CorEvitas Statistical Analysis Plan: Tofacitinib Use in Rituximab-Experienced RA Patients

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2. LIST OF ABBREVIATIONS

BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CDAI	Clinical Disease Activity Index
CDM	Clinical Data Management
CHF	Congestive Heart Failure
CI	Confidence Interval
csDMARD	Conventional Disease-Modifying Antirheumatic Drug
bDMARD	Biologic Disease-Modifying Antirheumatic Drug
DVT	Deep Venous Thrombosis
EQ-5D	Euro-QoL 5-Dimensional
ERB	Ethical Review Board
GPP	Good Pharmacoepidemiology Practices
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
MCID	Minimum Clinically Important Difference
MI	Myocardial Infarction
MTX	Methotrexate
PCI	Percutaneous Coronary Intervention
PGA	Physician Global Assessment
PII	Personally Identifiable Information
PRO	Patient Reported Outcome
RA	Rheumatoid Arthritis
RTX	Rituximab
SD	Standard Deviation
TIA	Transient Ischemic Attack
TNFi	Tumor Necrosis Factor inhibitors
Non-TNFi	Non-Tumor Necrosis Factor inhibitors
TOFA	Tofacitinib
VAS	Visual Analogue Scale

3. AMENDMENTS AND UPDATES

Amendment number	Date	Section(s) changed	Summary of the change(s)	Reason(s) for the change(s)
1	06-Jan-2023	Title page	Updated study Team members and version date	
1	06-Jan-2023	4.4.3.3.	Replaced sentence *"For patients who discontinued tofacitinib prior to follow-up and who do not switch to another drug, the clinical or patient-reported outcome (listed in Section 4.4.5.2).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. As a sensitivity analysis, we will employ the same approach to discontinuations as above, but in cases where a value for a clinical or patient-reported outcome is not available at switch (among patients who switch), we will impute non-response for all binary variables (listed in Section 4.4.5.2)"* **with** *"For patients who discontinue tofacitinib prior to 6 months window, the clinical or patient-reported outcome (listed in Section 4.4.5.2) will be imputed via last observation carried forward (LOCF), using only registry visits that occur before the discontinuation. Specifically, outcomes observed at a registry visit in the 6-month window will use data collected at that visit with the following exception. Patients that discontinue tofacitinib at a registry visit prior to the six month window will have the outcomes collected at that registry visit carried forward as the outcomes in the 6-month window. A patient that discontinues tofacitinib between registry visits will have the outcomes collected at the registry visit prior to the discontinuation carried forward as the 6-month outcome."*	CorEvitas has updated the general practices for handling discontinuations in effectiveness studies in real world settings.
1	06-Jan-2023	4.4.7.2.	*Aim 2 Sensitivity analysis* has been removed	With the proposed changes a sensitivity analysis is not needed.
2	04-May-2023	4.4.6.6.	*Added line of therapy of RTX and year of RTX discontinuation*	Data of last date of use of RTX requested by MSC team if available

2	04-May-2023	4.4.7.2.	*added sentence "A subgroup analysis related to the outcomes for Aim 2 will be carried out focused on patients who used rituximab immediately prior to tofacitinib".*	
2	04-May-2023	Table 1	*Added line of therapy of RTX and year of RTX discontinuation*	Data of last date of use of RTX requested by MSC team if available
2	04-May-2023	Table 4	*Effectiveness outcomes were reported for the subgroup of those with 6-months follow-up and had used rituximab immediately prior to tofacitinib (see Table 4).*	Data of last date of use of RTX requested by MSC team if available

4. RESEARCH METHODS

4.1. Background and Rationale

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.

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

4.2. Objectives

To characterize the use of tofacitinib after use of rituximab in patients with RA in a real-world setting.

4.2.1. Primary Objective(s)

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

4.2.1.1. Hypotheses

This is a descriptive aim without an a priori hypothesis.

