NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Comparative Effectiveness of New Initiators of Tofacitinib and Other Biologic/Targeted Synthetic DMARDs in Patients with Rheumatoid Arthritis
Protocol number	A3921445
Protocol version identifier	1.0
Date	07 May 2024
Medicinal Product	Tofacitinib
Research question and objectives	What is the effectiveness of tofacitinib compared to biologic disease-modifying antirheumatic drugs (bDMARDs) in rheumatoid arthritis (RA) patients, overall and by subgroups based on demographic and clinical characteristics? What is the effectiveness of tofacitinib compared to other bDMARDs in tumor necrosis factor inhibitor (TNFi)-experienced RA patients? The objectives of this study are to: 1. To compare the real-world effectiveness of tofacitinib compared to other advanced treatments in RA patients utilizing assessments performed in routine clinical care a. New initiators [regardless of treatment history, in alignment with United States (US) Food & Drug Administration (FDA) and European Medicines Agency (EMA) labeled indications]: i. Tofacitinib versus TNFi (as a group, defined as etanercept, adalimumab, certolizumab, golimumab, infliximab) ii. Tofacitinib versus abatacept iii. Tofacitinib versus tocilizumab / sarilumab (as a group) 2. To explore the comparative effectiveness of tofacitinib

	compared to other advanced treatments in RA patients, stratified by demographic and clinical characteristics 3. To compare the real-world effectiveness of tofacitinib compared to other advanced treatments in TNFi-experienced RA patients utilizing assessments performed in routine clinical care a. Tofacitinib versus abatacept b. Tofacitinib versus tocilizumab/sarilumab
Author	PPD Pfizer, Inc. 66 Hudson Boulevard East New York, NY 10001-2192, USA PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BID	bis in die (twice a day)
BMI	body mass index
CCI	Charlson Comorbidity Index
(Anti-)-CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	confidence interval
CRP	C-reactive protein
(c)/(b)/(ts)DMARD	(conventional)/(biologic)/(targeted synthetic) Disease-Modifying Anti-Rheumatic Drugs
CV	cardiovascular
EMA	European Medicines Agency
EMR	Electronic Medical Record
FDA	Food & Drug Administration
GPP	Good Pharmacoepidemiology Practices
HR	hazard ratio
ICD	International Classification of Diseases
IPCW	inverse probability of censoring weights
IPTW	inverse probability of treatment weighting
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IRB	Institutional Review Board

Abbreviation	Definition
JAKi	janus kinase inhibitor
JIA	juvenile idiopathic arthritis
MACE	major adverse cardiovascular event
NIS	non-interventional study
NMSC	non-melanoma skin cancer
PASS	post-authorization safety study
PhRMA	Pharmaceutical Research and Manufacturers Association
PS	Propensity Score
PsA	psoriatic arthritis
QC	quality control
RA	rheumatoid arthritis
RCT	randomized controlled trial
RF	rheumatoid factor
SQL	Structured Query Language
TNFi	Tumor Necrosis Factor inhibitor
UC	ulcerative colitis
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Milena Gianfrancesco, PhD MPH	Director, Epidemiology Scientist; Global Medical Epidemiology	Pfizer, Inc.	66 Hudson Boulevard East New York, NY 10001-2192, USA
Jose Rivas, MD	Sr. Director, Medical Strategy Head Rheumatology	Pfizer, Inc.	Av. de Europa, 20, B, 28108 Alcobendas, Madrid, Spain
Genevieve Gauthier	Director, I&I RWE Scientist	Pfizer, Inc.	17300 Trans-Canada Highway Kirkland, QC, Canada, H9J 2M5

4. ABSTRACT

None.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Final Protocol	15 May 2024
Start of data collection	16 May 2024
End of data collection	15 July 2024
Final study report	31 December 2024

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Patients experience impaired physical function, social participation, and health-related quality of life. Patients also have increased risk of significant comorbidities that are not musculoskeletal. For RA, therapeutic options currently available include conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs), biological DMARDs (bDMARDs), and targeted-synthetic DMARDs (tsDMARDs). Strategies have been developed to treat RA by inhibiting Janus kinase (JAK) pathways and the first JAK inhibitor approved for the treatment of RA in the U.S. was tofacitinib (Xeljanz®; Pfizer; November 2012).[1]

Unlike biological therapies, such as TNFi, monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity relative to other kinases in the human genome.

