NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS Information

Title	Canadian Non-Interventional Study of Xeljanz in Rheumatoid Arthritis (CANTORAL).
Protocol Number	A3921280
Version Identifier of the Final Study Report	1.0
Date	01 May 2023
EU Post Authorization Study (PAS) Register Number	EUPAS 21413
Active Substance	ATC Code: L04AA29 – Tofacitinib Citrate
Medicinal Product	Tofacitinib Citrate/Xeljanz
Research Question and Objectives	The primary objectives were to describe the profile of RA patients initiating treatment with tofacitinib in the Canadian real – world/clinical setting and to describe the clinical effectiveness of tofacitinib over time in patients with moderate to severe RA in the real-world/clinical setting.
Author	Redacted [redacted]

Redacted [redacted]

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Appendix 1. SIGNATURES

Not applicable.

Appendix 2. PROTOCOL

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Not applicable.

Appendix 3.1. List of Investigators by Country

Not applicable.

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Not applicable.

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT))

Not applicable.

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable.

Appendix 7.1 Withdrawn Subjects

Not applicable.

Appendix 7.2 Protocol Deviations

Not applicable.

Appendix 7.3 Subjects Excluded from the Analysis

Not applicable.

Appendix 7.4 Demographic Data

Not applicable.

Appendix 7.5 Medication/Treatment Data

Not applicable.

Appendix 7.6 Endpoint Data

Not applicable.

Appendix 7.7 Adverse Events

Not applicable.

Appendix 7.8 Laboratory listings

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Xeljanz_Covid Status_final.xlsx

Annex 2. Additional information

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

In ANNEX 1. LIST OF STAND-ALONE DOCUMENTS.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
ANA	Antinuclear Antibody
Anti-CCP	Anti-Cyclic Citrullinated Peptide
BID	Twice Daily
CDAI	Clinical Disease Assessment Index
CV	Cardiovascular
CFR	Code of Federal Regulations
CI	Confidence Intervals
CRA	Canadian Rheumatology Association
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CDISC	Clinical Data Interchange Standard Consortium
DAS-28	28-Joint Disease Activity Score
DBP	Diastolic Blood Pressure
DI	Disability Index
DMARD	Disease Modifying Anti-Rheumatic Drug
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

Abbreviation	Definition
EDP	Exposure During Pregnancy
ENcEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQol-5
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration (United States)
HAQ-DI	Health Assessment Questionnaire Disability Index
HCRU	Health Care Resource Utilization
HZ	Herpes Zoster
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus Kinase
LDAS	Low Disease Activity State
MACE	Major Adverse Cardiovascular Event
MDGA	Physician Global Assessment of Disease Activity
MTX	Methotrexate
NIS	Non-Interventional Study
NCT	National Clinical Trial Number
NMSC	Non-Melanoma Skin Cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug

Abbreviation	Definition
ORAL	Oral Rheumatoid Arthritis Phase 3 Trial
PACES	Post Approval Clinical Epidemiological Studies
PAS	Post Authorization Safety
PASS	PASS Post Authorization Safety Study
PRO	Patient-Reported Outcome
PtGA	Patient Global Assessment of Disease Activity
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RA-HCRU	Rheumatoid Arthritis Healthcare Resource Utilization Questionnaire
RAPID-3	Routine Assessment of Patient Index Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDAI	Simplified Disease Activity Index
SJC	Swollen Joint Count
TB	Tuberculosis
TJC	Tender Joint Count
VAS	Visual Analogue Scale
WPAI:RA	Work Productivity and Activity Impairment Questionnaire

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Redacted			

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned Date	Actual Date	Comment
Date of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) Approval of Protocol		05 September 2017	Initial approval of protocol for sites using Central Ethics Committee.
Start of Data Collection	31 October 2017	31 October 2017	
End of Data Collection	22 June 2022	30 June 2022	
Planned Date of EUPASS Registration	31 October 2017	31 October 2017	
Final Study Report	22 May 2023	01-May-2023	

6. RATIONALE AND BACKGROUND

This non-interventional study was designated as a PASS and was conducted voluntarily by Pfizer.

Rheumatoid Arthritis (RA) is a chronic, auto-immune, inflammatory disease that affects approximately 1.0% of the adult Canadian population.[1] The syndrome is characterized 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, and 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 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. At the time, tofacitinib was 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 using tofacitinib as monotherapy.[9]

On December 9th, 2021, following the assessment of results from the regulator-mandated post authorization safety study (NCT02092467),[10] the indication for moderate to severe RA was revised; the revision indicated tofacitinib, in combination with methotrexate, in adult patients with active RA who have had an inadequate response to MTX and to one or more DMARDs.[11] In cases of intolerance to methotrexate (MTX) and other DMARDs, physicians may consider use of tofacitinib as monotherapy.[11]

The mechanism of action of tofacitinib involves blocking of the immune response by inhibition of intra-cellular JAK signaling pathways.[12] This is different from that of currently available biologic DMARDS acting on the extracellular inflammatory pathways which involve pro inflammatory cytokines 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.[13-18] In the aforementioned regulator -mandated post-authorization safety study, which enrolled patients ≥50 years of age with additional cardiovascular risk factors, tofacitinib failed to demonstrate non-inferiority versus TNF-alpha for the co-primary endpoints of adjudicated Major Adverse Cardiovascular Events (MACE) and malignancy.[10] 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, 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 were conducted at regional levels in order to address the needs of the population. Prior to the current study, there was limited data describing the characteristics and the long-term effectiveness and safety of tofacitinib treated patients in Canadian clinical practice.

