NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Comparative Effectiveness of Tumor Necrosis Factor (TNF) inhibitors and Tofacitinib, overall, by line of therapy and by combination therapy
Protocol Number	A3921389
Protocol Version Identifier	2.0
Date	18 April 2022
Active Substance	L04AA29
Medicinal Product	Xeljanz (tofacitinib immediate release (IR) and extended release (XR))
Research Question and Objectives	The objectives of this study are as follows: 1. To compare the effectiveness of tofacitinib and TNFs at 6 months and 12 months, overall and stratified by mono- and combination therapy. 2. To investigate the association between line of tofacitinib therapy and response at 6 and 12 months.
Author	PPD PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive Protein
csDMARD	Conventional Synthetic Disease Modifying Antirheumatic Drug
CV	Cardiovascular
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
ESR	Erythrocyte Sedimentation Rate
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HEOR	Health Economics and Outcomes Research
ID	Identification
IEC	Independent ethics committee
IL	Interleukin
ILD	Interstitial Lung Disease
IR	Immediate Release
IRB	Institutional Review Board
JAK	Janus Kinase
mACR	Modified American College of Rheumatology
MD	Doctor of Medicine
mHAQ	Modified Health Assessment Questionnaire
MI	Myocardial Infarction
MOA	Mechanism of Action
MTX	Methotrexate
NI	Non-interventional
NSAID	Nonsteroidal Anti-inflammatory Drug
PASS	Post Authorization Safety Study
PCI	Percutaneous Coronary Intervention
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SD	Standard Deviation
TIA	Transient Ischemic Attack

Abbreviation	Definition
TNF	Tumor Necrosis Factor
US	United States
VAS	Visual Analogue Scale
XR	Extended Release

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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 (csDMARDs) 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-interleukin (IL)-6 receptor monoclonal antibodies that markedly inhibit one 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.

This study will help demonstrate if there has been a shift in the treatment landscape between 2016 (time of the last Corrona registry analysis of this type) and 2020, in regards to tofacitinib use in earlier lines of therapy and use as monotherapy. We hope to gain a more current understanding of comparative effectiveness of the two mechanisms of action (MOA) in clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

There are two primary objectives for this study:

1. To compare the effectiveness of tofacitinib and TNFs at 6 months and 12 months, overall and stratified by mono- and combination therapy.

2. To investigate the association between line of tofacitinib therapy and response at 6 and 12 months.

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. Patients receiving tofacitinib or TNF after failing a csDMARD (2^{nd}-4^{th} line patients) will be included to assess the comparative effectiveness of tofacitinib and TNF (stratified by monotherapy and combination therapy) as well as the impact of line of therapy on the effectiveness of tofacitinib.

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. Patients are excluded from the registry if they are unable or unwilling to provide informed consent. The inclusion/exclusion criteria for this particular analysis are described in Sections 9.2.1 and 9.2.2.

9.2.1. Inclusion Criteria

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

1. RA patients in Corrona initiating tofacitinib OR a TNF biologic (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol) after 06 November 2012 (market approval of Tofacitinib) during follow-up in Corrona with no prior use of tofacitinib. Only the patient's first initiation after 06 November 2012 will be included in the analysis.

2. Have a 6 and/or 12-month follow-up visit (with +/-2 month window).

3. Have Clinical Disease Activity Index (CDAI) measures at baseline and at the follow-up visit.

9.2.2. Exclusion Criteria

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

1. Patients who have not failed methotrexate (MTX) or another csDMARD (ie, 1st line initiators).

9.3. Variables

Patient characteristics at baseline:

- Gender, age, race, and ethnicity.
- Duration of RA (Age at onset).
- Comorbidity history:
    - Cardiovascular disease: Myocardial Infarction (MI), stroke, Transient Ischemic Attack (TIA), 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, other cardiovascular (CV) events, carotid artery disease;
    - Hypertension;
    - Chronic Obstructive Pulmonary Disease (COPD);
    - Asthma;
    - Interstitial Lung Disease (ILD)/Pulmonary Fibrosis;
    - Diabetes mellitus;
    - Serious infections;
    - Cancer: lung cancer, breast cancer, lymphoma, skin cancer (melanoma, basal, squamous), and other cancer;
    - Thromboembolic events: deep vein thrombosis, peripheral arterial thromboembolic and pulmonary embolism.
- C-reactive Protein (CRP).
- Erythrocyte Sedimentation Rate (ESR).
- Serum positive (Rheumatoid factor/Cyclic Citrullinated Peptide (CCP)).

- Smoking status.
- Work status.
- Height, weight, and body mass index (BMI).
- Insurance (patient reported).
- Prednisone use.

Disease activity measures:

- Physician reported:
  - CDAI;
  - MD global assessment;
  - Tender and swollen joint count (28);
  - Disease Activity Score (DAS) 28;
  - Modified American College of Rheumatology (mACR) 20/50/70.
- Patient reported:
  - Health Assessment Questionnaire (HAQ);
  - mHAQ;
  - Patient global assessment;
  - Patient pain VAS;
  - Patient fatigue VAS;
  - Morning stiffness.

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). 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 six 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 certain 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 Food and Drug Administration (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

We used significance level of 0.05 (p=0.05), 80% power (80% rejecting the null hypothesis), and two independent sample equal-variance t-test for power calculation. The null hypothesis is no difference in mean of CDAI measure between treatment groups.

Previous study using Corrona RA registry data shown standard deviation (SD) is about 14 which will be used to estimate the sample size. Using software, it is estimated that 342 subjects would be needed in each of the treatment groups in order to detect a statistically significant difference in mean CDAI of 3 between the two groups. Increasing the mean of CDAI difference to 6, would require 87 patients in each group.

Current feasibility within the registry is 1,383 tofacitinib patients (588 monotherapy patients and 795 combination patients) so the necessary sample size has been achieved.

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

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 three 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. Corrona and its designees are required to maintain the confidentiality of all subjects during and after an on-site monitoring visit.

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 identification (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 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. With multiple time points, some visits may have missing CDAI 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 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

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Date	Title
1	09 September 2020	Comparative Effectiveness of TNFs and tofacitinib, overall and by combination therapy
2	09 September 2020	Comparative Effectiveness of Tofacitinib by Line of Therapy

ANNEX 2. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

Document Name:	A3921389 Non Interventional Study Protocol Amendment 1 (clean) 18 Apr2022
Document Title:	A3921389 Non Interventional Study Protocol Amendment 1 (clean) 18 Apr2022

Signed By:	Date(GMT)	Signing Capacity
PPD	21-Apr-2022 18:45:17	Final Approval