NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Treatment Patterns and 6 and 12-Month Effectiveness of Tofacitinib in the Corrona Rheumatoid Arthritis Registry
Protocol number	A3921379
Protocol version identifier	2.0
Date	18 April 2022
Active substance	L04AA29
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	To describe treatment patterns and effectiveness of tofacitinib initiators in the Corrona rheumatoid arthritis (RA) Registry. • To describe the demographics, clinical characteristics, and treatment patterns of tofacitinib initiators at time of initiation including stratification by index year to identify changes across time To estimate 6-month and 12 effectiveness in tofacitinib initiators.
Author	PPD PPD PhD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BMI	body mass index
CABG	coronary artery bypass grafting
CDAI	Clinical Disease Activity Index
CHF	congestive heart failure
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	cardiovascular
DAS	Disease Activity Score
DAS28	Disease Activity Score in 28 joints
DMARD	disease-modifying antirheumatic drug
DVT	deep vein thrombosis
EQ-5D-5L	European quality of life-5 dimensions
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
ID	identifier
IL	interleukin
IRB	Institutional Review Board
JAK	Janus Kinase

Abbreviation	Definition
LDA	low disease activity
LLC	limited liability company
mACR	modified American College of Rheumatology (*score*)
mHAQ	modified Health Assessment Questionnaire
MI	myocardial infarction
MTX	methotrexate
NIS	non-interventional study
NSAID	nonsteroidal anti-inflammatory drug
PCI	percutaneous coronary intervention
RA	rheumatoid arthritis
SAP	Statistical Analysis Plan
TIA	transient ischemic attack
TNF	Tumor Necrosis Factor
TNFi	tumor necrosis factor inhibitor
US	United States
VAS	visual analog scale

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD , PhD	PPD	PPD	PPD
PPD PhD	PPD	PPD	PPD
PPD MD, MPH	PPD	PPD	
PPD Sc.D.	PPD	PPD	
PPD MSc	PPD	PPD	

4. ABSTRACT

Not Applicable.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 administrative	18 April 2022	6 Milestones	Milestones were updated.	The planned milestones were adjusted to align with information in sponsor's internal systems.

6. MILESTONES

Milestone	Planned date
Start of data collection	31 January 2021
End of data collection	30 November 2021
Final study report	30 October 2022

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Western populations.[1] RA is characterized by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities. These patients are also treated with multiple classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease modifying antirheumatic drugs (DMARDs) including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral Janus Kinase (JAK) inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[2,3,4] Tofacitinib reduces the production of proinflammatory mediators[5] by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA. Unlike biological therapies, such as tumor necrosis factor (TNF) inhibitors and anti-IL-6 receptor monoclonal antibodies that markedly inhibit 1 cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines.

Previous work in the Corrona registry described the early experience of tofacitinib initiators. As tofacitinib has been on the market since 2012, it is possible that there has been a shift in use of tofacitinib as an earlier line of therapy. Therefore, there is a need to update the analyses of treatment patterns and effectiveness. This query will inform the design of future comparative effectiveness analyses.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe treatment patterns and effectiveness of tofacitinib initiators in the Corrona RA Registry. Accordingly, we will:

- Describe the demographics clinical characteristics, and treatment patterns of tofacitinib initiators at the time of initiation including stratification by index year to identify changes across time.

- Estimate 6-month and 12-month effectiveness in tofacitinib initiators.

9. RESEARCH METHODS

9.1. Study Design

To meet the study objectives, an observational retrospective cohort study will be conducted using patients enrolled in the Corrona RA Registry initiating tofacitinib on or after November 2012. NOTE: Initiation is defined as first ever use of tofacitinib. Initiators will also be required to have initiated tofacitinib at a Corrona visit (enrollment or follow-up), have Clinical Disease Activity Index (CDAI) measured at baseline and have a 6-month follow-up visit and CDAI measured at the 6-month follow-up visit.

For further details, please refer to the detailed Statistical Analysis Plan (SAP) included as a stand-alone document.

9.2. Setting

The Corrona RA Registry is a prospective, multicenter, observational disease-based registry launched in 2001. This registry contains clinical data (eg, disease activity scores, laboratory results, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases. The current Corrona dataset includes 189 private and academic active clinical sites with over 817 providers throughout 42 states in the US. This registry collects data from both the providers and the patients at the time of a regular office visit. Corrona has enrolled over 54,000 patients with RA. The collection of data from Corrona represents over 195,750 patient years of data.