The current study aimed to assess the patterns of use of tofacitinib in the management of moderate to severe RA in a real-world setting in Canada. The study also described the real--life effectiveness and safety of RA patients initiating treatment with tofacitinib in Canada. Additionally, the study evaluated 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 patients for whom the treating physician has decided to initiate treatment with tofacitinib independently of the study. The long-term duration of patient observation extended beyond discontinuation of treatment with tofacitinib ensured that the effect of temporal changes on treatment patterns and access to care on effectiveness were assessed. The results of this comprehensive study have implications for the management of RA patients in Canada with a potential global impact.

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.*

* Major Adverse Cardiovascular Events (MACE), venous thromboembolism, malignancy (excluding Non-Melanoma Skin Cancer [NMSC]), NMSC, serious infections (ie, infections requiring hospitalization), and herpes zoster (serious and non-serious), gastrointestinal perforation, and hepatic events.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
1.0	02 October 2017	Section 3. Abstract	Section 3- Update to start date and clarifications aligned with changes in subsequent sections.	Substantial/Updates requested by Pfizer Safety group, post Pfizer approval of safety language and protocol version 1.
		Section 8.4. Data Source	Section 8.4- Clarity on data to be collected and sources of data and clarity on safety data collected for analysis.	
		Section 8.6. Data Management	Section 8.6- Removal of information not relevant to data management.	
		Section 10. Management and Reporting of Adverse Events/Adverse Reaction	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).	
2.0	01 December 2020	Table of Contents	Section 1.0. Table of Contents - Table of Contents was added as Section 1.0.	Administrative
2.0	01 December 2020	Section 1.	Section 2. List of Abbreviations	

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
		List of Abbreviations	Included additional abbreviations referenced in the document but not previously listed; deleted couple of abbreviations listed in this section which are not mentioned in the document; made corrections to some abbreviations previously listed.	
		Section 2. Responsible Parties	Section 3. Responsible Parties – Updated table.	
		Section 3. Abstract	Section 4. Abstract is a summary of the study protocol required for PASS. It was separated out as stand-alone document and included as Annex 1.	Substantial/The abstract is now a stand-alone document.
		Section 8.5. Study size	Section 9.5. Study size - The initial recruitment goal vs. the objectives of this study was re-evaluated. Based on this assessment, it was determined that a sample size of 500 patients allows adequate fulfilment of the study's objectives. In re-assessing sample size, reference is made to other similar studies in Canada. In fact, in recent Canadian real-world data studies (Real-World Tocilizumab Use in Patients with Rheumatoid Arthritis in Canada: 12-Month Results from an Observational,	Substantial/Based on the elements noted, a reduction of the sample size, from 800 patients (as originally targeted) to 500 patients was decided.

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
			Noninterventional Study (Haraoui et al., Rheumatol Ther. 2018 Dec;5(2):551-565;[25] Effectiveness and safety of certolizumab pegol in rheumatoid arthritis patients in Canadian practice: 2-year results from the observational FαsT-CAN study (Bessette et al., Ther Adv Musculoskeletal Dis. 2019 Mar 5;11:1759720X19831151) read out and were published. These studies included between 200-546 patients and yielded relevant information for rheumatologists on real world use and effectiveness for the respective medications evaluated.	
		Section 8.6. Data Management	Section 9.6.1. Case Report Forms (CRFs)/Electronic Data Record- Added this section under Data Management to include information regarding the data collection method used in this study.	Substantial/Updated to include this section from the most updated protocol template.
		Section 8.6. Data Management	Section 9.6.2. Record retention - Added this section under Data Management to include information regarding the retention of study records.	Substantial/Updated to include this section from the most updated protocol template.
		Section 9.1. Patient information and Consent	Section 10.1. Patient information - Previous title for this section was Patient Information and Consent. Section was separated out as 10.1.	Substantial/Updated to include this section from the most updated protocol template.

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
			Patient Information and 10.2. Patient Consent.	
		Section 9.1. Patient information and Consent	Section 10.2. Patient Consent - Previous title for this section was Patient Information and Consent. Section was separated out as 10.1 Patient Information and 10.2 Patient Consent	Substantial/Updated to include this section from the most updated protocol template.
		Section 10.1. Prospective Primary Data Collection (Collection of Data by Investigator on to a Case Report Form).	Section 11.1. Prospective Primary Data Collection (Collection of Data by Investigator on to a Case Report Form) - Updated table with requirements for recording safety events. Also, under Serious Adverse Event on page 44, added the last 3 paragraphs to align with the latest safety language template.	Substantial/Updated with the most updated and information from the latest safety language template for Primary Data Collection.
		Section 10.2. Secondary Data Collection-Includes Protocol Required Human Review of Unstructured Data.	Section 11.2. Secondary Data Collection-Includes Protocol Required Human Review of Unstructured Data -Updated language for consistency with most recent Secondary Data Collection template.	Substantial/Updated with the latest safety language template for Secondary Data Collection.
3.0	22 September 2021	Section 3. Responsible parties - Principal Investigator(s) of the Protocol	Redacted [redacted]	Administrative
		Section 9.6.2. Record Retention	Updated record retention requirement per local regulation.	Administrative

Redacted [redacted]

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
		Section 9.7.1. General Considerations	Added a sentence to clarify SAS and moved another sentence within the paragraph.	Administrative
3.0	22 September 2021	Section 11.1. Prospective Primary Data Collection (Collection of Data by Investigator on to a Case Report Form) REQUIREMENTS	Added numbering to the first column of the table that summarizes the requirements for recording safety events. Additional clarifications made to SAE/Special scenario reporting. Deleted last paragraph that referred to external Endpoint Adjudication Committee, as this is not applicable for the study.	Administrative
		Section 15. Annex 1	Added updated Abstract version	Administrative
4.0	19 January 2022	Section 2. List of Abbreviations	Included additional items on the list of abbreviations	Administrative
		Section 6. Milestones	End of data collection date and final study report date were updated	Substantial
		Section 7. Rationale and Background	Inserted 5th paragraph describing Dec. 9th, 2021, update to RA indication. Revised 7th paragraph to include Oral Surveillance (National Clinical Trial number -NCT02092467) study results.	Administrative
		Section 8.2. Secondary Objectives	Updated to reflect Adverse Event of Special Interest (AESIs) collected during the study.	Substantial