As a commitment to the US FDA, Pfizer conducted the ORAL Surveillance Study (A3921133),[2] a post-authorization safety study (PASS). A3921133 evaluated the risk of major adverse cardiovascular event (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) with tofacitinib (5 and 10 mg BID) versus TNFi in patients with moderately or severely active RA who had an inadequate response to methotrexate and who were 50 years of age or older and had at least 1 additional cardiovascular (CV) risk factor. In February 2019, a safety analysis of ongoing study, A3921133, reported the frequency of pulmonary embolism and all-cause mortality in patients receiving tofacitinib 10 mg BID was higher than in patients treated with a TNFi. On 26 July 2019, the FDA approved new warnings about an increased risk of blood clots and death with the 10 mg twice daily dose of tofacitinib, which was only approved for ulcerative colitis (UC). Use of the 10 mg twice daily dose became limited beyond the induction phase. The approved use of JAKi for UC also became limited to patients who demonstrated inadequate response or intolerance to one or more TNF blockers.

In January 2021, in the final analysis of ORAL Surveillance, for the combined tofacitinib doses (5 and 10 mg BID) versus TNFi, non-inferiority was not shown for either adjudicated MACE or adjudicated malignancies (excluding NMSC). In December 2021, a JAKi class label

extended the post-TNFi restriction to all gastroenterological and rheumatologic indications for all future approved JAKi in the US. These findings also led to a review by the EMA, not resulting in a change in the line of therapy, but a limitation of the use of JAKi in certain patient sub-populations (only be used if no suitable treatment alternatives are available in patients: 65 years of age and older; patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);

patients with malignancy risk factors (eg, current malignancy or history of malignancy). Though the efficacy and safety profile of tofacitinib has been established in prior randomized controlled trials,[3,4,5] the real-world effectiveness of tofacitinib in routine care settings compared to frequently used bDMARDs is lacking. The evidence from prior RCTs is limited by the relatively small sizes and due to strict eligibility criteria, which reduces the generalizability of the results. For example, there is limited evidence on the effectiveness of tofacitinib compared to individual agents such as abatacept and within clinically relevant subgroups such as patients with prior use of tumor necrosis factor inhibitors (TNFi). The majority of the RCT populations required background use of methotrexate and excluded patients who were treated with other bDMARDs. Though there are some studies of tofacitinib using real-world data,[6-9] they tend to be limited by sample size, and primarily focused on safety outcomes with limited research on effectiveness outcomes such as clinical disease activity.[10,11] The purpose of this study is to evaluate the real-world effectiveness of patients treated with tofacitinib compared to other select bDMARD in relation to indicated use according to the FDA[12] and EMA labels,[13] as well as within relevant subgroups harnessing data from the US based OM1 PremiOM™ RA dataset (OM1, Inc., Boston, MA).

8. RESEARCH QUESTION AND OBJECTIVES

Research Questions:

- What is the effectiveness of tofacitinib compared to bDMARDs in RA patients, overall and by subgroups based on demographic and clinical characteristics?
- What is the effectiveness of tofacitinib compared to other bDMARDs in TNFi-experienced RA patients?

The objectives of this study are to:

1. To compare the real-world effectiveness of tofacitinib compared to other advanced treatments in RA patients utilizing assessments performed in routine clinical care
    a. New initiators (regardless of treatment history, in alignment with FDA and EMA labeled indications):
        i. Tofacitinib versus TNFi (as a group, defined as etanercept, adalimumab, certolizumab, golimumab, infliximab)
        ii. Tofacitinib versus abatacept
        iii. Tofacitinib versus tocilizumab/sarilumab (as a group)
2. To explore the comparative effectiveness of tofacitinib compared to other advanced treatments in RA patients, stratified by demographic and clinical characteristics.
3. To compare the real-world effectiveness of tofacitinib compared to other advanced treatments in TNFi-experienced RA patients utilizing assessments performed in routine clinical care

