended beyond discontinuation of treatment with tofacitinib will ensure that the effect temporal changes on treatment patterns and access

to care on effectiveness are assessed. The results of this comprehensive study will have implications on the management of RA patients in Canada with potential global impact.

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

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Primary Objectives:

1. To describe the profile of RA patients initiating treatment with tofacitinib in the Canadian real – world/clinical setting.

2. To describe the clinical effectiveness of tofacitinib over time in patients with moderate to severe RA in the real-world/clinical setting.

7.2. Secondary Objectives:

In patients with moderate to severe RA that are initiated on treatment with tofacitinib to:

1. Describe treatment patterns and treatment trajectory.

2. Describe adherence to treatment and its association with clinical effectiveness

3. Identify determinants of therapeutic response.

4. Describe durability of response, persistence of treatment and reasons for discontinuation.

5. Describe the change in patient-reported pain, fatigue, quality of life and health care resource utilization.

6. Describe the incidence of adverse events (including serious adverse events) and AEs of special interest for tofacitinib.*

   **Cardiovascular events/MACE, opportunistic infections (including tuberculosis), malignancy, serious infections (ie, infections requiring hospitalization), and herpes zoster*

8. RESEARCH METHODS

8.1. Study Design

This will be an observational (non – interventional), multi-centre study using a prospective cohort design. Patients RA that are newly treated with tofacitinib as per the decision of their physician, in accordance with the Canadian label[9] and local practice standards, and meet all of the identified inclusion eligible to be enrolled in the study. As this is an observational study, patients will receive care based upon the standard of care in Canada and as per the judgement of the treating physician. Pfizer will not provide or pay for medicinal products for the purposes of this non-interventional study.

8.2. Setting

This observational study will be conducted on patients with RA who have had an inadequate response to methotrexate and are initiating treatment with tofacitinib. Patients will be recruited over an 18 month period from approximately 40-60 (50 sites to be targeted) by community and university based rheumatologists across Canada. The participating investigators and sites will be selected with a distribution across Canadian regions. The decision to treat participating patients with tofacitinib must be reached prior to and independently of being enrolled in the study.

As per CRA guidelines[4] and usual clinical practice, the recommended schedule for follow-up is: Baseline, Months 3, 6 (primary endpoint), 12 for year 1, and every 6 months in subsequent years of observation. According to the non-interventional nature of the study, only information and results of assessments that are part of routine care, or required for the management of the patient as per the physician's judgment will be collected during these time points. More specifically, there are no tests or clinical assessments mandated by the study. However, as part of their participation in the study patients will be asked to complete self-administered questionnaires ascertaining patient-reported outcomes (PROs) at specific time intervals.

Although the actual follow-up and data collection will be at the physician's discretion, the timing of study visits is expected to fall within the following defined ranges:

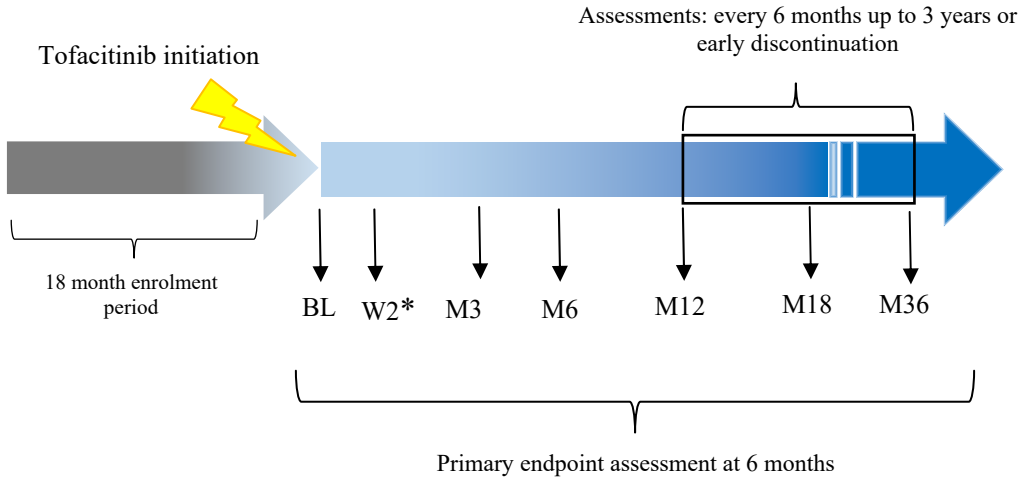
- Year 1 after treatment initiation with tofacitinib: maximum 5 visits, minimum of 3 visits. Expected visits would occur within 30 days of 3, 6, 12 months post treatment initiation (as per CRA guidelines and usual clinical practice).

- Years 2 – 3: minimum of 1 visit per year.

Unscheduled visits may occur as per the discretion of the treating physician. The reason for, and the results of any assessments performed during an unscheduled visit will be documented in the CRFs.