Amendment Number	Date	Substantial or Administrative Amendment	Summary of Amendment	Reason
		Section 8.3. Exploratory Objective	Exploratory objective added	Substantial
		Section 9.2. Setting	Figure 1 – Modified Study Design figure.	Administrative
		Section 9.5. Study Size	Updated sample size calculation to reflect tofacitinib 5 mg twice daily (BID) data at Month 6 from Wollenhaupt et al J Rheum 2014;41(5).	Substantial
		Section 9.7.1. General Considerations	Updated Section to include CV+ and non-CV+ cohorts.	Substantial
		Section 13. References	Added References 10 and 11 to include Dec. 9th, 2021, tofacitinib Product Monograph version and Oral Surveillance (NCT02092467) study, respectively.	Administrative
		Section 15. ANNEX 1	Updated Abstract Version	Administrative

9. RESEARCH METHODS

9.1. Study Design

This was an observational, multi-centre study using a prospective cohort design. Patients with RA that were newly treated with tofacitinib as per the decision of their physician, in accordance with the Canadian label[9] and local practice, and who met all the identified inclusion criteria were eligible to be enrolled in the study. All assessments described in this protocol were performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the country where this non-interventional study was conducted.

9.2. Setting

This observational study was conducted in patients with RA who had an inadequate response to methotrexate and were initiating treatment with tofacitinib. Patients were recruited over a 34-month period (from October 2017 until the end of recruitment in July 2020) from 45 sites (50 sites targeted) by community and university-based rheumatologists across Canada. The participating investigators and sites were selected with a distribution across Canadian regions. The decision to treat participating patients with tofacitinib was reached prior to and independently of being enrolled in the study.

As per CRA guidelines4 and usual clinical practice, the recommended schedule for follow-up was: 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 were part of routine care or required for the management of the patient as per the physician's judgment, were collected during these time points. More specifically, there were no tests or clinical assessments mandated by the study. However, as part of their participation in the study, patients were asked to complete self-administered questionnaires ascertaining patient-reported outcomes (PROs) at specific time intervals.

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

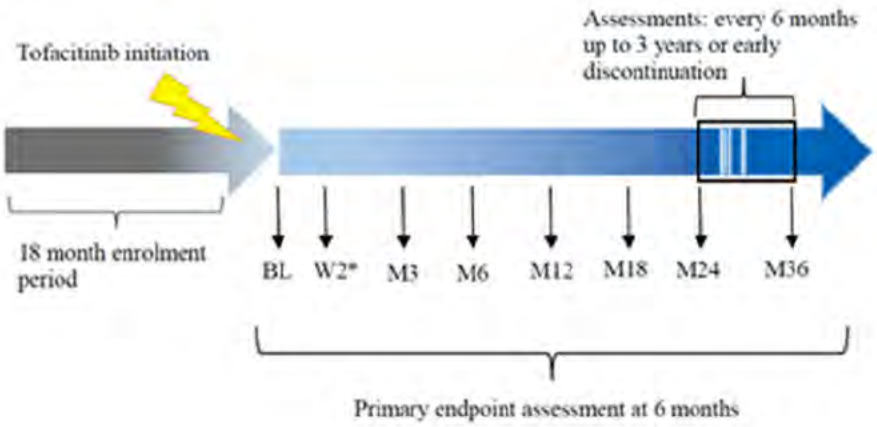
- Year 1 after treatment initiation with tofacitinib: maximum 5 visits, minimum of 3 visits. Expected visits would have occurred within 30 days of 3, 6, 12 months post treatment initiation (as per CRA guidelines and usual clinical practice).

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

Unscheduled visits were permitted at the discretion of the treating physician. The reason for, and the results of any assessments performed during the unscheduled visit were documented in the CRFs.

Figure 1 below provides a summary of the study design.

Figure 1. Study Design



9.3. Subjects

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

9.3.1. Inclusion Criteria

To be eligible for inclusion in the study, patients must have met each the following inclusion criteria:

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 American College of Rheum otology (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.

    - Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) was informed of all relevant aspects of the study.

9.3.2. Exclusion Criteria

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

1. Patients who do not have the ability to 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 (eg, Epstein Bass Virus (EBV) related lymphoproliferative disorder), have a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

9.4. Variables

9.4.1. Exposures/Treatments:

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

9.4.2. Outcomes Variables

9.4.2.1. Primary Outcome

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

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

- CDAI remission (CDAI <2.8).
- CDAI Low Disease Activity State (CDAI <10.0).

9.4.2.2. Secondary Outcome Measures

Secondary outcome measures were the change from baseline for each assessment of the following:

- CDAI as a continuous variable.
- Tender Joint Count (TJC).
- Swollen Joint Count (SJC).
- DAS-28.
- 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.

- Functional Assessment of Chronic Illness Therapy (FACIT).
- Health Care Resource Utilization (HCRU).

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

- CDAI remission (CDAI <2.8).
- CDAI Low Disease Activity State (CDAI <10.0).
- DAS-28 remission (DAS-28 <2.6).
- DAS 28 Low Disease Activity State (DAS-28 <3.2).
- SDAI remission (SDAI <3.3).
- SDAI Low Disease Activity State (SDAI <11.0).
- ACR20.
- ACR50.
- ACR70.