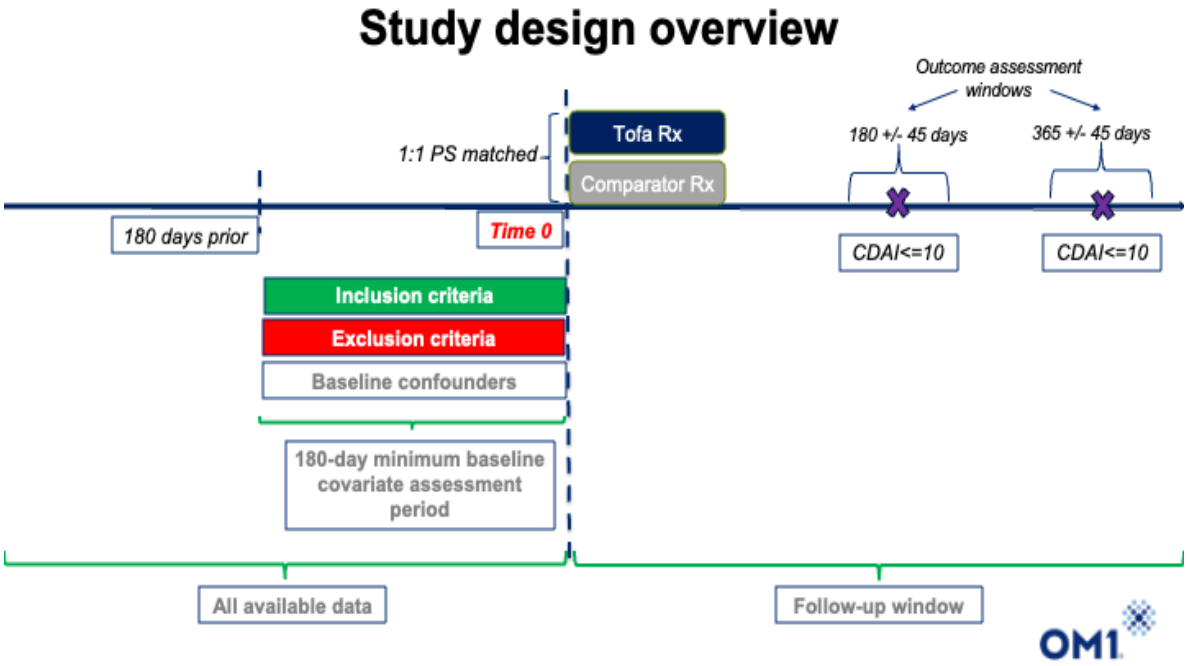
a. Tofacitinib versus abatacept

b. Tofacitinib versus tocilizumab/sarilumab

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study to evaluate the real-world effectiveness of patients with RA treated with tofacitinib compared to other select bDMARDs using data from the U.S. based OM1 PremiOM™ RA dataset (OM1, Inc., Boston, MA). A graphical summary of the study design is provided below.



9.2. Setting

The study period is from January 2013 through the date of the most recent data available at the time of analysis (anticipated to be December 2023). All available data will be included in the analysis; the length of follow-up time will vary per patient.

9.2.1. Inclusion Criteria

Eligibility (inclusion and exclusion) criteria will be assessed at baseline using all available data prior to and including the cohort entry date. All patients will have at least 180 days of baseline information available by design.

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

1. Age ≥18 years on the cohort entry date.

2. Diagnosed with RA at any time prior to cohort entry date:

    a. At least two RA diagnosis codes at least 30 days apart, each coming from an encounter with a rheumatologist;

    b. At least one inpatient visit with a RA diagnosis code;

    c. At least two outpatient records with a RA diagnosis code at least 30 days apart and within a year, regardless of physician specialty; or

    d. At least one outpatient record with an RA diagnosis and a prescription or fill for a DMARD from a specified list and does not have any of the non-RA conditions for which those drugs may also be prescribed.

3. Initiation of specified b/tsDMARDs of interest for treatment of RA (ie, tofacitinib, etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, tocilizumab, or sarilumab).

4. At least 180 days of baseline data available prior to and including the cohort entry date.

5. At least one Clinical Disease Activity Index (CDAI) score in 45 days prior to and including the cohort entry date (baseline).

9.2.2. Exclusion Criteria

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

1. Patients diagnosed with concomitant indications for tofacitinib [psoriatic arthritis (PsA), UC, and polyarticular course juvenile idiopathic arthritis (pcJIA)] at any time prior to cohort entry date, determined by at least two (2) diagnosis codes at least 30 days apart and prior to baseline.

2. Patients with >1 b/tsDMARD (ie, tofacitinib, etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept tocilizumab, or sarilumab) prescribed on index date.

9.3. Variables

9.3.1. Exposures

The study cohorts will be constructed using a new-user, active comparator design[14] as three pairwise comparisons between tofacitinib initiators and initiators of a comparator medication. ***Treatment initiation*** will be defined as no use of the study medication at any time prior to cohort entry (For example, a tofacitinib initiator will be required to have no tofacitinib use prior to cohort entry, however they are allowed to use other medications). The start date of a patient's b/tsDMARD will be termed the ***cohort entry date*** (also known as index date or time

zero). The cohort entry date will be operationalized as the first day of a prescription, fill, or administration for an eligible study medication. The pairwise comparisons are summarized below.

