NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Tofacitinib Use in Rituximab-Experienced RA Patients
Protocol number	A3921420
Protocol version identifier	3.0
Date	13 January 2023
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz
Research question and objectives	To characterize the use of tofacitinib after use of rituximab in patients with RA in a real-world setting. • Primary: Describe the characteristics of tofacitinib initiators with a history of rituximab exposure, at time of tofacitinib initiation. • Secondary: Describe 6-month outcomes for tofacitinib initiators with a history of rituximab exposure.
Author	PPD Pfizer, Inc PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AHRQ	Agency for Healthcare and Research Quality
CDAI	Clinical Disease Activity Index
CDM	Clinical Data Management
CRF	case report form
CSA	Clinical study agreement
DCT	Data collection tool
EDC	Electronic Data Capture
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
RA	rheumatoid arthritis
RMP	Registry Monitoring Plan
SAP	Statistical Analysis Plan
TB	tuberculosis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD , MD	PPD	PPD	PPD
PPD , MD	PPD	PPD .	PPD
PPD ,	PPD	PPD	PPD
PPD , PhD	PPD	PPD	PPD
PPD PhD	PPD	PPD	PPD
PPD ScD	PPD	PPD	PPD

4. ABSTRACT

Not Applicable.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0		Section 9.6.2.	Not applicable, however: To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, CorEvitas agrees to keep all study-related records. The records should be retained by CorEvitas according to local regulations or as specified in the vendor contract, whichever is longer. CorEvitas must ensure that the records continue to be stored securely for so long as they are retained.	Administrative change: Section 9.6.2. should be deleted for studies with no human review of unstructured data as per CT24 WI-GL02-RF02
1.0	August 4th Nov 4th	Section 3.	Job title update and change of 1 Pfizer Principal Investigator Change of 1 Pfizer Principal Investigator	Administrative change: Job position changed, and 1 Pfizer Principal Investigator change
1.0	Nov 11th	Section 6	Start of data collection	
2.0	13 January 2023	Section 9.1	Language added in the Study Design section.	To clarify that the data analyzed by Pfizer already exists in the CoreVitas registry.
2.0	13 January 2023	Section 3	Added 1 Pfizer Principal Investigator to the list	Administrative change: 1 Pfizer Principal Investigator added.

6. MILESTONES

Milestone	Planned date
Start of data collection	11 Nov 2022
End of data collection	31 December 2022
Final study report	30 November 2023

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, immune-mediated, inflammatory disease affecting many joints, including those in the hands and feet. RA has a wide global presence and is estimated to affect 0.5 to 1% of the general population.[1]

Some authorities in emerging markets prioritize use of rituximab in treatment of RA because of its relatively lower cost and availability in hospitals. Newer molecules (eg, tofacitinib) usually do not have clinical trial data in rituximab-experienced RA patients. There is a need to understand the use and effectiveness of tofacitinib in the real-world, to provide information for healthcare providers in these emerging market settings.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to characterize the use of tofacitinib after use of rituximab in patients with RA in a real-world setting.

8.1. Primary Objective(s)

Describe the characteristics of tofacitinib initiators with a history of rituximab exposure, at time of tofacitinib initiation.

8.1.1. Hypotheses

This is a descriptive study without an a priori hypothesis.

8.2. Secondary Objective(s)

Describe 6-month outcomes for tofacitinib initiators with a history of rituximab exposure.

8.2.1. Hypotheses

This study is descriptive with no formal hypothesis, but it is anticipated that outcomes will improve over the 6-month time period.

8.3. Exploratory Objective(s)

None.

9. RESEARCH METHODS

9.1. Study Design

This will be a retrospective analysis of a prospective observational cohort using the CorEvitas RA Registry. This study will evaluate existing data that was previously captured within the registry at the time of study start for analysis, which is specified in the protocol below. This study will describe demographic and clinical characteristics of adult patients with RA initiating tofacitinib with a history of rituximab use. This study will also describe changes in clinical and patient reported outcomes over time. The index date will be defined as the date of tofacitinib initiation at or after enrollment in the registry; initiation is defined as first ever use of tofacitinib.