9.4.3. Covariates

The following covariates were 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.

a. Tuberculosis (TB) history.

b. Vaccination history:

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

a. 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.

a. Concomitant medication use (non-RA):

- Indication.
- Date of onset.
- Dose and frequency.

a. 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.

a. 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.

9.5. Data Sources

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

Follow-up clinical assessments and physician reported outcomes were ascertained, prospectively, during the patient assessments.

Patient reported outcomes were ascertained by self-administered questionnaires completed at the physician's office, at home (paper copy) or via a secure internet portal as per the preference of the patients. The following table describes the study data collection schedule:

Table 2. 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 Medication-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
Functional Assessment of Chronic Illness Therapy (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.

9.5.1. Description of Activities

9.5.1.1. Inclusion/Exclusion

Patients were screened to ensure they met all inclusion criteria and did not meet any exclusion criteria prior to enrollment.

9.5.1.2. Informed Consent

Prior to the collection of any study data, patients were 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 were informed that they would be asked to complete PRO assessments via interview of self-administration at the physician's office or their home (paper copy) or via the internet (electronic version) using a secure portal as per their preference.

9.5.1.3. Socio-Demographics

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

9.5.1.4. Medical History

At the Enrollment/Baseline visit, the physician determined the patient's current health status and obtained 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, were ascertained. A history of previous TB infection, vaccinations, and pregnancies (females of child-bearing potential only) were also assessed.

Patients were continuously assessed at all follow-up study visits for any changes in comorbid conditions, as well as for changes in TB and pregnancy status.

9.5.1.5. Rheumatoid Arthritis History

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

9.5.1.6. 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 were collected.

In addition, the patient's prior and concurrent medication history were assessed. Concurrent RA and non-RA medications included any medications the patient received within 28 days of the Enrollment/Baseline Visit and continued during the study observation period. Concurrent medications included all those medications taken in addition to the tofacitinib treatment regimen prescribed, and information collected consisted 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, was collected. Emphasis was placed 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) were recorded through the course of the study. Any changes in treatment with tofacitinib were also 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 was captured, including details on start date, dose, and frequency. For patients who remained in the study regardless of tofacitinib termination, all changes in the subsequent RA treatment regimen(s) were captured at each follow-up visit. Medications used to treat SAEs were recorded at the time of the event in the appropriate page in the eCRF.

9.5.1.7. Physical Examination

Per the standard of care of the treating physician, a complete physical exam was performed at the Baseline/Enrollment visit, including an overview of body and systems. Any significant abnormal findings were noted in the CRF. During the observation period, only significant changes in physical examination were noted and recorded in the CRF. Vital sign determinations of sitting blood pressure, pulse, and weight were obtained at each visit, if collected as per standard of care. Each patient's height was measured only once during the study, typically at the Enrollment/Baseline Visit.

9.5.1.8. Rheumatoid Arthritis Disease Parameters and Assessments

All assessments were performed, and data collected, per the routine clinical care of the treating physician.

9.5.1.8.1. Laboratory Assessments

Laboratory assessment of inflammatory markers were ascertained when performed and the results were 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.

9.5.1.8.2. Tender Joint Count (TJC)

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

9.5.1.8.3. Swollen Joint Count (SJC)

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

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

A VAS was used to assess the physician's global assessment of disease activity. Each VAS consisted 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, with gradients of 5 mm indicated in between. Physicians were asked to indicate where on the 100 mm line they thought the patient's RA activity fell (being instructed specifically, "[to] please indicate below how would you rate the patient level of rheumatoid arthritis activity.")

9.5.1.8.5. Patient-Reported Outcomes

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

A VAS was used to assess the patient's global assessment of disease activity. Each VAS consisted of a horizontal 100 mm line anchored at either end by opposite adjectives, reflecting on how the patient had been doing during the past week with respect to their RA symptoms (0 = very well; 100 = very poor). Patients were asked to indicate where on the 100 mm line they perceived their RA state to be (being instructed specifically, "[to] please indicate below how have you been doing during the past week, with respect to your rheumatoid arthritis symptoms.")

9.5.1.8.5.2. Patient Subjective Assessment of Pain - VAS

A VAS was used to assess the patient's global assessment of pain. Each VAS consisted 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 indicated where on the 100mm line they perceived their pain to fall (being instructed specifically, "[to] please indicate below the severity of your pain during the past week, related to your rheumatoid arthritis symptoms")

9.5.1.8.5.3. 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.[19] Specifically, the HAQ-DI assesses patient disability across 20 questions converging to 8 categories of activities: dressing and grooming, arising, eating, walking, hygiene, reach and grip. Patients were 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 were also captured. The scores were averaged by the total number of sections completed, to derive a disability index (DI).

9.5.1.8.5.4. 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).[20] Eleven activities were 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 can deal with anxiety and depression. In addition, patients were asked to rate, on an interval scale from 0-10 (0.5 increments), how bad their pain had been over the past week (pain tolerance score: 0 = no pain; 10 = pain as bad as it could be), as well as how well they were doing at the time of the assessment (global estimate score: 0 = very well, 10 = very poorly). A formal score (FS) was derived from the average of the 11 activity scores and was 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).

9.5.1.8.5.5. EuroQoL EQ-5D

The Euro-QoL (EQ-5D) questionnaire is a generic health status instrument that measures quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[21] The EQ-5D is a preference-based scale that rates each dimension with three severity levels: 1. (no problems), 2. (some problems), and 3. (maximum problems). Following that, each score can be weighted to account for population-specific preferences in health-care states. Individual health dimension 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 recorded the patient's self-rated health on a horizontal scale ranging from "worst imaginable health state" to "best imaginable health state."