Table 1. Cohort Overview

Cohort	Exposure	Comparator
Cohort 1	Tofacitinib	TNFi (as a group, defined as etanercept, adalimumab, certolizumab, golimumab, infliximab)
Cohort 2	Tofacitinib	Abatacept
Cohort 3	Tofacitinib	Tocilizumab or sarilumab

9.3.2. Covariates

Potential confounders that will be considered include demographics, baseline RA disease severity, comorbidities, lab values and medication use and are detailed in Table 2. Confounders will be assessed using all available data prior to and including the cohort entry date unless otherwise stated (***the baseline covariate assessment period***).

Table 2. Study Variable Overview

Variable	Timing	Operational Definition
Cohort entry date		The start date of a patient's b/tsDMARD will be termed the ***cohort entry date*** (also known as index date or time zero)
Baseline covariate assessment period	All available data prior to and including the cohort entry date	All available data prior to and including the cohort entry date unless otherwise stated
Follow-up period	1 day after the cohort entry date	Patients will be followed up for outcomes within their pre-defined outcome assessment windows. The primary analysis will use an outcome assessment window of 135-225 days (ie, 180±45) after the cohort entry date to assess outcomes. A secondary analysis will use an outcome assessment window of 320-410 days (ie, 365±45) after the cohort entry date to assess outcomes
Treatment discontinuation		To define treatment discontinuation, medication-specific eras (referred to as drug eras hereafter) covering the period of one or more prescriptions, fills, or administrations for the index medication will be collapsed into a single period of continuous use if the end date of the prior prescription, fill, or administration falls within 90 days of the start date of the next. Treatment is defined as discontinued if there is no start date within 90 days after the end date of the first drug era. If the last encounter date is within 90 days after the first drug era end date, the treatment is considered as "ongoing" (ie, not discontinued).
Baseline characteristics		

Variable	Timing	Operational Definition
Age (years), continuous	On the cohort entry date	Year of the index date minus the year of birth
Age, categories	On the cohort entry date	18-24 25-39 40-64 65+
Duration of continuous enrollment prior to cohort entry date		
Year of index date	On the cohort entry date	
Race	Most recent prior to and including cohort entry date	White, Black, Asian, Other, Unknown/Not documented
Ethnicity	Most recent prior to and including cohort entry date	Hispanic, Non-hispanic, Unknown/Not documented
Geography	Most recent prior to and including cohort entry date	U.S. Census Division • East North Central • East South Central • Middle Atlantic • Mountain • New England • Pacific • South Atlantic • West North Central • West South Central • Unknown
Insurance type	Most recent prior to and including cohort entry date	Commercial Medicare Medicaid Other Multiple Unknown
RA disease duration (categorical)	Baseline	Categorical (< 2 years, ≥ 2 years)
BMI Continuous	Most recent prior to and including cohort entry date	Numeric BMI (in kg/m²)
BMI Categorical	Most recent prior to and including cohort entry date	Underweight: <18.5 Normal weight: 18.5-<25 Overweight: 25- <30 Obese: ≥30 Unknown
Smoking status	Most recent prior to and including cohort entry date	Ever smoker Never smoker Unknown
RA disease severity	Baseline	Continuous CDAI [mean (SD); median (Q1, Q3)] Categorical CDAI:

Variable	Timing	Operational Definition
		1. Remission: 0.0-2.8 2. Low activity: 2.9-10.0 3. Moderate activity: 10.1-22.0 4. High activity: 22.1-76.0 Joint count: ● Tender joint count (0-28) ● Swollen joint count (0-28)
Charlson Comorbidity Index	Baseline	Charlson Comorbidity Index score as of the cohort entry date using diagnosis codes from claims and EMR data during the baseline period.
Charlson Comorbidity Index	Baseline	Calculated category on the cohort entry date ● 0-1 ● 2-3 ● 4-5 ● 6+
Comorbidities	Baseline	Binary yes/no variables for present prior to and including the cohort entry date, defined based on at least two ICD diagnosis codes at least 30 days apart: ● Cardiovascular disease (coronary artery disease, atherosclerosis, peripheral arterial disease, hypertension, dyslipidemia) ● Chronic obstructive pulmonary disease ● Fibromyalgia ● Malignancies ● Osteoporosis ● Type 1 diabetes ● Type 2 diabetes ● Sjögren's syndrome
Laboratory results	Most recent prior to and including cohort entry date	● RF (positive (high, low), negative/unknown) ● Anti-CCP (positive, negative/unknown) ● CRP (categorical <3 mg/L versus ≥3 mg/L)
Prior cDMARD use	Baseline	A binary (yes/no) variable indicating use of any of the following medications ● cDMARDs (auranofin, azathioprine, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine, leflunomide, methotrexate, minocycline, penicillamine, sulfasalazine)
Prior bDMARD use	Baseline	A binary (yes/no) variable indicating use of any of the following medications ● bDMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab

Variable	Timing	Operational Definition
Prior tsDMARD use	Baseline	A binary (yes/no) variable indicating use of any of the following medications ● tsDMARDs (baricitinib, tofacitinib, upadacitinib)
Concurrent cDMARD use	On the cohort entry date	A binary (yes/no) variable indicating use of any of the following medications at baseline or at any time while on the index medication: ● cDMARDs (azathioprine, hydroxychloroquine, leflunomide, methotrexate, sulfasalazine)
Number of prior b/tsDMARD therapies	Baseline	Categorical (≥2, <2; ≥1, <1)
Corticosteroid use	180 days prior to and including the cohort entry date	Prescription, fill or administration of oral or injectable 6 months prior to index, binary yes/no
Any hospitalization	30 days prior to and including the cohort entry date	Any inpatient encounter
Dose of index Tofacitinib	On the cohort entry date	Dose: 5 mg vs 11 mg, frequency: Once vs twice daily

9.3.3. Patient Follow-Up

Patients will be followed up for outcomes within their pre-defined outcome assessment windows. Outcomes will be examined at two timepoints: an outcome assessment window of 135-225 days (ie, 180±45) after the cohort entry date; and a window of 320-410 days (ie, 365±45) after the cohort entry date. Patient follow-up will begin 1 day after cohort entry and will end at the occurrence of an outcome or a censoring event: 1) if they discontinue their index treatment, 2) switch to a different ts/bDMARD, 3) are lost to follow-up, or 4) on the last day of the outcome assessment window for each analysis, whichever comes first.

9.3.4. Outcomes

The primary outcome for this study will be a documented (yes/no) improvement or maintenance (depending on the patients' baseline CDAI score) in disease activity defined as a first record of low disease activity/remission which corresponds to a CDAI score lesser than or equal to 10.0 during the pre-defined outcome assessment windows. The outcome will be analyzed as a time-to-event variable using survival analysis methods. Cox proportional hazards regression will be used to analyze the outcome as time-to-event data, which accounts for the impact of censoring (eg, due to treatment discontinuation or switch) on the relationship between treatment and the event of interest. Further explanation is provided in Section 9.7.1.

Table 3. Clinical Outcomes

Outcomes		
Clinical Disease Activity Index (CDAI)	Follow-up [135-225 days (ie, 180±45) and 320-410 days (ie, 365±45) after the cohort entry date]	Remission or low disease activity: 0.0-10.0

9.4. Data Sources

A retrospective design will be used to explore the comparative effectiveness of tofacitinib among a cohort of patients with RA in the U.S. using the OM1 PremiOM™ RA dataset (OM1, Inc., Boston, MA). This dataset of over 244,000 patients with RA is derived from deterministically linked, de-identified, individual-level healthcare claims and EMR data. EMR data are derived from several healthcare systems and rheumatologist's EMR provider systems geographically representative of the U.S. population. The EMR data include encounters, medication history and prescription information, laboratory results, PROs, and clinical observations as documented by a rheumatologist. Additional medical and pharmacy claims data containing coding history on inpatient and outpatient encounters from clinics, acute care facilities, or ambulatory surgical centers are linked to the clinical data described above to fill information gaps in patients' clinical care. At the time of analysis, the OM1 PremiOM™ RA dataset covered the time period from 01 January 2013 through 31 December 2023.

9.5. Study Size

The sample size is not determined based on a formal statistical power analysis. Preliminary feasibility analyses indicated a sample size range of approximately 10,705 patients with RA with a prescription of tofacitinib in the OM1 dataset, and 44,595 patients with a prescription for a b/tsDMARD other than tofacitinib. Sample size will not be fully determined until all eligibility criteria are applied.