To be included in the Corrona RA Registry, patients must be at least 18 years of age and have a diagnosis of RA by a rheumatologist.

9.2.1. Inclusion Criteria

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

1. Enrolled in the Corrona RA Registry and initiated tofacitinib on or after November 2012.

2. Initiate tofacitinib (defined as first ever use of tofacitinib) at the Corrona enrollment visit or at a Corrona follow-up visit from November 2012 onward.

3. Have CDAI measured at baseline.

4. Have at least a 6-month follow-up visit and CDAI measured at the 6-month follow-up visit.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

Objective 1 (Demographics, clinical characteristics, treatment patterns):

Demographic/socioeconomic characteristics.

- Age, sex, race, education, work status, insurance.

Lifestyle.

- Weight, body mass index (BMI), smoking status.

History of comorbidities.

- History of cardiovascular (CV) disease (include the following: myocardial infarction [MI], stroke, acute coronary syndrome, coronary artery disease, congestive heart failure [CHF], revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, hypertension, other CV, deep vein thrombosis [DVT] and transient ischemic attack [TIA]).
- History of malignancy (breast cancer, lung cancer, lymphoma, skin cancer, other cancer).
- History of hypertension, diabetes, osteoporosis, fibromyalgia, and depression.

Clinical Characteristics and Assessments.

- Duration of disease.
- Age of onset.
- CDAI (continuous, categorical).
- Tender joint count (28).
- Swollen Joint count (28).
- Physician global assessment (0-100).
- Disease Activity Score (DAS)28/Erythrocyte Sedimentation Rate (ESR).

- Patient global assessment (0-100).
- Patient reported pain (0-100).
- Patient reported fatigue (0-100).
- Heath Assessment Questionnaire (HAQ) (0-3).
- Modified Heath Assessment Questionnaire (mHAQ).
- Morning stiffness (yes/no).
- Morning stiffness duration (hours).

Treatment Characteristics and Medication history.

- Concomitant therapies (Monotherapy, Combination with: methotrexate (MTX) alone, other conventional synthetic disease modifying antirheumatic drug (DMARD), conventional synthetic disease modifying antirheumatic drug (csDMARD), MTX + other csDMARD).
- Number of prior biologics/JAK inhibitors (TNFi: Enbrel, Humira, Remicade, Cimzia, Simponi; non-TNFi: Orencia, Actemra, Rituxan, Kineret, Kevzara; JAKis: Olumiant, Rinvoq).
- Number of prior csDMARDs (MTX, Arava, Azulfidine, Plaquenil, Cyclosporine, Imuran, Minocin, Cuprimine, Ridaura).
- Steroid use:
  - History of prednisone use (yes/no);
  - Current prednisone use (yes/no);
  - Prednisone dose (in users).

Reason for initiation of tofacitinib:

- Number of patients with at least 1 initiation reason reported;
- Total number of reasons;
- % Safety, % Effectiveness, % Cost/Insurance, % Other reasons.

Reason for Discontinuation of tofacitinib (Among those who discontinue at or before 6-months):

- Total number (%) of discontinuations;
- Number of patients with at least 1 reason reported;
- Total number of reasons;
- % Safety, % Effectiveness, % Cost/Insurance, % Other reasons.

Objective 2 (6-month effectiveness and 12-month effectiveness).

Primary outcomes:

- Achievement of low disease activity (LDA) (CDAI ≤10).

Secondary outcomes:

- Achievement of remission (CDAI ≤2.8);
- Δ CDAI;
- Δ HAQ;
- Δ patient pain;
- Δ patient fatigue;
- Achievement of modified American College of Rheumatology (mACR)20/50/70;
- Achievement of LDA or remission defined by DAS28(ESR) (<= 3.2);
- Achievement of "mild pain", defined as ≤20mm on 100 visual analog scale (VAS).

Additionally, all variables will be stratified in 2 year increments (eg, 2012-2014, 2015-2017, 2018-2020).