4.2.2. Secondary Objective(s)

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

4.2.2.1. Hypotheses

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

4.2.3. Exploratory Objective(s)

There was initial interest in stratifying by history of tuberculosis and history of lymphoma at time of tofacitinib initiation. At this time, sample size is not feasible for either analysis (n <10 for both TB and lymphoma), and so no exploratory objectives will be pursued.

4.3. Expected Results

The motivation for the study is to characterize patients who initiate tofacitinib and have a prior history of RTX in a real-world setting. The study will also provide evidence of the effectiveness of tofacitinib in the real world, in a population with prior rituximab experience.

4.4. Research Design

This will be a retrospective analysis of a prospective observational cohort using The CorEvitas RA Registry. This study will describe demographic and clinical characteristics of adult patients with RA initiating tofacitinib with a history of RTX 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.

4.4.1. Data Source

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.

The registry currently (as of 12 2021) includes 211 private and academic active clinical sites with over 910 physicians throughout 42 states in the U.S. This registry collects data from both the physicians and the patients at the time of a regular office visit. The registry has enrolled over 57,543 patients with RA. The collection of data from The CorEvitas RA Registry represents over 225,180 patient years of data. Structured clinical data is available in this Registry (e.g. disease activity scores, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases.

To be eligible for enrollment into The CorEvitas RA Registry, a patient must satisfy all of the inclusion criteria and none of the exclusion criteria listed below.

Registry Inclusion Criteria

The patient must:

1. Be at least 18 years of age
2. Be able and willing to provide written consent for participation in the registry as well as Personally Identifiable Information (PII) that includes Full Name and Date of Birth at a minimum.
3. Have been diagnosed with RA by a rheumatologist.
4. Meet at least one of the following criteria:
    a. Currently receiving an Eligible Medication* that was started within 365 days of the Enrollment Visit.

i. A temporary interruption of an Eligible Medication* is allowed if the interruption in treatment lasted <180 days.

b. Prescribed or receiving the first dose of an Eligible Medication* on the day of the Enrollment Visit.

c. Diagnosed with RA within 365 days of the Enrollment Visit regardless of treatment regimen ("Early RA").

* Eligible Medications are biologics, biosimilars, and JAK-inhibitors FDA-approved for the treatment of RA. Prior use of an Eligible Medication does not exclude a patient from enrollment.

Registry Exclusion Criteria

The patient must not:

1. Have a diagnosis of Juvenile idiopathic arthritis (JIA), Psoriatic arthritis (PsA), Spondyloarthritis (SpA), Ankylosing spondylitis (AS), Systemic lupus erythematosus (SLE), or any other form of autoimmune inflammatory arthritis.
2. Be starting *only* a non-eligible medication, unless the patient was diagnosed with RA within 365 days of the Enrollment Visit. Non-eligible medications include csDMARDs – for example methotrexate, sulfasalazine, leflunomide, etc. - and including prednisone.
3. Be participating in or planning to participate in a double-blind randomized clinical trial of an RA drug. Of note, concurrent participation in another observational registry or open-label Phase 3b/4 trial is not excluded.

Data Included in this Study

Data from The CorEvitas RA Registry as of 28, February, 2022 or the latest data available as of the time of statistical analysis plan (SAP) approval will be used for this study. The study will include visits from 06 November 2012, to the end of data collection.

4.4.2. Study Population of Interest

The primary analysis (Aim 1) will include patients that initiated tofacitinib at or post enrollment into the Registry and after tofacitinib approval, and who have any prior use of RTX. The secondary analysis (Aim 2) will include the subset of patients from the primary analysis who also have a 6-month follow-up visit (as defined below) after tofacitinib initiation with clinical and patient reported outcomes.

4.4.3. Time Period Definitions

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, i.e. 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.

4.4.3.1. *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.

4.4.3.2. *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.

4.4.3.3. *Discontinuations prior to follow-up*

For patients who discontinue tofacitinib prior to 6 months window, the clinical or patient-reported outcome (listed in Section 4.4.5.2) will be imputed via last observation carried forward (LOCF), using only registry visits that occur before the discontinuation. Specifically, outcomes observed at a registry visit in the 6-month window will use data collected at that visit with the following exception. Patients that discontinue tofacitinib at a registry visit prior to the six month window will have the outcomes collected at that registry visit carried forward as the outcomes in the 6-month window. A patient that discontinues tofacitinib between registry visits will have the outcomes collected at the registry visit prior to the discontinuation carried forward as the 6-month outcome.