9.6. Data Management

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the principles outlined in the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research), and any applicable national guidelines. Following these best practices, OM1 has standard operating procedures including internal quality audits, rules for secure and confidential data, methods to maintain and archive project documents, quality-control procedures for programming, and standards for writing analysis plans.

9.7. Data Analysis

Statistical analysis of this study will be the responsibility of OM1, Inc., with review and approval by Pfizer. Any change to the data analysis methods described in this study protocol will require an amendment ONLY if it changes a principal feature of the study protocol. Any other changes to the data analysis methods described in the study protocol and the justification for making the changes will be described in the study report or equivalent document. Analysis datasets will be prepared by Structured Query Language (SQL). Data analysis will be performed using R or SAS Software (SAS Institute, Cary, NC, U.S.), Version 9.4.

Continuous variables will be summarized by mean (standard deviation [SD]) and median (Q1, Q3). Categorical variables will be summarized by count and percentage for each category. Depending on the distribution of data, very small categories (for example, <5 patients) may be combined with a larger category for easier interpretation. The denominator for the percentages will be the number of patients with non-missing data. The number of patients with missing data will be presented, but these patients will not be included in the denominator in the calculation of percentages.

9.7.1. Objective 1: Real-World Comparative Effectiveness of Tofacitinib in New Initiators of Select bDMARDs

Statistical analysis:

Objective 1 will aim to assess the comparative effectiveness of tofacitinib initiators vs bDMARDs in achieving low disease activity as assessed by CDAI score.

We will use inverse probability of treatment weighting (IPTW) using stabilized weights[15] to adjust for baseline confounders. Patients will be weighted by the inverse probability of the treatment they actually received. For tofacitinib initiators the IPTW will be = 1/propensity score (PS), whereas, for the comparator medication the IPTW will be = 1/(1-PS). Stabilization will be done by incorporating the marginal probability of the treatment they actually received in the numerator of the weights.[16] Other weighting methods such as overlap weights[17,18] will be considered as an alternative if IPTW leads to extreme weights despite stabilization. Overlap weights are a weighting analogue of PS matching that targets an estimand similar to PS matching by standardizing the covariate distribution to those patients where there is overlap of the PS distributions. For each patient, the overlap weight will be calculated as the probability of receiving the opposite treatment (or the treatment they didn't receive). For tofacitinib initiators the overlap weight will be =(1 - PS), whereas, for a comparator medication the overlap weight will be = (PS).

The propensity score will be estimated (separately in the three pairwise cohorts) using logistic regression as the predicted probability of initiating tofacitinib vs. the comparator medication as a function of the baseline covariates. Baseline patient characteristics before and after weighting will be tabulated, and covariate balance will be assessed using

standardized differences. Standardized differences <0.1 indicate adequate balance between treatment groups.[19]

Number of events and incidence rates will be reported for each exposure group. Weighted hazard ratios (HR) and 95% confidence intervals (CIs) will be estimated in each weighted cohort using Cox regression with robust standard errors to account for the weighting. Two timepoints will be examined: an outcome assessment window of 135-225 days (ie, 180 ± 45) after the cohort entry date; and an outcome assessment window of 320-410 days after the cohort entry date.

Reasons for censoring will be reported separately for each exposure group and potential bias due to censoring will be evaluated and may be addressed analytically using inverse probability of censoring weights (IPCW). Additional sensitivity analyses may be conducted to further examine any bias due to censoring/loss-to-follow-up that may be associated with the exposure. This may include methods such as bias analysis with imputation of extreme values for missing outcome data, or intention to treat analyses (ie, not censoring at switch).

9.7.2. Objective 2: Treatment Effect Heterogeneity in Assessing the Comparative Effectiveness of Tofacitinib vs. bDMARDS

In objective 2, analyses from objective 1 will be stratified to assess treatment effect heterogeneity. Crude hazard ratios (95% CIs) will be reported within predefined subgroups from the overall weighted population in each of the three cohorts. Thus, it will be assumed that the PS generated across the entire cohort is also valid for the subgroups.[20] The pre-defined subgroups include the following; however, the final subgroups will be determined after running feasibility checks to ensure adequate sample size.

