**CorEvitas Statistical Analysis Plan:** A Observational Study within the CorEvitas Registry to Evaluate Safety and Effectiveness of Tofacitinib and Biologic Disease Modifying Antirheumatic Drugs in Japan among Patients Treated for Moderately to Severely Active Rheumatoid Arthritis

Prepared for: PPD

Prepared by: PPD ,

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## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| **ABA** | Abatacept |
| **ADA** | Adalimumab |
| **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 |
| **CSP** | Cyclosporine |
| **CTZ** | Certolizumab |
| **CVD** | Cardiovascular Disease |
| **DAS** | Disease Activity Score |
| **DMARD** | Disease-Modifying Antirheumatic Drug |
| **cDMARD** | Conventional Disease-Modifying Antirheumatic Drug |
| **bDMARD** | Biologic Disease-Modifying Antirheumatic Drug |
| **tsDMARD** | Targeted Synthetic Disease-Modifying Antirheumatic Drug |
| **DVT** | Deep Venous Thrombosis |
| **ETA** | Etanercept |
| **EQ-5D** | Euro-QoL 5-Dimensional |
| **GOL** | Golimumab |
| **GPP** | Good Pharmacoepidemiology Practices |
| **HAQ** | Health Assessment Questionnaire |
| **IBD** | Inflammatory Bowel Disease |
| **ICMJE** | International Committee of Medical Journal Editors |
| **IEC** | Independent Ethics Committee |
| **IFX** | Infliximab |
| **IQR** | Interquartile Range |
| **IRB** | Institutional Review Board |
| **mCCI** | Modified Charlson Comorbidity Index (if required) |
| **MI** | Myocardial Infarction |
| **MTX** | Methotrexate |
| **OR** | Odds Ratio |
| **PCI** | Percutaneous Coronary Intervention |
| **PDE 4** | Phosphodiesterase 4 |
| **PGA** | Physician Global Assessment |
| **PII** | Personally Identifiable Information |
| **PRO** | Patient Reported Outcome |
| **RA** | Rheumatoid Arthritis |
| **RTX** | Rituximab |
| **SD** | Standard Deviation |
| **SOPs** | Standard Operating Procedures |
| **SSZ** | Sulfasalazine |

| | |
|---|---|
| **TCZ** | Tocilizumab |
| **TIA** | Transient Ischemic Attack |
| **TNFi** | Tumor Necrosis Factor inhibitors |
| **Non-TNFi** | Non-Tumor Necrosis Factor inhibitors |
| **NMSC** | Non-melanoma skin cancer |
| **TOFA** | Tofacitinib |
| **VAS** | Visual Analogue Scale |
| **WPAI** | Work Productivity and Activity Impairment |

## 3. AMENDMENTS AND UPDATES

| Amendment number | Date | Section(s) changed | Summary of the change(s) | Reason(s) for the change(s) |
|---|---|---|---|---|
| | | | | |
| | | | | |

## 4. RESEARCH METHODS BACKGROUND AND RATIONALE

Rheumatoid arthritis (RA) is a chronic, immune-mediated, inflammatory disease affecting many joints, including those in the hands and feet. A recent analysis from a Japanese health insurance dataset reported that the estimated prevalence of RA ranged from 706,000 to 1.2 million individuals, representing 0.6% to 1.0% of the Japanese population.[1]

Treatment patterns for RA may be markedly different in Japan versus those in North America and Europe. For example, a study shows that methotrexate (MTX) was prescribed for approximately one-quarter (27%) of RA patients in this Japanese cohort, in contrast with both European and US cohorts with >50% of RA patients treated with MTX.[2] The Japanese College of Rheumatology (JCR) also puts forth guidelines for the treatment of RA in Japanese patients, including specific recommendations for TNF biologics and tofacitinib which may differ or provide greater guidance, than the product label.[3]

More research capturing treatment patterns and corresponding effectiveness and safety in Japan are warranted.

To address this research gap, a previous study using CorEvitas RA Japan data was presented in ACR2020 (A3921256). This study will provide an updated analysis of safety and effectiveness outcomes in this population, with two additional years of patient data.

### 4.1. Objectives

The objectives of this study are to describe patients initiating tofacitinib, anti-TNF bDMARDs, non-TNF bDMARDS or methotrexate (MTX) and to evaluate safety and clinical effectiveness endpoints.

#### 4.1.1. Primary Objective(s)

The primary objective of this study is to evaluate safety events of interest in each DMARD group by estimating marginal means of incidence rates of selected safety events of interest.