9.5.1.8.5.6. 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:

Redacted

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 worked.
5. Degree to which health affected productivity while working.
6. Degree to which health affected regular (non-work) activities.

9.5.1.8.5.7. Treatment Satisfaction

Patient satisfaction with treatment was also 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).

9.5.1.8.5.8. Adherence to Treatment

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

9.5.1.8.5.9. 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.[22] 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 indicating severe fatigue.

9.5.1.8.5.10. RA Healthcare Resource Utilization Questionnaire.

The RA Healthcare Resource Utilization Questionnaire (RA-HCRU) is a 17-item scale designed to assess healthcare usage during the previous 3 months across many direct medical cost domains. The scale also assesses indirect costs associated with functional disability and impaired productivity at home and at work. This questionnaire was completed by the patient prior to any procedures being performed at the visit, when possible.

9.5.1.9. Safety

All adverse events were recorded and coded according to the MedDRA dictionary of terms version 25.0. and were included in the study database for analysis.

9.6. Bias

Not applicable.

9.7. Study Size

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

The primary endpoint of the current study was the proportion of patients who achieved CDAI remission or LDAS. According to data from long-term extension studies, at 6 months of treatment, 26.4% and 43.7% of patients had DAS-28-4-ESR <2.6 and <=3.2, respectively.[23] We anticipated comparable rates of CDAI remission and LDAS.

The 95% CI width for CDAI remission was ±3.9 with 500 evaluable patients, and the 95% CI width for CDAI LDAS was ±4.3. Both values were within acceptable precision levels. As a result, the study required approximately 500 evaluable patients with a 6-month follow-up period.

9.8. Data Management

Data collection was performed using an Electronic Data Capture (EDC) system designed specifically for the current study. The EDC system was based on a paper CRF that Pfizer approved. Edit checks were built into the EDC interface to ensure data quality and consistency. At the data management center, additional editing checks were performed. Edit checks generated queries, which the Investigator addressed, resulting in changes to the data. An audit trail tracks all data changes in accordance with FDA 21 CFR part 11 compliance. As necessary, study databases were with CDISC requirements.

As stated in Section 9.5, patient reported outcomes were obtained through self-administered questionnaires completed at the physician's office or home using a paper copy, or via a secure internet portal (electronic copy) as per the preference of the patients. For Patient reported outcomes, the EDC accommodated both patient interviews and direct data entry if the patient preferred to complete paper questionnaires. PRO data obtained via the internet was also integrated into the system.

The CRF is divided into the following sections:

1. Baseline/Screening:

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

2. Follow-Up Visits:

Follow-Up Visits 1 – 12 were labeled as such, with suggested time points of 3, 6 (primary endpoint), 9, 12, 18, 24, 30, and 36 months indicated. However, as previously stated, this was the recommended visit schedule, and the investigators were free to conduct the assessments based on their routine practice and judgment. As a result, investigators were instructed to use

the individual CRF visit sections for visits that occurred during the time period closest to the suggested time point. The date of the visit was clearly stated. There was a separate section for unscheduled visits. In the case of patient-reported outcomes, the EDC accommodated both patient interviews and direct data entry if the patient preferred to complete paper questionnaires. The system also integrated PRO data.

3. End of Study:

This was a separate section of the CRF that described the patient's final status in the study as "completed" or "withdrawn". The reason and date for patients' withdrawal from the study were reported.

The completed, signed, and dated case report forms for the enrolled patients were provided to the study data management center on an ongoing basis by the investigator for each patient enrolled in the study. Electronic signatures were used. For each unique instance when data was to be collected, a separate case report form was created; ONLY data specified in the protocol was collected and submitted to the study data management center.

9.8.1. Case Report Forms (CRFs)/Electronic Data Record

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

A CRF was required, and one was completed for each patient included. The completed original CRFs are Pfizer's sole property and will not be made available in any form to third parties, except authorized Pfizer representatives or appropriate regulatory authorities, without Pfizer's written permission. The Investigator ascertained that the CRFs were securely stored at the study site to prevent unauthorized third-party access.

The Investigator is responsible for collecting and reporting all clinical, safety, and laboratory data entered on CRFs and any other data collection forms (source documents), as well as ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when needed. The CRFs were signed by the Investigator or an authorized staff member attesting to the accuracy of the data contained on the CRFs. Any changes made to entries in the CRFs, or source documents are dated, initialed, and explained (if necessary), and the original entry is obscured.

In most cases, the source documents were the hospital or the physician's charts. In these cases, data collected on the CRFs matched these charts.

The CRF was used as the source document in some cases. In these cases, the source documents were available at the Investigator site and at Pfizer, clearly identifying those data recorded on the CRF and for which the CRFs serve as the source document.

9.9. Data Analysis

The detailed methodology for summary and statistical analyses of data collected in this study is documented in a Statistical Analysis Plan (SAP), which was dated, filed, and maintained by the sponsor and which was prepared prior to data closure and any data analyses. The SAP may have modified the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses are reflected in a protocol amendment.

9.9.1. General Considerations

The analyses conducted for the study were predominantly descriptive with several associations assessed with bivariate and multivariate methods. However, because no specific a-priori defined hypotheses were tested, multiplicity correction for the number of associations tested and outcomes assessed was unnecessary. To maintain the study's observational nature, the analyses were conducted on observed cases with no imputation for missing data, except as a sensitivity analysis for the analysis of CDAI remission at Month 6, where the method of last observation carried forward (LOCF) was used to carry forward any of the missing components.

Nonetheless, using mixed effects models assisted in compensating for missing observations, patient attrition, and unequal time intervals between assessments. The Full Analysis Set (FAS) included all enrolled patients who agreed to participate in the study. The Safety Analysis Set (SAS) and the FAS were the same.