Figure 1 below provides a summary of the study design.

Figure 1. Study Design



The following inclusion and exclusion criteria will be applied to select the study sample:

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Adult patients, at least 18 years of age or older at the time of recruitment.
2. Diagnosis with RA as per the revised 1987 ACR criteria or 2010 ACR/EULAR criteria.
3. Patients for whom the treating physician has made the decision to commence tofacitinib treatment in accordance with the Canadian Product Monograph.
4. Initiation of treatment with tofacitinib within 28 days from study enrolment.
5. Acceptance for patients to participate in the study and the signing of the informed consent.

8.2.2. Exclusion Criteria

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

1. Patients who do not have the ability answer the questionnaires by themselves or who have any kind of disorder that may affect their answers.
2. Patients diagnosed with autoimmune rheumatic diseases other than RA.
3. Cannot or will not sign informed consent.

4. Active participation or enrollment in an interventional trial.

5. Previous experience with tofacitinib through either a clinical trial or previous treatment.

6. Is not expected to be available for follow up assessments as required for adequate management.

7. According to the judgment of the physician will not be able to participate in the study including the presence of any condition that, in the opinion of the treating physician, prohibits the patient from participating in the study or obscures the assessment of the treatment of RA.

8. Pregnant and breastfeeding women.

9. Patients with lymphoproliferative disorders (e.g. Epstein Bass Virus (EBV) related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

8.3. Variables

8.3.1. Exposures/Treatments:

All patients will be treated with tofacitinib according to the product monograph and the judgment of the treating physician. Exposure to treatment will be estimated from the prescription dates while adherence will be ascertained with patient self-reported number of doses missed. For patients that terminate treatment with tofacitinib, details on the duration of treatment and the reasons for termination will be recorded.

8.3.2. Outcomes Variables

8.3.2.1. Primary Outcome

The primary outcome variable of the study will be the Clinical Disease Assessment Index (CDAI).

The co-primary effectiveness measures will be the 6 month rate (proportion of patients) of achieving:

- CDAI Remission (CDAI < 2.8).

- CDAI Low Disease Activity (CDAI < 10.0).

8.3.2.2. Secondary Outcome Measures

Secondary outcome measures will be the change from baseline to each assessment in the following:

- CDAI as a continuous variable.
- Tender Joint Count (TJC).
- Swollen Joint Count (SJC).
- DAS28.
- SDAI.
- Physician Global Assessment of Disease Activity (MDGA) -VAS.
- Patient Global Assessment of Disease Activity (PtGA)-VAS.
- Patient Subjective Assessment of Pain-VAS.
- Health Assessment Questionnaire Disability Index (HAQ-DI).
- Routine Assessment of Patient Index Data-3 (RAPID-3).
- EuroQol EQ-5D.
- Work Productivity and Activity Impairment: Rheumatoid Arthritis (WPAI:RA) Questionnaire.
- Treatment Satisfaction Questionnaire (Likert Scale).
- Adherence to treatment.
- Fatigue Questionnaire (FACIT).
- Health Care Resource Utilization (HCRU).

In addition, the rate (proportion at each interval) and time to achieving the following therapeutic endpoints will be assessed as secondary endpoints:

- CDAI remission (CDAI < 2.8).
- CDAI Low Disease Activity (CDAI < 10.0).
- DAS 28 remission (DAS 28 < 2.6).
- DAS 28 Low Disease Activity (DAS 28 < 3.2).

- SDAI remission (SDAI < 3.3).
- SDAI Low Disease Activity (SDAI < 11.0).
- ACR20.
- ACR50.
- ACR70.

8.3.3. Covariates

The following covariates will be collected and incorporated in the data analysis of the current study:

1. Patient Socio - Demographics:
    a. Age/Date of Birth.
    b. Gender.
    c. Race.
    d. Education.
    e. Occupation (of employed).
    f. Household income range.
    g. Insurance coverage.
    h. Residency status.
    i. Geographic location (city, province).
    j. Smoking History as measured by yes/no.
    k. Alcohol use (weekly use).
2. Patient Medical History:
    a. Charlson/ADG co-morbidities group.
    b. Chronic conditions of clinical importance and relevance to RA:
        - Cardiovascular and metabolic risks and disease.
        - Diabetes.

- Malignancy.
- Known extra-articular manifestations of RA:
  - Rheumatoid nodules.
  - Rheumatoid vasculitis.
  - Eye disease.
  - Other.

c. Tuberculosis (TB) history.

d. Vaccination history:

- TB.
- Herpes zoster (HZ).
- Pneumonia.
- Influenza.
- Other.

e. Pregnancy.

3. Rheumatoid Arthritis History:

   a. Year of onset.

   b. Family history.

4. Medication History:

   a. Concomitant Medication Use (RA):

   - Date of onset.
   - Dose and frequency.

   b. Concomitant medication use (non-RA):

   - Indication.
   - Date of onset.