#### 4.1.2. Secondary Objective(s)

The secondary objective of the study is to evaluate clinical effectiveness at six months in each DMARD group by estimating marginal means of selected clinical outcomes and patient-reported outcomes (PROs).

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### 4.2. Research Design

This is a secondary database observational study conducted in a cohort of RA patients treated with biologic and nonbiologic DMARDs, including tofacitinib, collected as part of the CorEvitas Japan RA Registry.

### 4.2.1. Data Source

The CorEvitas RA Japan Registry is a prospective, multicenter, observational disease-based registry launched in February 2016. Longitudinal follow-up data is collected from both patients and their treating rheumatologist during routine clinical encounters using the CorEvitas RA Japan 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 June 2022) includes 48 private and academic active clinical sites with over 219 physicians throughout 27 prefectures in Japan. This registry collects data from both the physicians and the patients at the time of a regular office visit. The registry has enrolled over 2,359 patients with RA. Structured clinical data is available in this Registry (eg, 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 Japan Registry, a patient must satisfy all the inclusion criteria and none of the exclusion criteria listed below.

**Registry Inclusion Criteria**

The patient must:

1. Be diagnosed with rheumatoid arthritis according to the 1987 ACR or the ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria

2. Be at least 18 years of age or older

3. Was/Must be prescribed or switching to the following eligible medication for the first time ever at the enrollment visit:

csDMARD: methotrexate (closed in February 2018)

Anti-TNF bDMARD: adalimumab (originator or biosimilar), certolizumab pegol, etanercept (originator or biosimilar), golimumab, infliximab (originator or biosimilar), or any other anti-TNF biosimilar approved during the study

Non-TNF bDMARD: abatacept, tocilizumab, sarilumab (closed in June 2020)
JAK inhibitor: tofacitinib, baricitinib, peficitinib, filgotinib, upadacitinib

**Registry Exclusion Criteria**

The patient is not willing and able to provide informed consent.

**Data Included in this Study**

Data from CorEvitas RA Japan Registry as of September 2022, or the most recent data cut available at the start of the analysis, will be used for this study. The study will include visits from March 2016 to June 2022 for both effectiveness and safety outcomes.

**Study Population of Interest**

There are two populations of interest: one for the primary objective (safety outcomes) and one for secondary objective (clinical effectiveness and PRO outcomes). Both populations include RA Japan patients who initiate tofacitinib, MTX, TNFi bDMARD, or nonTNFi bDMARD and have a baseline available, where initiation is defined as the first ever use of the drug. The MTX group will exclude those who initiated MTX in combination with other biologics or JAKi. Furthermore, each population will have additional inclusion criteria:

Safety:

- At least one day of registry follow-up time after initiation of the drug, unless the individual had an event on the day of the initiation.

Effectiveness:

- A 6-month (±3 months) follow-up visit after initiation of the drug

**4.2.2. Time Period Definitions**

The CorEvitas RA Japan 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

For both populations, initiators will have a baseline, defined as the CorEvitas visit associated with the drug initiation, ie, the index visit. If the drug is initiated at a CorEvitas visit, the CorEvitas visit is the index visit.

*Assigning the index (ie, baseline) visit if the drug is initiated between visits*

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

Index date

For each patient, the index date is defined as the initiation date of the therapy of interest.

**Study period (safety outcomes)**

For patients with more than one initiation in a drug class, the index date is the initiation date of the first drug. Therefore, the analysis will be carried out with one index date per patient for each drug class.

Risk Window

Patients will be followed according to a risk window. There will be two different definitions of the risk window, depending on the safety outcome of interest:

> For all events except malignancy, the risk window will begin with the start of the index visit and continue until the visit closest to 90 days after the end of therapy or end of data collection, whichever comes first. Events which occur beyond this risk window will not be counted for purposes of incidence rate estimation. However, in instances when a patient starts a second therapy within the visit closest to 90 days after discontinuing a first one, the risk windows will overlap, and the event will be attributed to both therapies.
>
> For analyses of risk for malignancies, an "any exposure" approach will be utilized. Specifically, the risk window for any therapy will include all person-time in the designated time period (since therapy initiation) and extend until the end of data collection, even in the case of subsequent switching to another therapy. When a malignancy is diagnosed after a second therapy has been begun, the event will be attributed to both therapies in the incidence rate estimations. Using the once-exposed, always-exposed approach means that an individual may contribute exposure time and events to more than one drug class.