9.9.2. Primary Analyses

The profile of patients initiated on treatment with tofacitinib is described with respect to the sociodemographic parameters, and baseline disease characteristics including severity, duration since diagnosis, prior treatments as well as comorbidities and concomitant medication use. The mean, median, standard deviation, and 95% confidence intervals of the mean and range (minimum and maximum) were reported for continuous variables while categorical variables were described by frequency distribution with 95% confidence intervals (CIs).

The primary effectiveness outcome measure for this study is the percentage of patients achieving CDAI ≤2.8 (remission) and CDAI ≤10 (LDAS) at 6 months. This is described by the proportion and 95% confidence interval of patients achieving these endpoints at 6 months. This assessment was conducted for the study cohort as a whole but also for meaningful strata defined according to the patient’s age, gender, duration of disease, prior treatment and presence of comorbidities.

The change from baseline to all time points in DAS28, CDAI, and SDAI was used to calculate effectiveness over the entire follow-up period. To produce least square mean estimates of the change in these outcome measures at each assessment, mixed effects, repeated measures, linear regression models adjusting for within patient variances, unequal follow-up periods, and missing observations were used. Furthermore, at quarterly intervals, the proportion of patients achieving therapeutic endpoints (CDAI remission, CDAI LDAS, DAS28 remission, DAS28 LDAS, SDAI remission, SDAI LDAS, and ACR20/50/70 response) will be reported. Kaplan Meier estimates of the survival function will be used to describe the time to the therapeutic endpoints and the cumulative proportion with the endpoint at specific time points.

9.9.3. Secondary Analyses

In the first secondary analysis, frequency distributions were used to evaluate patients' treatment patterns while on tofacitinib, as well as all subsequent changes in RA treatment regimens. The treatment patterns over time were described using decision node analysis, which evaluated the impact of treatment response and the incidence of adverse events on treatment changes.

For the 2nd secondary objective, adherence to treatment was ascertained based on missed doses of each RA-treatment regimen component, as reported by the patient. A patient was considered treatment adherent if they had completed 80% of the doses of each component of their prescribed treatment regimen. Adherence was assessed both by treatment regimen and overall. Bivariate and multivariate models were used to examine the relationship between treatment adherence and clinical or patient reported outcomes.

For the 3rd secondary objective, potential predictors of therapeutic response (as measured by CDAI remission and CDAI LDAS) were assessed with appropriate bivariate and multivariate methods. To assess the association of variables of interest on therapeutic response endpoints, the latter included linear regression, generalized linear models, multivariate logistic regression, Cox's proportional hazards models, and categorical regression.

For the 4th secondary objective, durability of response and tofacitinib persistence was assessed with the Kapan-Meier estimator of the survival function. Descriptive statistics were used to evaluate the reasons for discontinuation.

The 5th secondary objective was to assess the 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 using descriptive statistics that included estimates of the mean change with 95% confidence intervals. Statistical significance of changes over time was determined using paired comparisons, including the Student's t-test or the Wilcoxon signed-rank test, depending on the data distribution. Least Square Estimates of mean changes were calculated using mixed effects, repeated measures, and linear models, after adjusting for within-patient variances, unequal follow-up periods, and missing observations.

9.10. Quality Control

This study was submitted to central ethics committees or local ethics review boards, as required by individual sites, for review and approval. The study protocol, patient authorization for data use/disclosure, and patient questionnaires were all reviewed by the boards. The review boards were given a list of the participating physicians. No research activities were done before receiving approval from the Independent Ethics Review Boards.

Prior to enrolling in the study, the patient provided written consent for the use/disclosure of data. The Investigator informed the patient about the study and the requirements for completing the self-administered questionnaires. The patient authorization for data use/disclosure allowed the patient's data to be collected and used anonymously in the study.

Patient confidentiality was always maintained by employing randomly generated patient study identification numbers that identified each individual patient. On any page of the CRF or questionnaire, the name, initials, address, phone numbers, provincial insurance numbers, hospital record numbers, or any other identifier was NEVER collected/entered. Prior to inclusion in the study, all sites were evaluated for compliance with local medical practice requirements, such as the validation of the physician's license and specialization certificates. Furthermore, all site personnel were educated in Good Clinical Practices (GCP) and the requirements for data reporting, specifically adverse event reporting for the study. Sites with prior scientific research or clinical experience were selected.

Data management quality assurance involved monitoring of a random 25% sample of observations as well as implementing data edit checks and statistical assessments. To ensure that the patients enrolled in the study met the inclusion and exclusion criteria, 100% of the sites were reviewed.

9.11. Limitations of the Research Methods

This study's limitations were those inherent in single-armed cohort observational studies. In particular, the absence of a control or comparison group, a variable visit schedule, and missing data.

Concerning the lack of a control group, the study research question was limited to assessing the impact of tofacitinib treatment on study outcomes and did not include a comparative assessment. As a result, the single cohort design was appropriate for answering this specific question. Furthermore, the baseline assessment provided control values that represented the status of the disease parameters prior to and thus while not on tofacitinib treatment. Only descriptive data on safety were provided.

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. When assessments at defined time intervals were required, this created a problem with unequal duration of treatment and follow-up. The mixed effects repeated measures models used in this study assisted in addressing this

variability. The least square mean was used in these models to estimate the value of the variable at specific time points.

Missing data is another issue with observational studies. In the case of clinical data, every effort was made to recover any missing data points. The coding for most of the tools used in the current study provided imputation solutions for missing responses on questionnaire items. Furthermore, the pattern of missing data was evaluated to determine whether these data follow a missing at random pattern or whether there was a systematic non-random missing data distribution in order to assess the likelihood of bias.

9.12. Other Aspects

Not Applicable.