- Dose and frequency.

c. Most recent treatments for RA prior to tofacitinib including all biologic DMARDs or JAK inhibitors:

- Date of onset.
- Dose and frequency.
- Date of termination of treatment.
- Reason for treatment termination.
- List of other prior treatments used for RA.

d. Treatment with tofacitinib:

- Date of onset.
- Dose and frequency.

5. Physical Examination:

a. Standard physical examination: overview of body and systems noting any significant abnormal findings.

b. Weight.

c. Height.

d. SBP/DBP.

e. Pulse.

6. Disease Parameters:

a. Laboratory and results (when available and of clinical relevance).

- Rheumatoid Factor (RF).
- Anti-CCP.
- ANA.
- ESR.
- CRP.

- Other such as erosive disease.

8.4. Data Sources

- Demographic and baseline data (including Patient Socio-Demographics, Patient Medical History, Rheumatoid Arthritis History, Medication History, etc.) will be obtained from the patient charts.

- Follow up clinical assessments and physician reported outcomes will be ascertained prospectively during the patient assessments.

- Patient reported outcomes will be ascertained by self-administered questionnaires completed at the physician's office or via a secure internet portal as per the preference of the patients.

The following table describes the study data collection schedule:

Table 1. Schedule of Assessments

Procedures	Baseline	Week 2	Month 3	Month 6 (primary endpoint)	Month 12	Follow-up visits (conducted every 6 months post Month 12	Maximum Follow-Up/ Early discontinuation
Informed Consent	X						
Inclusion and Exclusion Criteria	X						
Patient Socio-Demographics	X						
Medical History							
Comorbidities (changes)	X		(X)	(X)	(X)	(X)	(X)
TB assessment[1]	X		X	X	X	X	X
Pregnancy assessment[2]	X		X	X	X	X	X
Vaccination History	X						
RA History	X						
Medications							
Previous RA Medication	X						
Concomitant Médication-RA and non-RA (changes)	X		(X)	(X)	(X)	(X)	(X)
Tofacitinib/Current RA Treatment regimen[3] (changes)	X		(X)	(X)	(X)	(X)	(X)
Physical Examination (changes)*	X		(X)	(X)	(X)	(X)	(X)
Vital Signs*							
Height	X						
Weight	X		X	X	X	X	X
SBP/DBP	X		X	X	X	X	X
Pulse	X		X	X	X	X	X
RA disease parameters*							
Laboratory Tests[4]	X		X	X	X	X	X
Imaging	X		X	X	X	X	X
Physician Reported Clinical Outcomes*							
Tender Joint Count (TJC)	X		X	X	X	X	X
Swollen Joint Count (SJC)	X		X	X	X	X	X
Physician Global Assessment of Disease Activity (VAS)	X		X	X	X	X	X

Procedures	Baseline	Week 2	Month 3	Month 6 (primary endpoint)	Month 12	Follow-up visits (conducted every 6 months post Month 12	Maximum Follow-Up/ Early discontinuation
Patient-Reported Outcomes*							
Patient Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X
Patient Subjective Assessment of Pain (VAS)	X	X	X	X	X	X	X
Health Assessment Questionnaire Disability Index (HAQ-DI)	X	X	X	X	X	X	X
Routine assessment of patient index data (RAPID-3)	X	X	X	X	X	X	X
EuroQol EQ-5D	X	X	X	X	X	X	X
Work Productivity and Activity Impairment: Rheumatoid Arthritis (WPAI:RA) Questionnaire	X	X	X	X	X	X	X
Treatment Satisfaction Questionnaire (VAS)	X†	X	X	X	X	X	X
Adherence to Treatment	X†	X	X	X	X	X	X
Fatigue Questionnaire (FACIT)	X	X	X	X	X	X	X
Health Care Resource Utilization (HCRU)	X†	X	X	X	X	X	X
Adverse events	X†	X	X	X	X	X	X

*When assessed an available as per routine clinical care
† Baseline assessment will not take place for patients who have initiated treatment with tofacitinib at the Baseline/Enrollment visit

1. TB and TB history will be assessed at Baseline; follow up visits will include a TB assessment only.
2. Pregnancy and pregnancy history will be assessed in females of child-bearing potential at Baseline; follow up visits will include a pregnancy assessment only.
3. Patients who discontinue tofacitinib and who choose to be followed until the maximum follow-up date will have all subsequent RA treatment regimens documented on the CRF.
4. Anti-CCP, ESR, CRP, ANA, RF.

8.4.1. Description of Activities

8.4.1.1. Inclusion/Exclusion

Patients will be screened to ensure they meet all inclusion criteria and do not meet any exclusion criteria prior to enrollment.