- Age (≥65 vs. <65; ≥ 50 vs. <50)
- Sex
- Disease duration (categorical, at least 2 years versus less than 2 years)
- Obesity (≥30 kg/m^2 vs. <30 kg/m^2 at value closest to index)
- Baseline disease activity (CDAI >10 versus CDAI<=10)
- Number of documented prior b/tsDMARD therapies (≥2 vs. <2, ≥1 vs. <1)
- Rheumatoid factor (“RF”) status (positive, negative/unknown), in patients with Rh status available, if sample size allows
- Anti-CCP status (positive, negative/unknown)
- CRP level (closest to baseline, categorical <3 mg/L versus ≥3 mg/L)

- Corticosteroid use at index date (± 30 days)
- Smoking status (ever smoker, never smoker, unknown)
- Comorbid Sjögren's syndrome (yes, no; if sample size allows)

9.7.3. Objective 3: Real-World Comparative Effectiveness of Tofacitinib versus New Initiators of Select bDMARDs in TNFi-experienced Patients

Objective 3 will aim to assess the comparative effectiveness of tofacitinib initiators vs other bDMARDs in achieving low disease activity as assessed by CDAI score within Cohorts 2 & 3 amongst a subgroup of patients with TNFi use in the 365 days prior to the cohort entry date.

The analytic methods used in objective 3 will be identical to that of objective 1.

9.8. Quality Control

OM1 acquires data from disparate sources through batch transfers of data files. After receiving data, OM1 performs robust Quality control (QC) checks on the raw data (from the sources) as well as the processed data received. As the data goes through a series of normalization, harmonization, and enrichment processes, it is subjected to a series of industry-standard data quality checks which are further augmented with additional OM1-defined data quality checks whereby quality metrics and associated artifacts are gathered and reviewed by subject matter experts within OM1's Clinical Informatics and Research groups. Based on the findings within these checks, additional processing and resolution steps are implemented, and the steps are repeated. These steps are repeated until there are no data quality issues identified during these checks. These QC checks follow standard dimensions of quality, such as fidelity of the data through completeness and correctness, representativeness, validity, usability, and fit-for-use of the data. Additional quality checks are then performed when end points are defined and programmed to ensure validity, correctness, accuracy, and conformity to the study requirements.

OM1 performs deduplication on the data received through disparate data sources as part of processing whereby redundant patient records are removed from the OM1's Real-World Data Cloud, preventing fragmented and duplicated data points and records from being incorporated into the Cloud and ensuring that the most updated and accurate patient information is processed and represented in OM1's data.

9.9. Limitations of the Research Methods

The employment of real-world health history data for analysis may be subject to issues of missingness or incomplete data capture, compounded by errors stemming from inaccuracies in data recording or transcription which may lead to misclassification.

As this is an observational study, residual confounding due to unmeasured confounders cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at prespecified time points, which may have an impact on the amount of data and its interpretation. Patients who do not return for an office visit during the outcome assessment windows, who may actually have a CDAI<10, will not be captured in our study. Some patients may also be lost to follow-up before the pre-defined outcome assessment windows which may lead to some under-ascertainment of actual outcomes. If this under-ascertainment is differential, then there is the potential that the study results may be impacted by a substantial bias either towards or away from the null. If a treatment is ineffective in a given patient and that treatment is discontinued prior to measurement of outcomes, removal of patients for whom the treatment is ineffective could induce substantial bias where only patients who do well on treatment are included in the analysis. It is possible that a drug that has no effect on the outcome could appear beneficial because only patients who benefit from the drug are included in the analysis of outcomes. Sensitivity analyses (such as, but not limited to, intent to treat analysis, where patients are not censored at treatment switch or discontinuation) and examination of assumptions of non-differential loss-to follow-up will be required for the results to have a useful interpretation.

Another source of bias that may affect results if outcome measurement is related to the assessor's knowledge of the patient's condition. For example, if a physician believes the patient will have a poor CDAI score (or a very good CDAI score), they may be less likely to perform that assessment. This phenomenon could bias results either towards or away from the null. Further sensitivity analyses will be needed to quantify the potential impact of this bias, where the assumptions around lack of measurement at the time point of interest are examined. However, if the censoring process is sufficiently captured by the measured baseline covariates that also predict outcome occurrence, then such bias can be mitigated using IPCW.

The study population includes patients with CDAI scores ≤10 at baseline who may be more likely to experience the study outcome and the proportion of these patients may be different across exposure groups. To account for this, baseline CDAI scores will be included as a covariate to estimate the PS to ensure balance on this variable. Further, stratified analyses will be conducted (sample-size permitting) by baseline CDAI score.