9.13. PROTECTION OF HUMAN SUBJECTS

9.13.1. Patient Information

All parties followed all applicable laws, including those requiring the implementation of organizational and technical safeguards to protect patient personal data. Such precautions included omitting patient names or other directly identifiable data in any reports, publications, or other disclosures unless required by applicable laws. Personal data was stored in encrypted electronic and/or paper form at the study site and password protected or secured in a locked room to ensure that only authorized study staff had it. The research site took appropriate technical and organizational precautions to ensure personal data could be recovered in a disaster. In the event of a potential personal data breach, the study site is responsible for determining whether a breach had occurred and, if so, notifying the appropriate parties as required by law.

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

The Investigator site kept a confidential list of patients who took part in the study, with each patient's numerical code linked to his or her identity. Pfizer maintains high standards of confidentiality and protection of patients' personal data in the event of data transfer, in accordance with the clinical study agreement and applicable privacy laws.

9.13.2. Patient Consent

Except where required by law, all parties ensured the protection of patient personal data and did not include patient names on any sponsor forms, reports, publications, or other disclosures. Pfizer maintained high standards of confidentiality and patient personal data protection in the event of data transfer. The informed consent documents, as well as any

patient recruitment materials, were in accordance with local regulatory and legal requirements, including applicable privacy laws.

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

The Investigator ensured that each study patient, or his/her legally acceptable representative, was fully informed about the study's nature and objectives, data sharing related to the study, and potential risks associated with participation, including risks associated with the processing of the patient's personal data. The Investigator also ensured that each study participant or his or her legally authorized representative was fully informed of his or her right to access and correct his or her personal data, as well as withdraw consent for the processing of his or her personal data.

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

The Investigator, or a person designated by the investigator, obtained written informed consent from each patient or the patient's legally acceptable representative, or legal guardian and the patient's assent, when applicable before any study-specific activity was performed unless a waiver of informed consent had been granted by an IRB/IEC. The Investigator retained the original of each patient's signed consent form.

9.13.3. Patient Withdrawal

Patients could have withdrawn from the study at any time, either voluntarily or at the discretion of the Investigator or sponsor, for safety, behavioral, or administrative reasons. If possible, every effort was made to document the subject outcome. The Investigator inquired about the reason for the withdrawal and followed up with the subject for any unresolved adverse events.

If the patient withdrew from the study and withdrew consent for future information disclosure, no further evaluations or data was collected. The sponsor was permitted to keep and use any data gathered prior to the withdrawal of consent.

Patients who stopped taking tofacitinib for any reason were eligible to continue participating in the study for the maximum follow-up period (3 years from initiation of treatment with tofacitinib). These patients were followed according to the assessment schedule provided in Table 2 and as per the physician's routine clinical care. All assessments were recorded and documented in the eCRF.

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

It was the Investigator's responsibility to obtain IRB/IEC approval for the study protocol, protocol amendments, informed consent forms, and other relevant documents (eg, recruitment advertisements), if applicable. All correspondence with the IRB/IEC was retained in the Investigator File. Copies of IRB/IEC approvals were forwarded to Pfizer.

9.13.5. Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as scientific purpose, value, and rigor, and adhered to generally accepted research practices as outlined in 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), and the 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 met local regulatory requirements.

9.13.5.1. Plans For Disseminating and Communicating Study Results

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 was aware of any new information which might have influenced the evaluation of the benefits and risks of a Pfizer product, Pfizer would have been informed immediately. Furthermore, the Investigator would have immediately notified Pfizer of any urgent safety measures taken by the Investigator to protect the study patients from any immediate hazard, as well as any serious violations of this NI study protocol that the Investigator became aware of.

10. RESULTS

Interim results describing efficacy outcomes to month 18, including the coprimary outcomes of CDAI–defined LDA and REM (month 6), and safety to month 36 have been previously published.[24] An exploratory safety interim analysis was also conducted in patients aged ≥50 years with ≥1 CV risk factor; this abstract was first published at the ACR Convergence 2021 conference, and a future publication is planned.[24]

Below are the final results of this study representing a maximum follow-up period of 36 months from the initiation of treatment with tofacitinib; a future publication disseminating these final results is also planned. Of note, there was a protocol amendment in December 2020 to reduce the sample size from 800 patients (as originally targeted) to 500 patients, which was deemed adequate to fulfill the study's objectives.

There were 505 patients that initiated tofacitinib at baseline and that were included in the full analysis set. Baseline characteristics are shown in Table 1 below. The mean age at baseline was 59.3 years and the mean duration since rheumatoid arthritis diagnosis was 10.2 years. The majority of patients were also female, white and bDMARD naive.

Table 1: Select Baseline Patient Demographic and Disease Characteristics*	
Characteristic	**Full Analysis Set¥ (n = 505)**
Demographic Information	
Age, years	59.3 (58.2, 60.4)
Duration since RA diagnosis, years (n = 490)[ł]	10.2 (9.3, 11.1)
Female, no. (%)	393 (77.8%)
White Race, no (%)	419 (83.0%)
Prior and concomitant RA medications, no. (%)	
bDMARD-naive	299 (59.2%)
Concomitant csDMARDs[$]	333 (66.0%)
Concomitant glucocorticoid use	99 (19.6%)
Comorbidity status, no (%)[‡]	
Chronic pulmonary disease/asthma	77 (15.2%)
Coronary artery disease	5 (1.0%)
Diabetes	63 (12.5%)
Hypertension	121 (24.0%)
Malignancy[**]	34 (6.7%)
Myocardial infarction	23 (4.6%)
Active tuberculosis	3 (0.6%)
AIDS	4 (0.8%)
Disease Characteristics[łł]	
Clinical Disease Activity Index (n = 473)	29.4 (28.3, 30.5)

*Values are the mean (95% confidence interval) unless indicated otherwise.
¥ Defined as all enrolled patients providing consent to participate in the study and having started tofacitinib ≤28 days prior to baseline.