8.4.1.2. Informed Consent

Prior to the collection of any study data, patients will be asked to provide free and informed consent confirming their understanding of all study procedures and of their rights and responsibilities, allowing the release of their anonymized information to Pfizer for the exclusive use of the study. In addition, the patients will be informed that they will be asked to complete PRO assessments via interview of self-administration at the physician's office or their home or via the internet using a secure portal as per their preference.

8.4.1.3. Socio-Demographics

Once the study investigator has determined that the patient is eligible for inclusion, and the patient has agreed to be included in the observational study by providing informed consent, the patient's sociodemographic and baseline data will be recorded on the CRFs at the Enrollment/Baseline Visit.

8.4.1.4. Medical History

At the Enrollment/Baseline visit, the physician will determine the patient's current health status and obtain a complete medical history including past and current comorbid conditions of clinical importance, with an emphasis on assessing cardiovascular, metabolic and inflammatory diseases, and malignancy(ies). In addition, extra-articular manifestations of RA, such as rheumatoid nodules, rheumatoid vasculitis, and eye disease, will also be ascertained. A history of previous TB infection, vaccinations, and pregnancies (females of child bearing potential only) will also be assessed.

Patients will be continuously assessed, at all follow-up study visits, for any changes in co-morbid conditions, as well as for changes in TB and pregnancy status.

8.4.1.5. Rheumatoid Arthritis History

At the Enrollment/Baseline visit, patients will be assessed for their history of RA. This will include date of diagnosis and family history.

8.4.1.6. Medication History

At the Baseline/Enrollment visit, the date of tofacitinib treatment regimen initiation, the details of the treatment regimen (monotherapy vs. DMARD combination therapy), as well as the dose and frequency of all constituents of the tofacitinib treatment regimen prescribed will be collected.

In addition, the patient's prior and concurrent medication history will be assessed. Concurrent RA and non-RA medications include any medications that the patient has received within 28 days of the Enrollment/Baseline Visit and that will be continued during the study observation period. Concurrent medications include all those medications taken in addition to the tofacitinib treatment regimen prescribed, and information collected will consist of the date of onset, dose and frequency, and indication (non-RA only). Information related to all prior RA-treatment regimens (DMARDS, biologics, NSAIDs and corticosteroids) including date of onset, date of termination, and reason for termination, will be collected. Emphasis will be place on the RA treatment regimen immediately prior to tofacitinib.

At follow-up study visits, any changes in concomitant RA and non-RA medication (dose and frequency modifications, termination, addition of new medication) should be recorded through the course of the study. Any changes in treatment with tofacitinib will also be collected: the date of change, nature and details of change (dose or frequency adjustment, suspension, termination), and reason for change. For patients discontinued with tofacitinib, the subsequent RA treatment regimen will be captured, including details on start date, dose, and frequency. For patients who remain in the study regardless of tofacitinib termination, all changes in the subsequent RA treatment regimen(s) will nonetheless be captured at each follow-up visit.

Medications used to treat SAEs will be recorded at the time of the event in the appropriate page in the eCRF.

8.4.1.7. Physical Examination

When as per the standard of care of the treating physician, a complete physical exam will be performed at the Baseline/Enrollment visit, including an overview of body and systems. Any significant abnormal findings will be noted in the CRF. During the observation period, only significant changes in physical examination will be noted and recorded in the CRF.

Vital sign determinations of sitting blood pressure, pulse, and weight will be obtained at each visit, if collected as per standard of care. Each patient's height will be measured only once during the study, typically at the Enrollment/Baseline Visit.

8.4.1.8. Rheumatoid Arthritis Disease Parameters and Assessments

All assessments will be performed, and data collected, when as per the routine clinical care of the treating physician.

8.4.1.8.1. Laboratory Assessments

Laboratory assessment of inflammatory markers will be ascertained, when performed and the results are available, at the Baseline/Enrollment visit, and all subsequent study visits. This is inclusive of, but not limited to: RF, anti-CCP, ANA, ESR, and CRP.

8.4.1.8.2. Tender Joint Count (TJC)

An assessment of 28 tender joints or regions, by physical examination, is recommended to be performed by the physician and recorded at the Enrollment/Baseline Visit, and all subsequent in-office study visits.

8.4.1.8.3. Swollen Joint Count (SJC)

An assessment of 28 joints by physical examination is recommended to be performed by the physician and recorded at the Enrollment/Baseline Visit and all subsequent in-office study visits.

8.4.1.8.4. Physician Global Assessment of Disease Activity (MDGA) - VAS

A VAS will be used to assess the physician's global assessment of disease activity. Each VAS will consist of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the severity of disease activity (0 = no activity; 100 = extremely active). Physicians will be asked to indicate where on the 100mm line they perceive the activity of the patient's RA to fall. The recall time is now.