9.2. Setting

The CorEvitas RA Registry is an ongoing longitudinal clinical registry that was established in 2001. Longitudinal follow-up data is collected from both patients and their treating rheumatologist during routine clinical encounters using the CorEvitas RA Registry questionnaires. These questionnaires collect data on patient demographics, disease duration, medical history (including all prior and current treatments for RA), smoking status, alcohol use, cannabis use, disease activity, patient reported outcome measures, disease characteristics, comorbidities and adverse events, infections, hospitalizations, and other targeted safety outcomes. Blood collection, endoscopy and other diagnostic tests are not required for participation; however, relevant standard of care laboratory and imaging results are reported when available.

9.2.1. Inclusion Criteria

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

Objective 1 Inclusion Criteria:

- Enrolled in the CorEvitas RA Registry and initiated tofacitinib on or after November 2012.
- Initiate tofacitinib (defined as first ever use of tofacitinib) at Registry enrollment visit or at a Registry follow-up visit after November 2012.
- Have prior use of rituximab.
- Have Clinical Disease Activity Index (CDAI) measured at baseline.

Objective 2 Inclusion Criteria:

- Enrolled in the CorEvitas RA Registry and initiated tofacitinib on or after November 2012.

- Initiate tofacitinib (defined as first ever use of tofacitinib) at Registry enrollment visit or at a Registry follow-up, after November 2012.
- Have prior use of rituximab.
- Have CDAI measured at baseline and appropriate follow-up visit.
- Have any of the following:
    a. A 6-month follow-up visit with persistent use of tofacitinib.
    b. A 6-month follow-up visit with a tofacitinib discontinuation occurring prior to the 6-month visit, with no new biologic systemic drug used prior to the 6-month study visit.
    c. A study visit at or prior to the 6-month window with a tofacitinib discontinuation occurring at the study visit.
    d. (Sensitivity analysis only) Any tofacitinib discontinuation prior to the 6-month study window.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study (ie, for either Objective 1 or Objective 2).

9.3. Variables

Please refer to Statistical Analysis Plan (SAP).

9.4. Data Sources

The CorEvitas RA Registry is an observational registry and therefore collects patient and physician data at patient clinical visits with the rheumatologist. Unlike clinical studies, visits are not timed at exact uniform time periods. Thus, time period definitions for the current study need to accommodate this unique feature of observational registries.

"Index visit" is defined as the visit when tofacitinib was initiated, ie, first ever use of tofacitinib. Only initiations at or after enrollment into the Registry are included.

A "6-month" follow-up is defined as a clinical visit to the rheumatologist 3 to 9 months from the enrollment visit in accordance with the Registry protocol.

Initiations between visits

If tofacitinib is initiated between visits, then baseline variables from the visit prior to the initiation of tofacitinib will be used, as long as the prior visit occurred within four months of the tofacitinib start date. Initiations that occur between visits and where the prior visit is greater than 4 months from the initiation will be excluded.

Multiple visits in the same time window

Given the observational nature of the data, it is possible for patients to have more than one visit that falls within a given follow-up period's allowed time window. For example, a patient might have a visit with outcomes collected at 5 months and then 9 months, both of which would qualify as a "6-month" visit. In that case, the latest visit will be chosen as the "6-month" follow-up since we would like to consider the longest follow-up possible. The exception to this rule is if values for the primary outcome are unavailable for the latest visit, in which case the first visit will be used instead.

Discontinuations prior to follow-up

For patients who discontinued tofacitinib prior to follow-up and who do not switch to another drug, the clinical or patient-reported outcome value at the follow-up visit will be used. If a patient discontinues and switches to another biologic/tsDMARD, the value at the switch visit, if available, will be used; otherwise, the value will be set to missing.