**Study period (effectiveness outcomes)**

Patients will be followed until their 6-month (±3months) follow-up visit, which will be calculated from the index date

*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 6-month 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.

### 4.2.3. Exposure/Independent Variable

#### 4.2.3.1. Primary and Secondary Exposures/Independent Variables

The primary and secondary exposures in this study are the DMARD drug class: tofacitinib, MTX, TNFi, and nonTNFi.

**Study Outcomes**

### 4.2.3.2. Primary Outcome(s)

We will evaluate the following safety outcomes: total CVD, serious infections, total Herpes Zoster, and total malignancy excluding NMSC (non-melanoma skin cancer). See additional information in "Safety Data Collection, Recording, and Reporting" section.

**Secondary Outcome(s)**

We will evaluate the following effectiveness outcomes:

- Change in disease activity: mean change from baseline to 6-months of CDAI, J-HAQ, patient pain, patient global assessment, patient fatigue, morning stiffness, and EQ-5D-5L.

- Achievement of minimally clinically important difference (MCID)[4] at 6-month follow-up, based on the CDAI value at initiation. Specifically,

  MCID >1 if CDAI at baseline is ≤10,
  MCID >6 if CDAI at baseline ranges between (10, 22],
  MCID >12 if CDAI at baseline >22.

- Modified ACR20/50/70 (mACR20/50/70), defined as 20/50/70% improvement in tender and swollen joint count, and 20/50/70% improvement in 2 of the following four domains at the 6-month follow-up visit: patient pain assessment, patient global assessment, physician global assessment, patient self-addressed disability, measured by the J-HAQ score.

*Note on outcome measures for the effectiveness analysis at six months*: For patients who discontinue the index therapy and switch to another therapy prior to the six- month follow-up visit:

- For binary outcome measures, we will impute non-response (ie, non-achievement of outcomes) for these initiators

- For continuous variables, we will use the last observed value prior to discontinuation (ie, LOCF (last observation carried forward)) as the six month value when calculating change from baseline for continuous outcome variables.

- For patients who discontinue index therapy but do not switch to another therapy prior to the six-month visit:The value of the outcome at the six-month visit will be used

### 4.2.4. Covariates

The following measures will be recorded at the baseline visit:

**Sociodemographic and Lifestyle Characteristics**

- Age
- Gender

- Race (Japanese, Korean, Chinese, Other)
- Education (college – yes/no)
- Work Status (full-time - yes/no)
- Body weight and body-mass index (normal, overweight, obese)
- Smoking status (yes - current, no)

**History of Comorbidities**

History of cancer, serious infection, herpes zoster, cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, GI perforation, peptic ulcer, IBD, depression

**RA Disease Characteristics**

- Duration of RA disease
- Serum positive (RF+ and/or CCP+)

**RA Disease Activity Measures (physician-derived elements)**

- CDAI (continuous)
- CDAI (remission, low, moderate, high)
- Tender joint count (28)
- Swollen Joint count (28)
- Disease activity score –28 (DAS-28)
- Physician global assessment VAS (0-100)

**Treatment characteristics**

Previous drug therapies

- Number of prior cDMARDs, bDMARDs, tsDMARDs
- Prior steroid use
- Concomitant therapies
    - Monotherapy or combination with prednisone, methotrexate, or other cDMARDs.
    - For concomitant prednisone at initiation, provide mean dose
    - For concomitant MTX at initiation, provide mean dose, % <8mg, % ≥8mg

**Patient Reported Outcome Measures**

- Patient global assessment VAS (0-100)
- Patient fatigue VAS (0-100)
- J-HAQ
- Patient pain VAS (0-100)
- Morning stiffness (hrs./mins)

- Euro-QoL 5-Dimensional 3 Level (EQ-5D-3L)
- EQ Health Status VAS (0-100)
- Work Productivity and Activity Impairment (WPAI)

### 4.2.5. Analysis Plan

For all patients included in the study, means and standard deviations (SD) and frequencies and percentages will be reported for patient characteristics at DMARD initiation, separately for the safety and clinical effectiveness cohorts (Table 1A. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT BASELINE (SAFETY COHORT) and Table 1B).