8.4.1.8.5. Patient-Reported Outcomes

8.4.1.8.5.1. Patient Global Assessment of Disease Activity (PtGA) -VAS

A VAS will be used to assess the patient's global assessment of disease activity. Each VAS will consist of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting how the patient has been doing in the past week with respect to their RA symptoms (0 = very well; 100 = very poor). Patients will be asked to indicate where on the 100mm line they perceive their state to be. The recall time is now.

8.4.1.8.5.1.1. Patient Subjective Assessment of Pain - VAS

A VAS will be used to assess the patient's global assessment of pain. Each VAS will consist of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the severity of pain (0 = no pain; 100 = unbearable pain/pain as bad as you can imagine). Patients will indicate where on the 100mm line they perceive their pain to fall. The recall time is the previous week.

8.4.1.8.5.2. Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI is a generic instrument used to assess, via self-report, the physical function and health-related quality of life in patients with rheumatic disease.[17] Specifically, the HAQ-DI assess patient disability across 20 questions converging to 8 categories of activities: dressing and grooming, arising, eating, walking, hygiene, reach and grip. Patients are asked to rate each activity in the past week on a 4 point Likert scale (0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to do). Any aides or devices used to assist the abovementioned activities are also captured. The scores are averaged by the total number of sections completed, to derive a disability index (DI).

8.4.1.8.5.3. The Routine Assessment of Patient Index Data (RAPID-3)

The RAPID-3 is a self-administered questionnaire which includes a subset of core variables found in the multi-dimensional HAD (MD-HAQ.[18] Eleven activities are assessed for the patients ability to perform on a 4 point Likert scale (0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to do), with 2 additional questions related to how well the patient is able to deal with anxiety and depression. In addition, patients are asked to rate, on an interval scale from 0-10 (0.5 increments), how bad their pain has been in the past week (pain tolerance score: 0 = no pain; 10 = pain as bad as it could be), as well as how well they are doing at the time of the assessment (global estimate score: 0 = very well, 10 = very poorly). A formal score (FS) is derived from the average of the 11 activity scores, and is added to the pain tolerance and global estimate scores to generate a total score used to derive the state of the patient's disease (near remission, low severity, moderate severity and high severity).

8.4.1.8.5.4. EuroQoL EQ-5D

The Euro-QoL (EQ-5D) questionnaire is a generic health status instrument which evaluates, via self-report, quality of life based on the measurement of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[19] A preference based scale, the EQ-5D assesses each dimension with three levels of severity; 1 (no problems), 2 (some problems), and 3 (maximum problems). Each score can then be weighted to adjust for population-specific preferences in health-care states. Individual health dimensions scores are converted to a single EQ-5D summary score, with EQ-5D summary scores closest to 1 indicative of a better quality of life. The VAS component of the EQ-5D questionnaire (EQ-5D VAS) also records the patient's self-rated health on a horizontal scale, ranging from "worst imaginable health state" to "best imaginable health state".

8.4.1.8.5.5. Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA)

The RA-specific Work Productivity and Activity Impairment Questionnaire (WPAI:RA), is a validated self-administered questionnaire used to assess the extent of work productivity (absenteeism, presentism, and impairment in daily activities) attributable to RA. It is comprised of six questions:

1. Current employment status.
2. Number of hours missed due to a health problem.
3. Number of hours missed due to other reasons.
4. Hours actually worked.
5. Degree to which health affected productivity while working.
6. Degree to which health affected regular (non-work) activities.

8.4.1.8.5.6. Treatment Satisfaction

Patient satisfaction to treatment will be assessed via a 5 – point Likert scale (1 = not at all satisfied, 2 somewhat dissatisfied, 3 = neutral (neither satisfied nor dissatisfied), 4 – somewhat satisfied and 5 = very satisfied).

8.4.1.8.5.7. Adherence to Treatment

Self-reported adherence to treatment will be assessed by the number of RA medication doses missed. The recall period will be during the last month. Patients prescribed a combination RA treatment regimen will be asked to report adherence to each individual component.

8.4.1.8.5.8. Functional Assessment of Chronic Illness Therapy (FACIT) Questionnaire

The FACIT Questionnaire is a self-report questionnaire that has been validated for use in older adults.[20] It is a short, 13 item tool that's asks patients to assess, on a 5 point Likert scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much), their level of fatigue during their daily activities in the past week. The range of possible scores is from 0-52, with higher scores indicating a lower level of fatigue; scores below 30 indicate severe fatigue.

8.4.1.8.5.9. RA Healthcare Resource Utilization Questionnaire.

The RA Healthcare Resource Utilization Questionnaire (RA-HCRU) is a seventeen-item scale that is designed to assess healthcare usage during the previous three months across a wide number of direct medical cost domains. The scale also assesses indirect costs associated with functional disability and impaired productivity at home and at work. This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible.

8.4.1.9. Safety

All adverse events will be recorded and coded according to the MedDRA dictionary of terms and will be included in the study database for analysis.

