NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	An Observational Study within the CorEvitas Registry to Evaluate Safety and Effectiveness of Tofacitinib and Biologic Disease Modifying Antirheumatic Drugs (bDMARDs) in Japan among Patients Treated for Moderately to Severely Active Rheumatoid Arthritis
Protocol Number	A3921429
Protocol Version Identifier	2.0
Date	02 May 2023
Active Substance	L04AA29
Medicinal Product	Toficitinib Citrate
Research Question and Objectives	The research question is to determine the safety and efficacy endpoints of patients initiating tofacitinib, anti-TNF bDMARDs, non-TNF bDMARDs or methotrexate (MTX). The primary objective is to evaluate safety events of interest in each DMARD group by estimating marginal means of incidence rates of selected safety events of interest.
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
bDMARDs	Biologic Disease-Modifying Antirheumatic Drug
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
CDM	Clinical Data Management
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
DAS	Disease Activity Score
DMARD	Disease-Modifying Antirheumatic Drug
EDC	Electronic Data Capture
EQ-5D	Euro-QoL 5-Dimensional
GPP	Good Pharmacoepidemiology Practices
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus Kinase
JCR	Japanese College of Rheumatology
MCID	Minimally Clinically Important Difference
MTX	Methotrexate
NMSC	Non-Melanoma Skin Cancer

Abbreviation	Definition
Non-TNFi	Non-Tumor Necrosis Factor Inhibitors
PGA	Physician Global Assessment
PRO	Patient Reported Outcome
RA	Rheumatoid Arthritis
RMP	Registry Monitoring Plan
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
TNFi	Tumor Necrosis Factor inhibitors

3. RESPONSIBLE PARTIES

Name, Degree(s)	Job Title	Affiliation	Address
PPD	PPD	PPD	PPD
PPD	PPD	PPD	PPD

4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	02-May-2023	8.2. Secondary Objectives	Updated language: how discontinuations handled in effectiveness analysis	The persistence measure has become simpler from analysis and interpretation perspectives. Therefore, there is an increase in precision as well.
1	02-May-2023	9.7. Data Analysis	A clarification added regarding CDAI usage	CDAI was not used in this project. No re-calculation.
1	02-May-2023	3. Responsible Parties	Address change of a responsible party	Address change of a responsible party

6. MILESTONES

Milestone	Planned Date
Start of Data Collection	07 October 2022
End of Data Collection	10 October 2022
Final Study Report	10 September 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. 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 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 Pfizer sponsored study (A3921256) using CorEvitas RA Japan data was presented in ACR2020. This study will provide an updated analysis of safety and effectiveness outcomes in this population, with two additional years of patient data.

8. RESEARCH QUESTION AND OBJECTIVES

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

8.1. Primary Objective(s)

The primary objective of this study is to evaluate safety events of interest ie, total Cardiovascular Disease (CVD), serious infections, total Herpes Zoster, and total malignancy excluding NMSC (non-melanoma skin cancer) in the Tofacitinib, non-TNF, anti-TNFi, and MTX cohorts by estimating marginal means of incidence rates of selected safety events of interest.

The safety events are defined as follows:

- 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, Congestive Heart Failure (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. This includes the following malignancy types collected in the registry: lymphoma, lung cancer, breast cancer, skin cancer (melanoma), and other cancer

8.2. Secondary Objective(s)

- The secondary objective of the study is to evaluate clinical effectiveness at six months follow-up visit following medication initiation in each DMARD group by estimating marginal means of selected clinical outcomes and patient-reported outcomes (PROs).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 (PGA), 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 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 therapyat their 6-month visit:

- The value of the outcome at the six-month visit will be used.

9. RESEARCH METHODS

9.1. Study 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.

9.2. Setting

This is a structured database study using the CorEvitas Japan RA Registry. Data from the CorEvitas RA Japan Registry as of September 2022, will be used for this study. The study will include data from March 2016 to the latest data cut available in 2022 for both effectiveness and safety outcomes.

9.2.1. Inclusion Criteria

Data from the CorEvitas RA Japan Registry as of September 2022, will be used for this study. The study will include data from March 2016 to to the latest data cut available in 2022 for both effectiveness and safety outcomes. Registry inclusion criteria:

1. Be diagnosed with RA according to the 1987 ACR or the ACR/EULAR 2010 RA 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.