**Analysis of the primary outcome measure (safety)**

Mean and median follow-up time will be described for each DMARD group (Table 5). Unadjusted incidence rates (ie, number of events per 100 person-years of follow-up) and associated 95% confidence intervals (CIs) will be computed for each DMARD group (Table 6). A separate Poisson model for each safety outcome, adjusted for a priori-defined potential confounders**, will be used to estimate marginal incidence rates of each safety outcome for each DMARD drug group (Table 7). Specifically, a multiplicative Poisson regression model will be fitted as a log-linear regression (ie, a log link and a Poisson error distribution), with an offset equal to the natural logarithm of person-time.

**Analysis of the secondary outcome measure (effectiveness)**

Discontinuations will be described for each drug group (Table 4). A separate regression model will be fit for each effectiveness outcome with DMARD group as the exposure variable; linear models will be used for continuous measures and logistic models will be used for binary measures. Unadjusted mean outcomes and SDs will be presented for each DMARD (Table 2). Adjusted regression models will be fit and marginal means with associated 95% CIs will be estimated for each DMARD group (Table 3).

**For both primary and secondary outcomes, adjusted models will include the following potential confounders: age, sex, baseline CDAI, line of therapy, BMI, duration of RA, physician global, J-HAQ, and baseline value of outcome measurement.

Minor alterations to the analysis plan made by the CorEvitas team may be considered in response unforeseen challenges encountered during the analysis, including, but not limited to, departures from statistical assumptions, multicollinearity affecting interpretation, or difficulties in achieving algorithmic convergence. Any minor deviations in the analysis from the protocol will be noted in the final report.

### 4.2.6. Missing Data

Some patients may have missing patient characteristic data at baseline or index visit. These numbers are expected to be relatively small, thus, no special handling will be used. Patients with missing data will be omitted from both unadjusted and adjusted analysis.

### 4.2.7. Sample Size and Power Considerations

A preliminary data pull identified 225, 275, 475, and 734 patients initiating tofacitinib, MTX, TNFi, and nonTNFi, respectively, that meet the eligibility criteria based on the data available from the January 2022 data cut.

## 4.3. Strengths and Limitations

### 4.3.1. 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 Japan 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 of large sample size, and longitudinal follow-up on the real-world use of biologic drugs in Japan. The registry enables examination of response patterns based on measures relevant to patient-physician encounters and a large set of patient histories and characteristics to use as predictors of response. The registry contains clinical data (eg, disease activity scores, comorbidities, patient-reported outcomes data, etc.) that are not available in claims databases.

### 4.3.2. Limitations

The CorEvitas RA Japan Registry used in this research includes a sample of adults with RA that are not necessarily representative of all adults with RA in Japan. These are patients with RA with clinical visits with rheumatologists. In addition, history of medication use prior to enrollment is derived from what is reported by patients and their current rheumatologist within the registry. The “cause” of visits is not captured, although the assumption can likely be made that the rheumatology visit is “RA related.” The registry captures physician-reported prescribing, and there are no measures of patient adherence.

Since the registry is not based on an inception cohort, patients may not be able to recall their entire medication history, leading to misclassification in therapy cohorts.

Selection bias may be introduced if certain subgroups of patients (eg, healthier or sicker patients) are routinely included or excluded from the registry.

Confounding by indication can occur when factors determine physicians’ selection of a particular treatment (eg, disease severity) also affects the outcome being studied. It is also possible that drug benefit design and formulary status changes could have affected utilization patterns, and in turn, the number of patients who switched medications.

## 4.4. Intentional Data Masking

### Risk of Reidentification

Reidentification occurs when patient direct identifiers (name, address, etc.) are linked to the deidentified data. In the CorEvitas RA Japan 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.

### 4.5. 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 (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. Most of the 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.

### 4.6. Safety Data Collection, Recording, and Reporting

#### 4.6.1. Safety Events of Interest

The following safety events of interest will be examined:

- Total CVD- is defined as hypertension requiring hospitalization, cardiac revascularization procedure (CABG, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, CHF requiring hospitalization, stroke, transient ischemic attack, other serious cardiovascular event ***(***specify***),*** deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis) and pulmonary embolism.

- Serious infections – is defined as infections meeting serious adverse event criteria or requiring treatment with IV antibiotics. Serious infection types collected in the registry are pneumonia, sepsis, joint/bursa, cellulitis/skin, sinusitis, diverticulitis, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis, and other (free text) serious infections.