4.4.4. Exposure

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

4.4.5. Study Outcomes

4.4.5.1. Aim 1: Characterize Patients at tofacitinib initiation

4.4.5.1.1. Primary Outcome:

- Aim 1 is to characterize patients at tofacitinib initiation. All variables listed in Section 4.4.6 below will be summarized for this aim.

4.4.5.2. Aim 2: Describe change in 6-month outcomes

4.4.5.2.1. Primary Outcome:

- Change in Clinical Disease Activity Index (CDAI)

4.4.5.2.2. Secondary Outcomes:

- Achievement of Minimum Clinically Important Difference (MCID) (Curtis et al., 2015)[5]: (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

4.4.6. Variables

4.4.6.1. Sociodemographic and Lifestyle Characteristics

- Age (years)
- Sex (Male or Female)
- Race (White, Black, Asian, Other)
- Body weight
- Body-mass index
- Type of health insurance plan (private, Medicare, Medicaid, none; not mutually exclusive)
- Education (college or above)
- Smoking status (never, former, current)
- Work Status (full-time, part-time, work at home, student, disabled, retired, unemployed)

- Alcohol use (none/ <1 drink per week, 1-3 drinks per week, 1-2 drinks per day, ≥3 drinks per day)

4.4.6.2. History of Comorbidities

- Cardiovascular Disease (CVD) (MI, stroke, acute coronary syndrome, coronary artery disease, 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 CVD, Deep Venous Thrombosis (DVT), and Transient Ischemic Attack (TIA).
- Serious infections (Joint/bursa, cellulitis/skin, sinusitis, Candida, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract, upper respiratory, TB, and other)
- History of malignancy (lung cancer, breast cancer, lymphoma, skin cancer (melanoma, basal, squamous), and other cancer
- Lymphoma
- Hypertension
- Diabetes mellitus
- Anxiety/depression
- Interstitial Lung Disease (ILD)/Pulmonary fibrosis
- TB (active or latent)

4.4.6.3. RA Disease Characteristics

- Duration of RA disease (years)
- Age at onset of RA (years)

4.4.6.4. RA Disease Activity Measures (physician-derived elements)

- Clinical Disease Activity Index (CDAI): continuous range 0-76
- CDAI category: remission [0-2.8], low (2.8-10], moderate (10-22], high (22-76]
- MD global assessment VAS (0-100)
- Tender joint count (0-28)
- Swollen Joint count (0-28)

4.4.6.5. Patient Reported Outcome Measures

- Patient Global Assessment (PGA) VAS (0-100)
- Modified HAQ (mHAQ)
- Patient pain VAS (0-100)
- Patient fatigue VAS (0-100)

- Euro-QoL 5-Dimensional 3 Level (EQ-5D-3L)
    - Mobility
    - Self-care
    - Usual activities
    - Pain/discomfort
    - Anxiety/depression

4.4.6.6. Medications

- Previous drug therapies
    - Number of prior csDMARDs, (incl: MTX, Arava, Azulfidine, Plaquenil, Cyclosporine, Imuran, Minocin, Cuprimine, Ridaura)
    - Number of prior bDMARDs/JAKis (incl: TNFi: Enbrel, Humira, Remicade, Cimzia, Simponi; non-TNFi: Orencia, Actemra, Rituxan, Kineret, Kevzara; JAKis: Olumiant, Rinvoq)
    - History of prednisone use
- Line of therapy at tofacitinib initiation:
    - Number (%) with 2 prior biologics (I.e., RTX + 1 other biologic)
    - Number (%) with 3 prior biologics (I.e., RTX + 2 other biologics)
    - Number (%) with 4+ prior biologics (I.e., RTX + 3+ biologics)
- Concomitant therapies
    - Concomitant medications (none, MTX only, nonMTX csDMARD only, MTX & nonMTX csDMARD)
    - Current prednisone use
    - Prednisone dose, among current users
- Detailed description of RTX use:
    - Number (%) using RTX directly before tofacitinib
    - Duration of prior RTX use, where available
    - Line of therapy of RTX
    - Year of RTX discontinuation
- Total number (%) of discontinuations
- Reason for Discontinuation of RTX (among those who discontinue