8.5. Study Size

Given the observational nature of the study and the descriptive analyses used to address the study objectives sample size requirements are based on the precision of the estimates. The confidence intervals, and most commonly, the 95% CI are used to assess the precision of the estimate.

For the current study the primary endpoint will be the proportion of patients achieving CDAI remission or LDAS. The data reported from long term extension studies (Wollenhaupt 2016)[21] suggest that at 6 months of treatment 24.4% and 43.4% of the patients will have DAS-28 4(ESR) < 2.6 and < 3.2 respectively. We can expect similar rates for CDAI remission and LDAS.

With 800 evaluable patients the 95% CI width for CDAI Remission will be ± 0.029 or ±11.9% of the point estimate and that for CDAI LDA will be ± 0.034 or 7.8% of the point estimate. Both of these are within the acceptable levels of precision. Hence the study will require approximately 800 evaluable patients with 6 months of follow up.

8.6. Data Management

Data collection will be performed using an Electronic Data Capture (EDC) system that will be developed for the current study. The EDC system will be based on a paper CRF that will be approved by Pfizer. The EDC interface will incorporate edit checks to ensure data quality and consistency. Additional edit checks will be conducted at the data management center. Edit checks will generate queries that will be addressed by the investigator and will lead to respective changes in the data. All data changes will be tracked by an audit trail in compliance with FDA 21 CFR part 11compliance. Study databases will be compliant with CDISC requirements as necessary.

As noted in Section 8.4, patient reported outcomes will be ascertained by self-administered questionnaires completed at the physician's office or via a secure internet portal as per the preference of the patients. For Patient reported outcomes the EDC will accommodate patient interviews as well as direct data entry, in the case that patient prefer to complete paper questionnaires. The system will also integrate PRO data obtained via the internet.

The CRF consist of the following main sections:

1. Baseline / Screening:

This will be used to enter all the data collected during the baseline / screening visit.

2. Follow-Up Visits:

These will be labeled as Follow-Up Visits 1 –12 with the suggested time points of 3, 6 (primary endpoint), 9, 12, 18, 24, 30, and 36 months indicated. However, as mentioned earlier, this is the recommended schedule of visits and the investigators will be allowed to conduct the assessments according to their routine practice and judgment. Consequently, the investigators will be instructed to use the individual CRF visit sections for visits that take place on time period that is nearest to the suggested time point. The date of the visit will be clearly indicated. A distinct section for unscheduled visits will be provided. For Patient reported outcomes the EDC will accommodate patient interviews as well as direct data entry, in the case that patient prefer to complete paper questionnaires. The system will also integrate PRO data

3. End of Study:

This will be a separate section of the CRF describing the final status of the patient in the study as "completed" or "withdrawn". For patients that are withdrawn from the study, the reason and date will be reported.

The completed signed and dated case report forms for the enrolled patients should be provided to the study data management center by the investigator for every patient enrolled in the study on an ongoing basis. Electronic signatures will be used. As distinct case report form should be created for each unique instance when data is to be collected; ONLY data specified in the protocol should be collected and submitted to the study data management center

8.7. 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 and will be prepared prior to data closure and any data analyses. 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.

8.7.1. General Considerations

The analyses conducted for the study will be predominantly descriptive with several associations assessed with bivariate and multivariate methods. However, given that there are no specific a-priori defined hypotheses being tested, there is no need for multiplicity correction for the number of associations tested and the number of outcomes assessed. Hence any p-values presented should be considered as descriptive statistics themselves; and, there will be no declarations of statistical significance. The analyses will be conducted on observed cases without imputation for missing data in order to preserve the observational nature of the study. The Full Analysis Set (FAS) will be comprised of all enrolled patients providing consent to participate in the study. Nevertheless, the use of mixed effects models will help to compensate for missing observations, patient attrition and unequal time intervals between assessments.

8.7.2. Primary Analyses

The profile of patients initiated on treatment with tofacitinib will be described with respect to the sociodemographic parameters, baseline disease characteristics including severity, duration since diagnosis, prior treatments as well as comorbidities and concomitant medication use. For continuous variables descriptive statistics reported will be the mean, median, standard deviation, 95% confidence intervals of the mean and range (minimum and maximum). Categorical variables will be summarized as proportions with 95% confidence intervals (CI).

For the current study the primary effectiveness outcome measure is the rate of patients achieving CDAI ≤2.8 (Remission) and CDAI ≤10 (LDAS) at 6 months. This will be described by the proportion and 95% CI of patients achieving these endpoints at 6 months. This assessment will be conducted for the study cohort as a whole but also meaningful strata defined according to patient's age, gender, duration of disease, prior treatment and presence of comorbidities.

Effectiveness will also be measured over the entire follow-up period, using the change from baseline to all time points in DAS28, CDAI, and SDAI. Mixed effects, repeated measures, linear regression models adjusting for within patient variances, unequal follow up periods and missing observations will be used to produce least square mean estimates of the change in these outcome measures at each assessment.