9.4.1. Exposure

The exposure of interest in this study is first ever tofacitinib use after any prior rituximab use. All patients in the study will be classified as exposed.

9.4.2. Study Outcomes

Objective 1: Characterize Patients at tofacitinib initiation

Primary Outcome:

- Objective 1 is to characterize patients at tofacitinib initiation. All variables as outlined in the SAP will be summarized for this aim.

Objective: Describe change in 6-month outcomes.

Primary Outcome:

- Change in CDAI.

Secondary Outcomes:

- Achievement of Minimum Clinically Important Difference (MCID):[2] (change in CDAI from baseline to follow-up =ΔCDAI).

CDAI at Index	MCID to Define Improvement in Disease Activity at FU Visit If ΔCDAI>MCID
Low: CDAI≤10	1
Moderate: 10>CDAI≤22	6
High>22	12

- Change in HAQ.
- Change in patient pain.
- Change in patient fatigue.
- Number (%) of tofacitinib discontinuations prior to or at 6-month visit.

9.5. Study Size

As of the 31 March 2021 data cut, there were 390 tofacitinib initiators with history of rituximab use. Of these:

- ~376 have baseline CDAI information.
- Line of therapy (and baseline CDAI) is available for ~373, of whom n=8 (2%) are 3rd line and n=365 (98%) are 4th line.
    - Note: since population is restricted to those with prior rituximab use, 3rd line use reflects patients with prior rituximab use only 4th line reflects patients with one or more prior biologic in addition to rituximab.
- ~107 have CDAI information at baseline and 6 months follow-up.

9.6. Data Management

All statistical analyses will be conducted using Stata Release 16 (StataCorp LLC, College Station TX) and/or R Version 4.0.3 (The R Foundation for Statistical Computing, Vienna Austria).

9.6.1. Case Report Form (CRFs)/Data Collection Tool (DCTs) Data Record

Not Applicable, however:

- All study data exist as structured data by the time of study start.
- The conversion of unstructured data to structured data during the implementation of the protocol is performed solely by a computer using automated/algorithmic methods, such as natural language processing.

9.6.2. Record Retention

Not Applicable, however:

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, CorEvitas agrees to keep all study-related records. The records should be retained by CorEvitas according to local regulations or as specified in the vendor contract, whichever is longer. CorEvitas must ensure that the records continue to be stored securely for so long as they are retained.

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

Data quality is controlled, monitored, and managed according to the CorEvitas Master Registry Monitoring Plan (RMP). All study personnel must complete standardized protocol training prior to initiating data collection. Each Investigator is also required to designate one staff member as the primary Registry Coordinator responsible for addressing data clarifications requests from CorEvitas in a timely manner. All data collectors in the field have continuous access to a dedicated Registry Manager who answers questions and provides guidance on specific definitions and clinical situations.

Data quality review (ie, monitoring) occurs at the site level as well as in aggregate to check for Case Report Form completeness, consistency, and compliance with all data collection requirements set forth in the registry protocol. Monitoring is performed in addition to the edit checks and event completion rules configured in the 21 CRF Part 11 compliant EDC system. The majority of monitoring is conducted using centralized (ie, remote) methods in

accordance with the Agency for Healthcare and Research Quality's (AHRQ) data collection and quality assurance recommendations.[3] These methods include but are not limited to routine remote monitoring visits and automated database quality control listings. Onsite audits of source data are also performed for a subset of registry sites as defined by the Master RMP.

Remote monitoring visits are conducted for the duration of the registry beginning when the first patient is enrolled. Qualified monitors within CorEvitas' Clinical Data Management (CDM) department are responsible for conducting remote monitoring visits. Registry Managers are responsible for site retraining and resolving any compliance issues identified during these visits. Sites also receive data clarification requests (ie, queries) at regular intervals from designated CDM and Pharmacovigilance personnel. Queries are issued and tracked through the study's EDC system. Sites are required to respond to data queries within 5 to 7 business days of receipt.