- Total Herpes Zoster – is defined as serious and non-serious herpes zoster events

- Total malignancy excluding NMSC (non-melanoma skin cancer). This includes the following malignancy types collected in the registry: lymphoma, lung cancer, breast cancer, skin cancer (melanoma), and other cancer

All outcomes within CorEvitas data were identified via provider forms, Targeted Adverse Event (TAE) forms, supporting documentation sent along with the TAE form, and/or Registry exit forms. Any event reported by at least one of these methods went through review by the CorEvitas Pharmacovigilance team to verify the occurrence of the event, the event type, and event date. An event will be counted toward an exposure cohort if it is validated by CorEvitas Pharmacovigilance and occurred during the defined exposure period for the patient.

Related to the events evaluated for this project, provider forms specifically query MI, stroke, deep vein thrombosis, pulmonary embolism, several other cardiovascular events (acute coronary syndrome, cardiac arrest, cardiac revascularization procedure, carotid artery disease, coronary artery disease, congestive heart failure, hypertension, peripheral arterial thromboembolic event, stable peripheral arterial disease, peripheral ischemia or gangrene, transient ischemic attack, unstable angina, urgent peripheral arterial revascularization, ventricular arrhythmia, and other cardiovascular event), malignancies (breast, lymphoma, lung, melanoma skin cancer, non-melanoma skin cancer, and other cancer), infections and whether or not they were serious or were treated with intravenous anti-infectives (joint/bursa, cellulitis, herpes zoster, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, upper respiratory infection, urinary tract infection, active or latent tuberculosis, progressive multifocal leukoencephalopathy, and other infection), and also collect information on outcome, including whether the event resulted in death and whether Registry exit is due to patient death.

The table below gives a detailed description of the operationalization of each outcome variable.

| Variable | Role | Data source(s) | Operational definition |
|---|---|---|---|
| Total CVD | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |
| | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |
| | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |
| Serious infection | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |
| Total Herpes Zoster | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |
| Total Malignancy excluding NMSC | outcome | Provider-reported (follow-up, targeted event report, registry exit) | Indicator of outcome after index date; time to first occurrence after index date |

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

Observational studies using CorEvitas RA Japan Registry data are covered under the Ethical Review Board submitted for the Registry data collection. Observational studies will be submitted to Ethical Review Boards 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 Ethical Review Boards, 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)[5] 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.

### 5.2. Content of Report

The content of a report varies based on the type of analysis performed, but common features will include:

Executive summary

Detailed tables of characteristics presenting frequencies along with other summary statistics

Cross-tabulations such that one group is being compared to another (eg, patients on the subscriber's drug with and without a comorbidity or those taking the subscriber's drug versus one or more competitors)

Sections in the content of the report may be modified as needed. An example, CorEvitas may exclude the executive summary when it is an add on report that is internal.

## 6. LIST OF FIGURES, TABLES AND APPENDICES

## 7. FIGURES

**Figure 1.** Patient Flow Chart

## 8. TABLES

| Table 1A. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT BASELINE (SAFETY COHORT) | | | | |
|---|---|---|---|---|
| **Characteristics** | **Tofacitinib** | **MTX** | **TNFi** | **Non-TNFi** |
| **Total (N)** | | | | |
| ***Demographics/socioeconomic characteristics*** | | | | |
| **Age (years), mean (SD)** | | | | |
| **Gender – female, n (%)** | | | | |
| **Race, n (%)** | | | | |
| Japanese | | | | |
| Korean | | | | |
| Chinese | | | | |
| Other | | | | |
| **Education, n (%)** | | | | |
| Some college/college graduate | | | | |
| **Work status, n (%)** | | | | |
| Full time | | | | |
| ***Lifestyle characteristics*** | | | | |
| **Smoking history, n (%)** | | | | |
| Never smoked | | | | |
| Current smoker | | | | |
| **Body height (m), mean (SD)** | | | | |
| **Body weight (kg), mean (SD)** | | | | |
| **BMI (kg/m2) continuous, mean (SD)** | | | | |
| **BMI[0] (kg/m2) categorical, n (%)** | | | | |
| BMI <25 (underweight/normal) | | | | |
| BMI 25 - 30 (overweight) | | | | |
| BMI > 30 (obese) | | | | |