Redacted

ł Calculated among patients with known duration since RA diagnosis.
$ Patients may have reported >1 concomitant csDMARD.
‡ Any prior history of chronic pulmonary disease/asthma, malignancy, myocardial infarction, and AIDS is reported.
**Includes preferred terms: basal cell carcinoma, breast cancer, cholangiocarcinoma, chondrosarcoma, colon cancer, endometrial adenocarcinoma, invasive ductal breast carcinoma, lip squamous cell carcinoma, lung neoplasm malignant, malignant melanoma, osteosarcoma, prostate cancer, renal cancer, skin cancer, squamous cell carcinoma of skin, and uterine leiomyoma. A given patient could have had more than one condition.
Ł Calculated among patients with available data per routine care.

At month 6 (primary endpoint), 192/315 (61.0%) and 56/315 (17.8%) of patients were in CDAI-defined LDA and remission, respectively. At month 36 (last scheduled follow-up visit), 66/93 (71.0%) and 33/93 (35.5%) of patients were in CDAI-defined LDA and remission, respectively. Overall, CDAI-defined LDA and remission rates were generally maintained or numerically increased over time, demonstrating the effectiveness of tofacitinib for moderate to severe RA.

In total, 507 patients were included in the safety analysis set. Safety outcomes to month 36 are listed in Table 2 below. There was a total of 6 deaths reported in the study. The most frequent treatment-emergent adverse events (≥3%) were upper respiratory tract infection, hypertension, and urinary tract infection. Incidence density rates for treatment-emergent adverse events of special interest (HZ, MACE, Cancer and VTE) were infrequent.

Table 2: Safety Outcomes to Month 36*	
Patients with event	**Safety Analysis Set[¥] (n = 507)**
Treatment-emergent adverse events	354 (69.8%) [129.5]
Serious adverse events	69 (13.6%) [11.46]
Study discontinuations due to adverse events	95 (18.7%) [13.51]
Deaths	6 (1.2%) [1.02]
Most frequent treatment-emergent adverse events (≥3%)	
Upper respiratory tract infection	31 (6.1%) [3.86]
Hypertension	24 (4.7%) [2.72]
Urinary tract infection	23 (4.5%) [3.4]
Headache	22 (4.3%) [2.5]
Diarrhea	19 (3.7%) [2.16]
Pneumonia	17 (3.4%) [1.93]
Nausea	16 (3.2%) [1.93]
Treatment-emergent adverse events of special interest	
Serious Infection	21 (4.1%) [2.95]
Herpes Zoster (nonserious/serious)[$]	13 (2.6%) [1.48]
Vaccinated	5 (2.2%) [1.17]
Unvaccinated	5 (2.5%) [1.5]
Major adverse cardiovascular events	6 (1.2%) [0.68]
Malignancies (excluding nonmelanoma skin cancer)[**]	14 (2.8%) [1.7]
Nonmelanoma skin cancer	4 (0.8%) [0.57]

Table 2: Safety Outcomes to Month 36*	
Hepatic events	9 (1.8%) [1.13]
Venous thromboembolism	4 (0.8%) [0.57]
Deep vein thrombosis	2 (0.4%) [0.23]
Pulmonary embolism	3 (0.6%) [0.34]
Gastrointestinal perforation	0

* Values are the number of patients with events (%) [IDR]. IDR = Incidence density rate defined as the number of TEAEs over the sum of the length of time each patient at risk contributed to the study (expressed per 100 person -years).
¥ SAS is defined as all enrolled patients providing consent to participate in the study.
$ Vaccinated refers to patients receiving the herpes zoster (HZ) vaccine. Frequency and IDR of HZ in vaccinated and unvaccinated patients calculated in those patients with corresponding known vaccination status at baseline.
**Includes preferred terms: Acute myeloid leukemia, adenocarcinoma, bladder cancer, cholangiocarcinoma, malignant melanoma, malignant neoplasm progression, malignant pleural effusion, myeloproliferative neoplasm, neuroendocrine tumor, polycythemia vera, prostate cancer, small cell lung cancer metastatic, squamous cell carcinoma. A given patient could have had more than one condition.

11. OTHER INFORMATION

Please note that discrepancies between the published interim analysis and the final analysis in this CSR are due to the fact that the investigators provided additional data in the 1.5 years that elapsed between the 2 analyses (ie, the database was not locked at the time of the interim analysis that informed the manuscript).

Portions of this study were conducted during the COVID-19 pandemic. As such, many clinical sites were closed to in-patient visits from March to December 2020. After December 2020, patients could continue with remote visits or present for in-clinic assessments. Specific details of issues reported by sites especially in 2020 may be found in Xeljanz_Covid Status_final.xlsx in Appendix 8.

12. SUMMARY CONCLUSION

Overall, the results of this study indicate that tofacitinib provides early and sustained improvement of disease signs and symptoms in Canadian patients with RA, complementing other real-world data sets. The safety profile is consistent with previously published post marketing- and clinical data. These results further substantiate the established tofacitinib safety profile, provide insight into expected effectiveness outcomes, and inform real-world outcomes for patients with RA.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
Number 1		19-JAN-2022	Protocol
Number 2		29-AUG-2022	Statistical Analysis Plan
Number 3		14-DEC-2022	Tables, Listings and Figures
Number 4		01-MAY-2023	Abstract: *Canadian Non-Interventional Study of Xeljanz in Rheumatoid Arthritis* (CANTORAL).
Number 5		07-DEC-2020	Additional Documents: Xeljanz_Covid Status_final.xlsx

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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