In addition the proportion of patients achieving therapeutic endpoints (CDAI remission, CDAI LDA, DAS28 remission, DAS28 LDA, SDAI remission, SDAI LDA, and ACR20/50/70 response) at quarterly intervals will be reported. Kaplan Meier estimates of the survival function will be used to describe the time to the above mentioned therapeutic endpoints and the cumulative proportion with the endpoint at specific time points.

8.7.3. Secondary Analyses

For the 1st secondary analysis, frequency distributions will be used to assess the treatment patterns of patients while on tofacitinib, and of all subsequent changes in RA treatment regimens. The treatment patterns over time will also be described using decision node analysis assessing the impact of response to treatment and incidence of adverse events on treatment changes.

For the 2nd secondary objective, adherence to treatment will be ascertained on the basis of missed doses of each RA-treatment regimen component, as reported by the patient. A patient will be considered adherent to treatment if they have taken 80% of the doses of each individual component of their prescribed treatment regimen. Adherence will be assessed by treatment regimen, and overall. The association between adherence to treatment and clinical or patient reported outcomes will be assessed with bivariate and multivariate models.

For the 3rd secondary objective, potential predictors of therapeutic response will be assessed with appropriate bivariate and multivariate methods. The latter will include linear regression, generalized linear models, multivariate logistic regression, Cox's proportional hazards models and categorical regression to assess the association of variables of interest on therapeutic response endpoints.

For the 4th secondary objective, durability of response and tofacitinib persistence will be assessed with the Kapan-Meier estimator of the survival function. Reasons for discontinuation will be assessed with descriptive statistics.

For the 5th secondary objective, change in MDGA and PROs (PtGA, patient pain, HAQ-DI, RAPID-3, EQ-5D, WPAI:RA, treatment satisfaction, and FACIT) from Baseline to all time points will be addressed with descriptive statistics of the change in which will include estimates of the mean change with 95% confidence intervals. Changes over time will be assessed for statistical significance using paired comparisons, including the Student's t-test or Wilcoxon signed-rank test, depending on the distribution of the data. Mixed effects, repeated measures, linear models will be used to produce Least Square Estimates of the mean changes adjusting for within patient variances, unequal follow up periods and missing observations.

Health care utilization will be described the frequency distributions of each health care resource utilized specifically, physician visits, ER visits, hospitalizations as well as prescription and non-prescription medications used. Poisson distributions will be used to describe the health care resource utilization during the study period. Bivariate and multivariate analyses will be used to assess differences with respect to health care utilization between patient groups defined according to age, gender, duration of disease, baseline severity of disease, prior treatments and changes in treatment over time.

For the 6th secondary objective, adverse events including SAEs and TEAEs and adverse events of special interest will be coded according to the MedDRA dictionary of terms. The incidence of adverse events (including SAEs and TEASs) and adverse events of special interest will be described as the proportion of patients with an event and the incidence density rate defined as the number of events per 100 person – years.

8.8. Quality Control

The study will be submitted for review and approval at a central ethics committee or local ethics review boards as required for individual sites. The boards will review the study protocol, the patient authorization for use/disclosure of data and patient questionnaires. A list of participating physicians will be provided to the review boards. No study activities will be undertaken prior to obtaining the relevant approval of the Independent Ethics Review Boards.

Prior to being enrolled in the study, written patient authorization for use/disclosure of data will be obtained from the patient. The investigator will explain the study to the patient along with the requirements for completion of the self-administered questionnaires. The patient authorization for use/disclosure of data will provide permission for the patient's data to be collected and used anonymously in the study.

Patient confidentiality will be protected at all times by using a randomly generated patient study identification number that will identify each unique patient. The name, initials, address, telephone numbers, provincial insurance numbers, hospital record numbers or any other identifier will NEVER be collected/entered in any page of the CRF or questionnaire. Prior to being included in the study, all sites will be assessed for compliance with local requirements for the practice of medicine including validation of the physician's license and specialization certificates. In addition, all site personnel will be educated with respect to Good Clinical Practices (GCP) and the requirements for data reporting and in particular adverse event reporting of the study. Sites with prior scientific research or relevant clinical experience will be selected.

Data management quality assurance will involve monitoring of a random 25% sample of observations as well as implementing data edit checks and statistical assessments. A review of 100% of the sites will be conducted to ensure that the patients entered in the study fulfill the inclusion and exclusion criteria.

8.9. Strengths and Limitations of the Research Methods

The limitations of the current study are those inherent in single armed cohort observational studies. More specifically the lack of a control or comparison group, variable visit schedule and missing data.

With respect to the lack of a control group, the study research question is specific to the assessment of the impact of treatment with tofacitinib on the study outcomes and does not include a comparative assessment. Hence the single cohort design is appropriate to answer this specific question. Furthermore, the baseline assessment will provide the control values representing the status of the disease parameters prior to and hence, while not on treatment with tofacitinib. Safety data will be reported descriptively only.