| Table 1A. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT BASELINE (SAFETY COHORT) | | | | |
|---|---|---|---|---|
| **History of comorbidities, n (%)** | | | | |
| Cancer[2] | | | | |
| Serious infection[3] | | | | |
| Herpes zoster | | | | |
| Cardiovascular disease[4] | | | | |
| Hypertension | | | | |
| Hyperlipidemia | | | | |
| Diabetes Mellitus | | | | |
| GI perforation | | | | |
| Peptic Ulcer | | | | |
| IBD | | | | |
| Depression | | | | |
| ***Disease activity characteristics*** | | | | |
| **Duration of RA (years), mean (SD)** | | | | |
| **Serum positive (RF+ and/or CCP+)** | | | | |
| **CDAI, mean (SD)** | | | | |
| **CDAI categorical, n (%)** | | | | |
| Remission (CDAI < 2.8) | | | | |
| Low (2.8 ≤ CDAI < 10) | | | | |
| Moderate (10 ≤ CDAI < 22) | | | | |
| High (22 ≤ CDAI) | | | | |
| **Tender Joints continuous, mean (SD)** | | | | |
| **Swollen Joints continuous, mean (SD)** | | | | |
| **Physician Global Assessment continuous, mean (SD)** | | | | |
| **DAS28-ESR, mean (SD)** | | | | |

| **Table 1A. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT BASELINE (SAFETY COHORT)** | | | | |
|---|---|---|---|---|
| ***Treatment characteristics*** | | | | |
| **Number of prior therapies** | | | | |
| cDMARD | | | | |
| bDMARD | | | | |
| tsDMARD | | | | |
| **Prior steroid use, n (%)** | | | | |
| **Concomitant therapy, n (%)** | | | | |
| Prednisone, n (%)<br>Dose, mean (SD)<br>Methotrexate, n (%)<br>Dose, mean (SD)<br>< 8 mg, n (%)<br>≥ 8 mg, n (%) | | | | |
| Other cDMARDs | | | | |
| ***Patient reported measures*** | | | | |
| **Patient global assessment (VAS range 0-100), mean (SD)** | | | | |
| **Patient fatigue (VAS range 0-100), mean (SD)** | | | | |
| **Patient pain (VAS range 0-100), mean (SD)** | | | | |
| **EQ-5D-5L 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. Serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with IV antibiotics. Serious infection types collected in the registry are: Joint/bursa, cellulitis/skin, sinusitis, Candida, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract, upper respiratory, active 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: cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, coronary artery disease, congestive heart failure; Cerebrovascular disease includes baseline history of any of the following: stroke, TIA, peripheral vascular disease, peripheral arterial disease

**Table 1B: Patient Demographics and Clinical Characteristics at Baseline (Effectiveness Cohort)**

| Characteristics | Tofacitinib | MTX | TNFi | Non-TNFi |
|---|---|---|---|---|
| **Total (N)** | | | | |
| ***Demographics/socioeconomic characteristics*** | | | | |
| **Age (years), mean (SD)** | | | | |
| **Gender – female, n (%)** | | | | |
| **Race, n (%)** | | | | |
| Japanese | | | | |
| Korean | | | | |
| Chinese | | | | |
| Other | | | | |
| **Education, n (%)** | | | | |
| Some college/college graduate | | | | |
| **Work status, n (%)** | | | | |
| Full time | | | | |
| ***Lifestyle characteristics*** | | | | |
| **Smoking history, n (%)** | | | | |
| Never smoked | | | | |
| Current smoker | | | | |
| **Body height (m), mean (SD)** | | | | |
| **Body weight (kg), mean (SD)** | | | | |
| **BMI (kg/m2) continuous, mean (SD)** | | | | |
| **BMI[0] (kg/m2) categorical, n (%)** | | | | |
| BMI <25 (underweight/normal) | | | | |
| BMI 25 - 30 (overweight) | | | | |
| BMI > 30 (obese) | | | | |
| **History of comorbidities, n (%)** | | | | |

| | | | | |
|---|---|---|---|---|
| Cancer[2] | | | | |
| Serious infection[3] | | | | |
| Herpes zoster | | | | |
| Cardio/cerebrovascular disease[4] | | | | |
| Hypertension | | | | |
| Hyperlipidemia | | | | |
| Diabetes Mellitus | | | | |
| GI perforation | | | | |
| Peptic Ulcer | | | | |
| IBD | | | | |
| Depression | | | | |
| ***Disease activity characteristics*** | | | | |
| **Duration of RA (years), mean (SD)** | | | | |
| **Serum positive (RF+ and/or CCP+)** | | | | |
| **CDAI continuous, mean (SD)** | | | | |
| **CDAI categorical, n (%)** | | | | |
| Remission (CDAI < 2.8) | | | | |
| Low (2.8 ≤ CDAI < 10) | | | | |
| Moderate (10 ≤ CDAI < 22) | | | | |
| High (22 ≤ CDAI) | | | | |
| **Tender Joints continuous, mean (SD)** | | | | |
| **Swollen Joints continuous, mean (SD)** | | | | |
| **Physician Global Assessment continuous, mean (SD)** | | | | |
| **DAS28-ESR, mean (SD)** | | | | |
| ***Treatment characteristics*** | | | | |
| **Number of prior therapies** | | | | |
| cDMARD | | | | |