RTX at or after enrollment in registry)

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

- Tofacitinib initiation year

4.4.7. Analysis Plan

4.4.7.1. *Aim 1: Describe the characteristics of tofacitinib initiators with a history of rituximab exposure, at time of tofacitinib initiation*

Descriptive statistics for the variables listed in Section 4.4.6 will be provided for all tofacitinib initiators with history of rituximab use. All variables will be measured at the index visit, as defined above. Categorical covariates will be described by frequency distribution while continuous covariates will be expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate.

4.4.7.2. *Aim 2: Describe 6-month outcomes for tofacitinib initiators with a history of rituximab exposure*

Descriptive statistics for index visit characteristics will be provided for the subsets of patients included in this Aim (tofacitinib initiators who have a 6-month follow-up visit), as described in Aim 1.

Analyses of outcomes at the 6-month follow-up after tofacitinib initiation will be descriptive. Primary and secondary outcomes will be described as mean absolute differences for continuous measures and as frequencies and proportions for dichotomous measures, with corresponding 95% confidence intervals (95% CI). Mean absolute difference will be defined as the value at the 6-month follow-up visit minus the value at baseline. The number of patients that discontinue tofacitinib will also be summarized. A subgroup analysis related to the outcomes for Aim 2 will be carried out focused on patients who used rituximab immediately prior to tofacitinib.

All 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).

4.4.8. Missing Data

Missing data could be expected for demographic characteristics (e.g., age, etc.); however, the number of patients with missing data is expected to be very small, and is not expected to vary systematically. For every variable, the number of patients with nonmissing information will be reported. Effective sample size may differ across outcome measures due to missingness; because missingness is expected to be very minimal, no imputation of missing values will be applied.

4.4.9. Sample Size and Power Considerations

As of the March 31, 2021 data cut, there were 390 tofacitinib initiators with any 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 RTX use only. 4th line reflects patients with one or more prior biologic in addition to RTX.
- ~107 have CDAI information at baseline and 6mo follow-up
- <10 patients have history of tuberculosis or history of lymphoma

4.5. Strengths and Limitations

4.5.1. 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 (e.g., disease activity scores, comorbidities, patient-reported outcomes data, etc.) that are not available in claims databases.

4.5.2. Limitations

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 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 TNFi. It is also given as a first-line bDMARD to patients with contraindications to TNF inhibitors (e.g., interstitial lung disease) [1]. 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 United States.

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 RTX. 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 (e.g. disease severity, comorbidities) also affect the outcome being studied. There are certain conditions (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.

4.6. Intentional Data Masking

4.6.1. Risk of Reidentification

Reidentification occurs when patient direct identifiers (name, address, etc.) are linked to the deidentified data. In The CorEvitas RA Registry, the risk of this sort of reidentification is thought to be extremely rare. However, increased computing power and improved mathematical algorithms have raised the risk of reidentification of subjects from publicly available information especially for rare conditions or comorbidities [2]. Thus, CorEvitas may suppress cells and/or population subsets with less than 5 individuals.

4.7. Data Quality

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 (i.e. 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 (i.e. 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 (i.e. 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.

4.8. Safety Data Collection, Recording, and Reporting

4.8.1. Serious Adverse Events

N/A

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

Observational studies using The CorEvitas RA Registry data are covered under the Ethical Review Board (ERB) submitted for the Registry data collection. Observational studies will be submitted to ERBs for approval or waivers sought whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) [4] and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

5. REPORTS AND PUBLICATIONS

5.1. 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.