9.4. Data Sources

Patients are enrolled in the Corrona RA Registry during regularly-scheduled office visits. Upon enrollment, providers complete a set of Enrollment Questionnaires, including a 28 joint count on RA patients. Patients also complete an Enrollment Questionnaire, which captures several data elements, including the Health Assessment Questionnaire (HAQ) and the European Quality of Life-5 Dimensions (EQ-5D-5L). Both patient and provider reported

disease activity measures obtained at each visit are captured in Corrona; this includes tender and swollen joint counts (28 joint counts), patient and physician global disease assessment, patient pain assessment and HAQ scores. Providers and patients complete follow-up Questionnaires approximately every 6 months. During the course of a regularly-scheduled office visit, the provider performs assessments as mandated on the Corrona Provider Questionnaires with recording of pertinent data. Results from specific laboratory tests are included, but not mandated. Likewise, during regularly-scheduled office visits, patients are asked to complete Questionnaires designed to capture information ranging from their general demographics and experience with prescription drug use to an overall global assessment of their disease. Early follow-up visits occur and questionnaires are completed whenever a registry patient is being prescribed or receiving a first dose of a new (different) *eligible medication* at a routine office visit. Eligible medications are biologics, biosimilars, and JAK inhibitors FDA-approved for the treatment of RA. The next regularly scheduled visit is calculated from the previous visit. Data are collected on patients for as long as they consent to remain in the study.

9.5. Study Size

This is a descriptive study thus sample size calculations are not applicable.

9.6. Data Management

All statistical analyses will be performed using STATA Version 15.1 (StataCorp, LLC, College Station, TX). All analyses will be carried out under the direction of Dr. Ying Shan of Corrona.

9.6.1. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Corrona agrees to keep all study-related records, including safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by Corrona according to local regulations or as specified in the vendor contract, whichever is longer. Corrona must ensure that the records continue to be stored securely for so long as they are retained.

If Corrona becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Corrona and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data Analysis

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

9.8. Quality Control

Corrona or its designee monitors the conduct of the registry at each investigative site. Monitoring is primarily conducted remotely. Onsite monitoring visits are conducted once every 3 years, as needed, or as requested. A review of registry records including, but not limited to, the informed consent forms, Questionnaires, original source documents such as supporting medical records and office notes, subject study files, and any other registry documentation is conducted in accordance with applicable regulatory guidelines and the protocol.

Quality control checks are built into the on-screen data entry systems in an attempt to reduce queries and provide immediate feedback to the investigator regarding inadvertent omissions and out of range or noncompliant values. Changes made at any time are recorded in an audit trail that includes the date, time, and electronic ID of the person making the change.

Corrona will address and resolve discrepancies by requesting clarifications and/or missing data from the investigator as needed. Each investigator is expected to designate a point of contact to address such inquiries and to promptly address and resolve issues. Representatives or designees from Corrona reserve the right to perform random or systematic audits of Corrona Questionnaires at an investigator's site in order to assess the accuracy of the reported data compared to the information contained in the original medical records.

9.9. Limitations of the Research Methods

The Corrona RA Registry includes a sample of adults with RA that are not necessarily representative of all adults with RA in the US. In particular, these are RA patients with clinical visits with rheumatologists. Patients are recruited by rheumatologists who are required to indicate diagnosis upon enrollment of the patient into the Corrona RA Registry. In addition, history of medication use prior to enrollment is derived from what is reported by patients and their current rheumatologist within the registry. Since registry reporting is not based on a fixed visit schedule, exact timing of visits to fit 6, 12, 24, or 36 months of post index data is not available for all patients so windows of time are used to determine eligible visits. The "cause" of visits is not captured, although the assumption can likely be made that the rheumatologist visit is "RA related." The registry captures provider reported prescribing; there are no measures of patient adherence.

As this is a real-world study, missing data could be expected for demographic characteristics (eg, age, etc.); however, the number of patients with missing data is expected to be very small. CCI [redacted]

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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 party responsible for collecting data from the participant 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.

13. REFERENCES

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005;4(3):130-6.

2. Walker JG, and Smith MD. The Jak-STAT pathway in rheumatoid arthritis. J Rheumatol, 2005;32(9):1650-3.

3. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007; 7(6):429-42.

4. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011; 365(23):2205-19.

5. Meyer DM, Jesson MI, Li XO, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm 2010; 7:41.

14. LIST OF TABLES

Table shells are included in the SAP.

15. LIST OF FIGURES

Figures are included in the SAP.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Date	Title
1	09 September 2020	Treatment Patterns and 6 and 12-Month Effectiveness of Tofacitinib in the Corrona Rheumatoid Arthritis Registry

ANNEX 2. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

Document Name:	A3921379 Non-Interventional Study Protocol Amendment 1 (clean) 18 Apr2022
Document Title:	A3921379 Non-Interventional Study Protocol Amendment 1 (clean) 18 Apr2022

Signed By:	Date(GMT)	Signing Capacity
PPD	21-Apr-2022 18:44:52	Final Approval