| | | | | |
|---|---|---|---|---|
| bDMARD | | | | |
| tsDMARD | | | | |
| **Prior steroid use, n (%)** | | | | |
| **Concomitant therapy, n (%)** | | | | |
| Prednisone, n (%)<br>Dose, mean (SD)<br>Methotrexate, n (%)<br>Dose, mean (SD)<br>< 8 mg, n (%)<br>≥ 8 mg, n (%) | | | | |
| Other cDMARDs | | | | |
| ***Patient reported measures*** | | | | |
| **Patient global assessment (VAS range 0-100), mean (SD)** | | | | |
| **Patient fatigue (VAS range 0-100), mean (SD)** | | | | |
| **Patient pain (VAS range 0-100), mean (SD)** | | | | |
| **EQ-5D-5L 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. Serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with IV antibiotics. Serious infection types collected in the registry are: Joint/bursa, cellulitis/skin, sinusitis, Candida, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract, upper respiratory, active 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: cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, coronary artery disease, congestive heart failure; Cerebrovascular disease includes baseline history of any of the following: stroke, TIA, peripheral vascular disease, peripheral arterial disease

| Table 2. Unadjusted Effectiveness Outcomes (Baseline to 6 Months) by Drug Group | | | | |
|---|---|---|---|---|
| **Variable** | **Tofacitinib** | **MTX** | **TNFi** | **Non-TNFi** |
| N | | | | |
| **Disease Characteristics** | | | | |
| CDAI, mean (SD) | | | | |
| Achieving CDAI MCID, n (%) | | | | |
| Achieving mACR 20, n (%) | | | | |
| Achieving mACR 50, n (%) | | | | |
| Achieving mACR 70, n (%) | | | | |
| **Patient Reported Outcomes** | | | | |
| Pain, mean (SD) | | | | |
| Fatigue, mean (SD) | | | | |
| Patient global assessment, mean (SD) | | | | |
| Morning stiffness * | | | | |
| J-HAQ, mean (SD) | | | | |
| EQ-5D-5L **, means (SD) | | | | |
| Mobility | | | | |
| Selfcare | | | | |
| Usual activities | | | | |
| Pain/discomfort | | | | |
| Depression/anxiety | | | | |

*: Change is percentage points from baseline to 6 months
**: For each domain, change in the percentage points reporting moderate, severe, or extremely difficult from baseline to 6 months.

**Table 3. Adjusted Effectiveness Outcomes (Baseline to 6 months; Marginal Means) by Drug Group**

| Variable | Tofacitinib | MTX | TNFi | Non-TNFi |
|---|---|---|---|---|
| N | | | | |
| **Disease Characteristics** | | | | |
| CDAI, mean (95% CI) | | | | |
| Achieving CDAI MCID, % (95% CI) | | | | |
| Achieving mACR 20, % (95% CI) | | | | |
| Achieving mACR 50, % (95% CI) | | | | |
| Achieving mACR 70, % (95% CI) | | | | |
| **Patient Reported Outcomes** | | | | |
| Pain, mean (95% CI) | | | | |
| Fatigue, mean (95% CI) | | | | |
| Patient global assessment, mean (95% CI) | | | | |
| Morning stiffness *, mean (95% CI) | | | | |
| J-HAQ, mean (95% CI) | | | | |
| EQ-5D-5L, mean (95% CI) | | | | |
| Mobility | | | | |
| Selfcare | | | | |
| Usual activities | | | | |
| Pain/discomfort | | | | |
| Depression/anxiety | | | | |

**Table 4. Discontinuations Description by Drug Group**

| Drug group | Tofacitinib | MTX | TNFi | nonTNFi |
|---|---|---|---|---|
| Total | | | | |
| Remain on drug at 6 months, n (%) | | | | |
| Discontinue prior to 6 months, n (%) | | | | |
| Switch to another therapy | | | | |
| Do not switch to another therapy | | | | |