9.2.2. Exclusion Criteria

Data that are prior to March 2016 and after June 2022.

9.3. Variables

Detailed definitions and an exhaustive list of variables will be included in the statistical analysis plan (SAP). Some of the variables included in the study are as below:

- **Baseline Information**: Age, Gender, Race, Education, Work Status, Smoking History, Body Height, Body Weight, BMI, History of Comorbidities, Duration of RA, Serum Positive
  (RF+ and/or CCP+), CDAI, Tender Joints, Swollen Joints, PGA, DAS28-ESR, Number of Prior Therapies, Prior Steroid Use, Concomitant Therapy, Patient Global Assessment, Patient Fatigue, Patient Pain, and the EQ-5D-5L.

- **Effectiveness Outcomes**: CDAI, Achieving CDAI MCID, Achieving mACR 20, Achieving mACR 50, Achieving mACR 70, Pain, Fatigue, Patient Global Assessment, Morning Stiffness, J-HAQ, EQ-5D-5L, and Remain on Drug.

- **Safety Event of Interest**: Total CVD, Total Serious Infections, Total Herpes Zoster, and Total Cancer excluding NMSC.

9.4. Data Sources

The CorEvitas RA Japan Registry is a prospective, multicenter, observational disease-based registry. 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, PRO measures, disease characteristics, comorbidities and adverse events, infections, hospitalizations, and other targeted safety outcomes. Relevant standards of care laboratory and images results if reported may also be used. 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 are available in this Registry (eg, disease activity scores, comorbidities, imaging results, PRO data, etc.) that is not available in claims databases.

9.5. Study Size

There are two populations of interest: one for the primary objective (safety outcomes) and one for secondary objective (clinical effectiveness and PRO). Both populations include RA Japan patients who initiate tofacitinib, MTX, TNFi bDMARD, or non-TNFi 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.

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. Latest data cut available will be used in this study.

9.6. Data Management

According to internal SOPs, CorEvitas conducts and documents a series of quality reviews. All deliverables are reviewed and quality checked by members internal to the analytic team, and by senior staff external to the writing team. Deliverables including protocols/SAP, interim, final reports, abstracts and manuscripts are subject to review. The following checks are covered in this review.

1. Confirm the source of the data and/or results has been documented and verified against the source.

2. Check the internal consistency of the medical research data presented in the document.

3. Confirm the conclusions are accurate, objective, balanced, and consistent with other published or released results.

4. Confirm the format and content of the document is aligned with applicable external requirements.

5. Final annotated version of any publication(s) (if optional tasks are requested).

Investigators are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Pfizer. The investigator follows local laws and regulations or institutional practices for document retention.

All information about this observational study and individual subject medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

All statistical analyses will be conducted using Stata Release 16 PPD and/or R Version 4.2.0 PPD

9.6.1. Record Retention

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 a 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.

Pfizer obtained the CDAI scores from third-party study reports and Pfizer did not administer the questionnaire.

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. 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.[5] 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 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.

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 that determine physicians' selection of a particular treatment (eg, disease severity) also affect 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.

Misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While CorEvitas has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exists in anonymized structured format and contains 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. Patient Withdrawal

Not applicable.

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

IRB/IEC review was not required as the data from the registry are anonymized and structured.

10.5. 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 Guidelines for Good Pharmacoepidemiology Practices (GPP).

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, 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

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 responsible party for collecting data from the participants 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. The protocol and study results will be disclosed on ct.gov.

13. REFERENCES

1. Yamanaka H, Sugiyama N, Inoue E et al. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort. Mod Rheumatol 2014 Jan;24(1):33-40.

2. Solomon DH, Kremer J, Curtis JR et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010; 69(11): 1920-5.

3. Yamanaka, H. Rheumatoid Arthritis Management Guidelines 2014 in Japan. 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. Curtis JR, Yang S, Chen L, Pope JE, Keystone EC, Haraoui B, et al. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. Arthritis care & research. 2015;67(10):1345–53.

5. Battisti WP, Wager E, Baltzer L, et al. *Good publication practice for communicating company sponsored medical research: GPP3*. Annals of Internal Medicine 2015;**163**(6):461-64.

14. LIST OF TABLES

Not applicable.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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