6. LIST OF FIGURES, TABLES AND APPENDICES

7. FIGURES

Figure 1. Selection of eligible population.

The figure will be populated in the study report.

8. TABLES

Table 1: Patient Demographics and Clinical Characteristics at Index Visit, Primary Cohort and Subset with 6-month Visit (Secondary analysis cohort)

Characteristics	Primary Cohort	Subset w/ 6-month visit
Total (N)	**N =**	**N =**
Demographics/socioeconomic characteristics		
Age in years, mean (SD)		
Gender – female, n (%)		
Race, n (%) White African American Asian Other		
Health insurance type, n (%) Private, n (%) Medicare, n (%) Medicaid, n (%) No Insurance, n (%)		
Education, n (%) College graduate or higher		
Work status, n (%) Full time Part time Work at home Student Disabled Retired Unemployed		
Lifestyle characteristics		
Smoking history, n (%) Never smoked Former smoker Current smoker		
Current alcohol use, n (%) None/<1 drink per week 1-3 drinks per week 1-2 drinks per day > 3 drinks per day		
Body weight (kg), mean (SD)		

BMI (kg/m2) continuous, mean (SD) **BMI[1] (kg/m2) categorical, n** **(%)** BMI <25 (underweight/normal) BMI 25 – <30 (overweight) BMI > 30 (obese)		
History of comorbidities, n (%)		
Malignancy[2] Serious Infection[3] Tuberculosis (active or latent) Cardiovascular disease[4] Hypertension Diabetes Mellitus Interstitial Lung Disease (ILD)/Pulmonary fibrosis		
Disease activity characteristics		
Duration of RA (years) continuous, mean (SD) **Age at onset of RA (years) continuous, mean (SD)** **CDAI continuous, mean (SD)** **CDAI categorical, n (%)** Remission (CDAI < 2.8) Low (2.8 ≤ CDAI < 10) Moderate (10 ≤ CDAI < 22) High (22 ≤ CDAI)		
mHAQ continuous, mean (SD) **Tender Joints continuous, mean** **(SD)** **Swollen Joints continuous, mean (SD)** **Physician Global Assessment continuous, mean (SD)**		
Treatment characteristics		
Concomitant therapy, n (%) Monotherapy Combination with MTX only Combination with nonMTX csDMARD only Combination with MTX & nonMTX csDMARD **Prednisone** Prednisone dose, among current users		
Prior csDMARD Use, n (%)[5] 0 previous csDMARDs 1 previous csDMARD ≥2 previous csDMARDs		

Prior bDMARD Use, n (%)[6] 0 previous bDMARDs 1 previous bDMARD ≥2 previous bDMARDs		
Line of therapy at tofacitinib initiation: 2 prior biologics (i.e., RTX + 1 other biologic) 3 prior biologics (i.e., RTX + 2 other biologic) 4 prior biologics (i.e., RTX + 3 other biologic) **Duration of tofacitinib use, continuous, mean (SD)**		
Rituximab as immediate prior treatment, n (%) Duration of prior RTX use, n (%) Line of Therapy at rituximab initiation Rituximab Discontinuation Year **Reasons for discontinuing RTX, categorical, n (%)**[7] Efficacy, n/ N1 (%) Safety, n/ N1 (%) Insurance, n/ N1 (%) Active disease, n/ N1 (%) Other reasons, n/ N1 (%) **Tofacitinib initiation year** 2012-2013 2014-2015 2016-2017 2017-2018 2019-2022		
Patient reported measures*		
Patient global assessment (VAS range 0-100), *n* mean (SD) median (IQR)		
Modified HAQ, *n* mean (SD) median (IQR)		
Patient fatigue (VAS range 0-100), *n* mean (SD) median (IQR)		
Patient pain (VAS range 0-100), *n* mean (SD) median (IQR)		

EQ-5D-3L categorical domains Walking, n (%) Self-care, n (%) Usual activities, n (%) Pain and discomfort, n (%) Anxiety and depression, n (%)		

1. Based on the CDC cut-offs for normal/underweight (under 25); Overweight (25.0 – 29.9); and Obese (30.0 and above)

2. Cancer includes lymphoma, lung, breast, skin [basal cell, squamous cell, melanoma], and any other cancers

3. Infections include Joint/bursa, cellulitis/skin, sinusitis, Candida, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract, upper respiratory, TB, and other. Infections resulting in Hospitalization or administration of IV antibiotics indicates serious infection

4. Cardiovascular disease includes baseline history of any of the following: MI, stroke, acute coronary syndrome, coronary artery disease, 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 CVD, Deep Venous Thrombosis (DVT), and Transient Ischemic Attack (TIA).