**Table 5. Follow-up Time for Each Drug Group**

| | Follow-up time (years) | | |
|---|---|---|---|
| **Drug group** | **Total** | **Mean** | **Median** |
| tofacitinib | | | |
| MTX | | | |
| TNFi | | | |
| nonTNFi | | | |

**Table 6. Unadjusted Incidence Rates of Safety Events for Each Drug Group**

- Repeat table for each drug group

| Safety Event of Interest | Tofacitinib Initiators | | | | |
|---|---|---|---|---|---|
| | N | PYR | Rate | 95% CI | |
| Total CVD* | | | | | |
| Total Serious Infections** | | | | | |
| Total Herpes Zoster*** | | | | | |
| Total Cancer excluding NMSC**** | | | | | |

*Total CVD is defined as hypertension requiring hospitalization, cardiac revascularization procedure (CABG, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, CHF requiring hospitalization, stroke, transient ischemic attack, other cardiovascular event *(*specify*),* deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis) and pulmonary embolism.

**Total serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with IV antibiotics. Serious infection types collected in the registry are pneumonia, sepsis, joint/bursa, cellulitis/skin, sinusitis, diverticulitis, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis and other serious infections.

***Total herpes zoster includes both serious and non-serious herpes zoster.

****Total cancer excluding non-melanoma skin cancer includes lymphoma, lung cancer, breast cancer, skin cancer (melanoma), and other cancers.

**Table 7. Adjusted Incidence Rates of Safety Events for Each Drug Group (Marginal Means with associated 95% CI)**

| Safety Event of Interest | Tofacitinib | MTX | TNFi | Non-TNFi |
|---|---|---|---|---|
| N | | | | |
| Total CVD* | | | | |
| Total Serious Infections** | | | | |
| Total Herpes Zoster*** | | | | |
| Total Cancer excluding NMSC**** | | | | |

*Total CVD is defined as hypertension requiring hospitalization, cardiac revascularization procedure (CABG, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, CHF requiring hospitalization, stroke, transient ischemic attack, other serious cardiovascular event *(*specify*),* deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis) and pulmonary embolism.

**Total serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with IV antibiotics. Serious infection types collected in the registry are pneumonia, sepsis, joint/bursa, cellulitis/skin, sinusitis, diverticulitis, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis and other serious infections

***Total herpes zoster includes both serious and non-serious herpes zoster

****Total cancer excluding non-melanoma skin cancer includes lymphoma, lung cancer, breast cancer, skin cancer (melanoma), and other cancer

## 9. APPENDICES

**Appendix A: Detailed Definitions of Disease Activity Measures and Patient Reported Outcomes in the CorEvitas Rheumatoid Arthritis Japan Registry**

| | |
|---|---|
| **Patient Reported Outcomes Measures (Range)** | |
| Pain VAS score (0 to 100) | VAS measurement |
| Fatigue VAS score (0 to 100) | VAS measurement |
| WPAI (0 to 100%) | **Questions**:<br>1 = Currently employed?<br>2 = Hours missed due to RA?<br>3 = Hours missed other reasons?<br>4 = Hours worked?<br>5 = Degree problem affected productivity while working (VAS (0 to 100) measurement)?<br>6 = Degree problem affected regular activities (VAS (0 to 100) measurement)?<br><br>**Scores**:<br>Multiply scores by 100 to express in percentages for reported categories:<br>**Percent work time missed due to problem**: Q2/(Q2+Q4)<br>**Percent impairment while working due to problem**: Q5/10<br>**Percent overall work impairment due to problem**:<br>Q2/(Q2+Q4) +[(1-(Q2/(Q2+Q4))) x(Q5/10)]<br>**Percent activity impairment due to problem**: Q6/10 |
| *EQ-5D-3L domains and score (modify to 5L as applicabl* | |
| Mobility (1-2-3) | No problems<br>Some problems<br>Confined to bed |
| Self-care (1-2-3) | No problems<br>Some problems<br>Unable to do |

| | |
|---|---|
| Usual activity (1-2-3) | No problems<br>Some problems<br>Unable to do |
| Pain/discomfort (1-2-3) | No pain<br>Moderate pain or discomfort<br>Extreme pain or discomfort |
| Anxiety/depression (1-2-3) | Not anxious or depressed<br>Moderately anxious or depressed<br>Extremely anxious or depressed |
| EQ Health Status VAS (0 to 100) | VAS measurement |

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