9.9. Limitations of the Research Methods

The CorEvitas RA Registry used in this research includes a sample of adults with RA that are not necessarily representative of all adults with RA in the US, or of those in emerging markets outside the United States (US). In particular, these are patients with RA with clinical visits with rheumatologists.

Most importantly for this study, in the US rituximab is typically prescribed as a later line therapy, after failure of one or more tumor necrosis factor inhibitor (TNFi). It is also given as a first-line bDMARD to patients with contraindications to tumor necrosis factor (TNF) inhibitors (eg, interstitial lung disease).[4] This may differ from prescribing patterns in countries other than the US, which could influence the generalizability of the results to RA patients outside of the US.

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 the registry is not based on an inception cohort, patients may not be able to recall their entire medication history, leading to possible mischaracterization regarding prior use of rituximab. The registry captures physician-reported prescribing, but there are no measures of patient adherence.

Confounding by indication can occur when factors that determine physicians' selection of a particular treatment (eg, disease severity, comorbidities) also affect the outcome being studied. There are certain conditions (tuberculosis [TB], lymphoma) that would prompt the prescribing of rituximab. This population could have different outcomes than a population without these comorbidity histories.

Patients who maintain treatment at 6 months may have different outcomes compared to the outcomes those who discontinue or switch would have had, had they not discontinued/switched. This study takes steps to mitigate this potential bias by including values at follow-up for those who discontinue treatment and values at switch for those who switch, as described above.

9.10. Other Aspects

9.10.1. Strengths

CorEvitas was founded in 2000 without any ownership links to the pharmaceutical industry. CorEvitas has a clear track record of published scientific research using the CorEvitas data to provide answers to clinically relevant questions in a real-world setting.

The CorEvitas RA Registry is a longitudinal prospective registry collecting data from both patients and providers on RA treatment and a wide range of both physician- and patient-reported disease outcomes. This provides a unique resource on the real-world use of biologic drugs in the US. The registry contains clinical data (eg, disease activity scores, comorbidities, patient-reported outcomes data, etc.) that are not available in claims databases.

9.11. CorEvitas Publication Policy

All analyses for the public domain are subject to the CorEvitas publication policy (please see the full policy for details; the policy is available upon request). Briefly, the policy describes our adherence to industry best practices for the development, conduct and reporting of research. For comparative studies (any study that assesses effectiveness, persistency, safety and other outcomes in >1 treatment group), analyses need to mitigate sources of systematic bias. In addition, safety studies cannot be performed where the analyses may undermine ongoing or recently completed regulatory commitments. Lastly, courtesy review is provided for comparative studies that impact subscribers including safety studies for subscribers with current or recently conducted regulatory commitments.

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)

This study does not contain any identifying patient information (eg, name) and is exempt from IRB review.

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) and contained in the CT24-WI-GL02-RF04.

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. A. J. Silman and J. E. Pearson, "Epidemiology and genetics of rheumatoid arthritis," *Arthritis Res,* vol. 4 Suppl 3, no. Suppl 3, pp. S265-72, 2002.

2. J. R. Curtis, S. Yang, L. Chen, J. E. Pope, E. C. Keystone, B. Haraoui, G. Boire, J. C. Thorne, D. Tin, C. A. Hitchon, C. O. 3. Bingham and V. P. Bykerk, "Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients," *Arthritis Care Res (Hoboken),* vol. 67, no. 10, pp. 1345-53, 2015.

3. Agency for Healthcare Research and Quality (AHRQ), "Data Collection and Quality Assurance," in *Registries for Evaluating Patient Outcomes: A User's Guide*, 4 ed., vol. 1, September 2020.

4. L. Garcia-Montoya, C. Villota-Eraso and M. Yusof, "Lessons for rituximab therapy in patients with rheumatoid arthritis," *The Lancet Rheumatology,* 2020.

14. LIST OF TABLES

Table shells are included in the SAP.

15. LIST OF FIGURES

Figures are included in the SAP.

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not Applicable.

17. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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