Finally, treatment effects reported in stratified analyses conducted as part of Objective 2 should be interpreted with caution as these analyses will likely be limited by sample size.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves de-identified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethnics Committee (EC)

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and aggregate analyses that omit subject identification, therefore informed consent, ethics committee or institutional review board (IRB) approval are not required. Any publications and reports will not include subject identifiers.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidance, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and applicable regulatory requirements.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Manuscripts based on specific endpoints of interest may be developed for external publication purposes.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer will be informed immediately.

13. REFERENCES

1. FDA Approves Xeljanz for Rheumatoid Arthritis. Drugs.com. Accessed February 5, 2024. https://www.drugs.com/newdrugs/fda-approves-xeljanz-rheumatoid-arthritis-3558.html.

2. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med*. 2022;386(4):316-326. doi:10.1056/NEJMoa2109927.

3. Wang F, Sun L, Wang S, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Mayo Clin Proc*. 2020;95(7):1404-1419. doi:10.1016/j.mayocp.2020.01.039.

4. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):508-519. doi:10.1056/NEJMoa1112072.

5. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet Lond Engl*. 2017;390(10093):457-468. doi:10.1016/S0140-6736(17)31618-5.

6. Shouval A, Lidar M, Reitblat T, et al. Real-world effectiveness of tofacitinib in patients with rheumatoid arthritis: a prospective observational study. *Clin Exp Rheumatol*. 2021;39(6):1378-1384. doi:10.55563/clinexprheumatol/do2uxu.

7. Harrold LR, Wittstock K, Kelly S, et al. Comparative Effectiveness of Abatacept vs. Tofacitinib in Rheumatoid Arthritis Patients who are CCP+. *Rheumatol Ther*. 2023;10(3):575-587. doi:10.1007/s40744-022-00523-z.

8. Pappas DA, St John G, Etzel CJ, et al. Comparative effectiveness of first-line tumour necrosis factor inhibitor versus non-tumour necrosis factor inhibitor biologics and targeted synthetic agents in patients with rheumatoid arthritis: results from a large US registry study. *Ann Rheum Dis*. 2021;80(1):96-102. doi:10.1136/annrheumdis-2020-217209.

9. Mori S, Urata Y, Yoshitama T, Ueki Y. Tofacitinib versus tocilizumab in the treatment of biological-naïve or previous biological-failure patients with methotrexate-refractory active rheumatoid arthritis. *RMD Open*. 2021;7(2):e001601. doi:10.1136/rmdopen-2021-001601.

10. Khosrow-Khavar F, Kim SC, Lee H, Lee SB, Desai RJ. Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. *Ann Rheum Dis*. 2022;81(6):798-804. doi:10.1136/annrheumdis-2021-221915.

11. Khosrow-Khavar F, Desai RJ, Lee H, Lee SB, Kim SC. Tofacitinib and Risk of Malignancy: Results From the Safety of Tofacitinib in Routine Care Patients With Rheumatoid Arthritis (STAR-RA) Study. *Arthritis Rheumatol Hoboken NJ*. 2022;74(10):1648-1659. doi:10.1002/art.42250.

12. Xeljanz | U.S. Food and Drug Administration. Accessed March 11, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf.

13. Xeljanz | European Medicines Agency. Accessed March 11, 2024. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf.

14. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.

15. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164.

16. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ*. 2019;367:l5657. doi:10.1136/bmj.l5657.

17. Li F, Thomas LE, Li F. Addressing Extreme Propensity Scores via the Overlap Weights. *Am J Epidemiol*. 2019;188(1):250-257. doi:10.1093/aje/kwy201.

18. Thomas LE, Li F, Pencina MJ. Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial. *JAMA*. 2020;323(23):2417-2418. doi:10.1001/jama.2020.7819.

19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697.

20. Wang SV, Jin Y, Fireman B, et al. Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses. *Am J Epidemiol*. 2018;187(8):1799-1807. doi:10.1093/aje/kwy049.

14. LIST OF TABLES

15. LIST OF FIGURES

NA.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	NA	29 March 2024	A3921445 Pfizer RA Table shells_FINAL.xlsx
2	Page 13	29 March 2024	Diagnosis Codes to Define RA.xlsx

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921445 Non Interventional Protocol Final Version 1.0_07 May 2024
Document Title:	A3921445 Non Interventional Protocol Final Version 1.0_07 May 2024

Signed By:	Date(GMT)	Signing Capacity
PPD	13-May-2024 11:52:48	Business Line Approver
PPD	13-May-2024 13:33:14	Author Approval
PPD	13-May-2024 16:33:38	Scientific Review