5. Prior non-biologic systemic use count does not include the current non-biologic systemic therapy, if applicable

6. Prior biologics count does not include subject's current biologic

7. Efficacy reasons: IR-inadequate initial response, FR-failure to maintain initial response; Safety reasons: SE-serious side effect, ME-minor side effect; Other reasons: FE-fear of future side effect, TI-temporary interruption, PP-patient preference, IC-to improve compliance, IT-to improve tolerability, FA-frequency of administration, RA-route of administration, AM-alternate mechanism of action, OT-other; Insurance reasons: CP-co-pay/patient cost, DI-denied by the insurance; AD-Active disease (for starts or increasing dose); DW-Patient doing well.

*See Appendix A for comprehensive list of definitions

Table 2: Reasons for Discontinuation of Rituximab among Patients who Discontinued at or after Enrollment in the Registry

	N =
Reasons for discontinuing rituximab, categorical, n (%)[1]	
Efficacy, n/ N1 (%)	
Safety, n/ N1 (%)	
Insurance, n/ N1 (%)	
Active disease, n/ N1 (%)	
Other reasons, n/ N1 (%)	

[1] Efficacy reasons: IR-inadequate initial response, FR-failure to maintain initial response; Safety reasons: SE-serious side effect, ME-minor side effect; Other reasons: FE-fear of future side effect, TItemporary interruption, PP-patient preference, IC-to improve compliance, IT-to improve tolerability, FAfrequency of administration, RA-route of administration, AM-alternate mechanism of action, OT-other; Insurance reasons: CP-co-pay/patient cost, DI-denied by the insurance; AD-Active disease (for starts or increasing dose); DW-Patient doing well.

Table 3: Change in Outcomes from Baseline to 6months Follow-up

Outcomes:	N=	
	Mean (SD)	95% CI
∆ CDAI		
Achievement of MCID (n, %, 95% CI)		
∆ HAQ		
∆ Patient pain		
∆ Patient fatigue		

Table 4: Change in outcomes from baseline to 6-months follow-up restricted to patients with RTX as immediate prior treatment

Outcomes:	N=				
	N	Baseline Mean (SD)	6-month Mean (SD)	Difference Mean (SD)	95% CI
CDAI					
Achievement of MCID (n,%)[1]					
HAQ					
Patient pain VAS (0-100)					
Patient fatigue VAS (0-100)					

[1] restricted to patients who had greater than remission (e.g., CDAI≥2.8) at baseline

CDAI= Clinical Disease Activity Index; MCID=minimal clinically important difference; HAQ=Health Assessment Questionnaire; VAS=Visual Analog Score;

9. APPENDICES

Appendix A: Detailed Definitions of Disease Activity Measures and Patient Reported Outcomes in The CorEvitas RA Registry

Patient Reported Outcomes Measures (Range)	
Pain VAS score (0 to 100)	VAS measurement
Fatigue VAS score (0 to 100)	VAS measurement
EQ-5D-3L domains and score	
Mobility (1-2-3)	No problems Some problems Confined to bed
Self-care (1-2-3)	No problems Some problems Unable to do
Usual activity (1-2-3)	No problems Some problems Unable to do
Pain/discomfort (1-2-3)	No pain Moderate pain or discomfort Extreme pain or discomfort
Anxiety/depression (1-2-3)	Not anxious or depressed Moderately anxious or depressed Extremely anxious or depressed
Patient Global Assessment VAS (0 to 100)	VAS measurement

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