In observational studies, patient assessments are not dictated by a strict protocol but as per the real-life setting and they are based on routine clinical practice, the judgment of the physician, and the availability of the patient. This creates a problem with unequal duration of treatment and follow-up when assessments at defined time intervals are required. The mixed effects repeated measures models that will be used in the current study will help address this variability. With these models, the least square mean will be used to estimate the value of the variable at specific time points.

Another problem with observational studies is missing data. For clinical data, all efforts will be made to retrieve any missing data point. For missing responses on questionnaire items, the coding for the majority of the tools used in the current study provide imputation solutions for missing responses. Furthermore, in order to assess the likelihood of bias, the pattern of missing data will be evaluated to determine whether these data follow a missing at random pattern or whether there is a systematic non-random missing data distribution.

9. PROTECTION OF HUMAN SUBJECTS

9.1. 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 both the IRB/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.

9.2. 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 subject regarding any unresolved adverse events.

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.

Patients discontinuing tofacitinib for any reason, are eligible to remain in the study for the maximum follow-up period (3 years from initiation of treatment with tofacitinib). These patients will be followed as per the schedule of assessments provided in Table 1 and as per the routine clinical care of the physician. All assessments performed will be collected and documented in the eCRF.

9.3. 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, (e.g., 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.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the International Ethical Guidelines for Biomedical Research principles (Council for International Organizations of Medical Sciences 2002), the Good Clinical Practice guidelines (International Conference on Harmonization 1996), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and the Helsinki Statement (world Medical Association 2008).

In addition, the study will meet local regulatory requirements.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Prospective Primary Data Collection (Collection of Data by Investigator on to a Case Report Form)

REQUIREMENTS

The first component of data collection in this protocol involves the collection of data by the investigator onto a case report form, which may include information obtained from the patient-reported outcome surveys completed by the participant. The table below summarizes the requirements for recording safety events on the case report form 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, and occupational exposure. These events are defined in the section "Definitions of safety events".

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	None
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)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" 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 a 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 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 case report form. In general, this will include a description of the adverse event 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 tofacitinib or the time of the patient's informed consent if s/he is already exposed to tofacitinib, 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, failed screening criteria), 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 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 adverse event. For AEs with a causal relationship to 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 tofacitinib caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether 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 tofacitinib did not cause the event, this should be clearly documented on the case report form 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 adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- 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;
- 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 adverse event 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 adverse event by the investigator or sponsor.

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

Serious adverse events

A serious adverse event 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 adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

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).
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol).

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) tofacitinib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to 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 tofacitinib 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 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.

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

In addition, the information regarding environmental exposure to tofacitinib in a pregnant woman (e.g., a subject 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.

Review of completed PRO surveys for potentially reportable safety information

Study participants will complete the PRO survey at the investigator's office by paper or online, or at the participant's home by paper or online. The surveys provide an opportunity (eg, free text fields, blank margins on the paper survey) where study participants may provide information that may constitute a safety event (e.g., serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure). Within 1 business day of receiving a completed survey, regardless of whether completed on paper or online and regardless of whether completed at the investigator's office or at home, the vendor reviews the areas in the survey in which the study participant may have volunteered potential safety information. If the survey does contain potential safety information, the vendor forwards any such information to the investigator for assessment as to whether it constitutes an adverse event. If upon review, the investigator determines that the information constitutes an adverse event, s/he collects the adverse event information on the CRF and forwards serious adverse events to Pfizer Safety within 24 hours of his/her awareness, per the process described above.

10.2. Secondary Data Collection-Includes Protocol Required Human Review of Unstructured Data (Collection of Previous Medical History, Baseline Data and Patient Characteristics From Patient Charts)

The second component of data collection in this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the case report forms and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

10.3. Single Reference Safety Document

The Xeljanz Canadian Product Monograph[9] 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 SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

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.

12. REFERENCES

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

2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108.

3. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.

4. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559-82.

5. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2016(5):CD012183.

6. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.

7. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.

8. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009;3:335-44.

9. Pfizer Canada Inc. XELJANZ Tofacitinib tablets. Product Monograph. 15 Septemember 2015. Available at http://www.pfizer.ca/sites/g/files/g10028126/f/201511/Xeljanz_PM_E.pdf.

10. Lundquist LM, Cole SW, Sikes ML. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. World J Orthop. 2014;5(4):504-11.

11. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

12. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.

13. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253-61.

14. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.

15. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381(9865):451-60.

16. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-70.

17. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45.

18. Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. Rheum Dis Clin North Am. 2009;35(4):773-8, viii.

19. Prieto L, Sacristan JA. What is the value of social values? The uselessness of assessing health-related quality of life through preference measures. BMC Med Res Methodol. 2004;4:10.

20. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

21. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol. 2014;41(5):837-52.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

None