NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	An Observational Study of Xeljanz® (tofacitinib citrate) and Biologic Rheumatoid Arthritis Treatments to Characterize their General Treatment Patterns, Effectiveness and Safety in a Real-World Taiwanese Population
Protocol number	A3921275
Version identifier of the final study report	1.0
Date	25 March 2022
EU Post Authorization Study (PAS) register number	EUPAS13431
Active substance	L04AA29 Tofacitinib
Medicinal product	Tofacitinib
Research question and objectives	The objective of this study was to understand general treatment patterns, effectiveness, and safety of tofacitinib in a non-restricted population of rheumatoid arthritis Taiwanese patients in the real-world setting.
Author	Redacted

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ACR50	American College of Rheumatology response criteria for 50% improvement
AE	Adverse Event
bDMARD	Biologic Disease-modifying Anti-Rheumatic Drugs
cDMARD	Conventional Disease-Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
CRP	C-reactive Protein
DAS28-ESR	Disease Activity Score 28 Erythrocyte Sedimentation Rate
DMARD	Disease-modifying Anti-Rheumatic Drug
EFF	Effectiveness Analysis Set
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IR	Incidence Rates
IRB	Institutional Review Board
MACE	Major Adverse Cardiovascular event
MCID	Minimum Clinically Important Difference
NHI	National Health Insurance
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PDC	Proportion of Days Covered
PRO	Patient-reported Outcome
PS	Propensity Score

Abbreviation	Definition
PT	Preferred Term
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SOC	System Organ Class
TAE	Targeted Adverse Event
TB	Tuberculosis
TNFi	Tumor Necrosis Factor inhibitor
WPAI	Work Productivity and Activity Index
WPAI-RA	Work Productivity and Activity Index-Rheumatoid Arthritis

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Redacted	[redacted]	Pfizer Taiwan

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol The IEC/IRB approval dates for the protocol and any amendments is provided in Appendix 3.2.	March 2016 April 2018	May 2016 May 2018	
Start of data collection	April 2016	12 August 2016	
End of data collection	April 2021	31 May 2021	
Registration in the EU PAS register		11-May-2016	
Interim analysis I	April 2017	July 2017	
Interim analysis II	April 2018	July 2018	
Interim analysis III	April 2019	June 2020	
Interim analysis IV	April 2020	April 2021	
Final report of study results	August 2021	25 March 2022	

6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disorder that mainly affects the diarthrodial joint, often causing pain and deformity in affected persons.[1] It is the most common form of inflammatory arthritis and has a substantial societal effect in terms of cost, disability, and lost productivity.[2] The global prevalence of RA between 1980 and 2019 was, 0.46% (or 460 per 100,000 population; 95% confidence interval 0.39-0.54; I2 = 99.9%) with a 95% prediction interval (0.06-1.27), with variations due to geographical location and study methodology.[3,4] In Asia, the RA prevalence is 0.1–0.3% of the general population and the average age-adjusted annual incidence rate is 15.8 per 100,000 people in Taiwan.[5,6] It is more common in developed countries and is highly prevalent in women compared to men.[3] While the specific etiology of the disease is unknown, risk factors such as gender, age, carrier of specific human leukocyte antigen alleles, bacterial infection, cigarette smoking, and stress are considered to increase one's likelihood of developing RA.[1]

The primary aim of RA treatment involves symptomatic management of pain and inflammation.[7] The medications used in the management of RA symptoms include non-steroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs), and corticosteroids. The choice of therapeutic agent(s) is influenced by the severity of disease, medication risk for a particular patient, and patient preference. The available literature supports early aggressive treatment with DMARDs (methotrexate, sulfasalazine or leflunomide), used alone or in combination with low-dose glucocorticoids, to induce and maintain tight control of disease.[8-15] When treatment goals are not achieved with this treatment approach, a biologic DMARD (bDMARD) as second line is often added. At the start of this study, bDMARDs included tumor necrosis factor inhibitors [(TNFi) such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab)], abatacept, tocilizumab and under certain circumstances rituximab.[16]

There are limitations associated with bDMARDs which include the mode of administration (parenteral), high costs, and side-effects as well as the potential for antidrug antibodies.[17,18] Tofacitinib (Xeljanz®), an orally administered non-biologic and potent, selective inhibitor of the Janus kinase family of kinases with a high degree of selectivity against other kinases in the human genome, can be considered as a good alternative if traditional DMARDs fail. It was approved in Taiwan for patients with moderate to severe RA in December 2013 and nationally reimbursed as of December 2014.

At the time of this study initiation there was limited data describing the characteristics of patients who received tofacitinib in Taiwan, as well as the long-term clinical effectiveness, and safety of tofacitinib in the real-word setting. In the context of the treatment of RA patients in Taiwan and the current reimbursement guidelines, it was also important to study clinical outcomes, and patient-reported outcomes (PRO) associated with current treatment practice. Pfizer has therefore conducted a real-world study of Xeljanz® (tofacitinib) and TNFi users in Taiwan. This non-interventional study was also designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer. The study was registered on the

European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) with the EU PAS Register Number EUPAS13431.

7. RESEARCH QUESTION AND OBJECTIVES

The main objectives of this multicenter, prospective, observational comparative study in Taiwan were to understand effectiveness, general treatment patterns, and safety of tofacitinib in a non-restricted population of RA patients in the real-world setting.

The primary objective of this study was to describe and compare the baseline characteristics and effectiveness of the treatment group (ie, newly initiated patients on tofacitinib) and the comparison group [ie, newly initiated patients on commonly used treatments either Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)]. This included the following:

1. Describe the baseline characteristics of RA patients prescribed tofacitinib or TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)] and evaluate whether baseline characteristics of patients treated with tofacitinib were comparable to patients prescribed TNFi within line of therapy.
2. Describe measures of short-term and long-term effectiveness for tofacitinib and TNFi:
    a. Clinical effectiveness after one-week following the start of treatment as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) which is a patient-administered questionnaire, and the Clinical Disease Activity Index (CDAI).
    b. Clinical effectiveness over the long-term as measured by the HAQ-DI, CDAI, and the Disease Activity Score 28 (DAS28) - Erythrocyte Sedimentation Rate (ESR).
3. Compare the long-term effectiveness of tofacitinib and TNFi if baseline characteristics of patients treated with tofacitinib and TNFi were comparable.

The secondary objectives of this study were to:

1. Describe safety outcomes in patients receiving tofacitinib and TNFi. The safety outcomes of interest [Targeted Adverse Events (TAE)] included cardiovascular events, hepatitis B and C reactivation, tuberculosis (TB), serious infections, herpes zoster, malignancy, and liver enzyme abnormalities.
2. Describe the treatment patterns of RA patients prescribed tofacitinib and TNFi in the study.
3. Describe adherence and persistence to tofacitinib and TNFi in RA patients in the study.
4. Describe clinical outcomes and patient-reported outcomes following mandated reduction of dose/weaning off tofacitinib or TNFi after 24 months per national insurance requirements.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1. Study Design

This was a prospective, observational, multicenter, comparative effectiveness study of tofacitinib and TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)] in Taiwanese patients with RA. The treatment group comprised of patients newly initiated on tofacitinib for RA as prescribed by the physician in Taiwan. Tofacitinib is labelled for treatment as a 5 mg tablet twice daily and was approved in combination with methotrexate or other non-biologic DMARDs for moderately to severely active RA patients who have inadequate response or are intolerant to methotrexate. The comparison group comprised of patients newly prescribed either Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) for RA at a given dose per label instructions and as directed by the physician in Taiwan. Patients could have been treated with another TNFi previously.

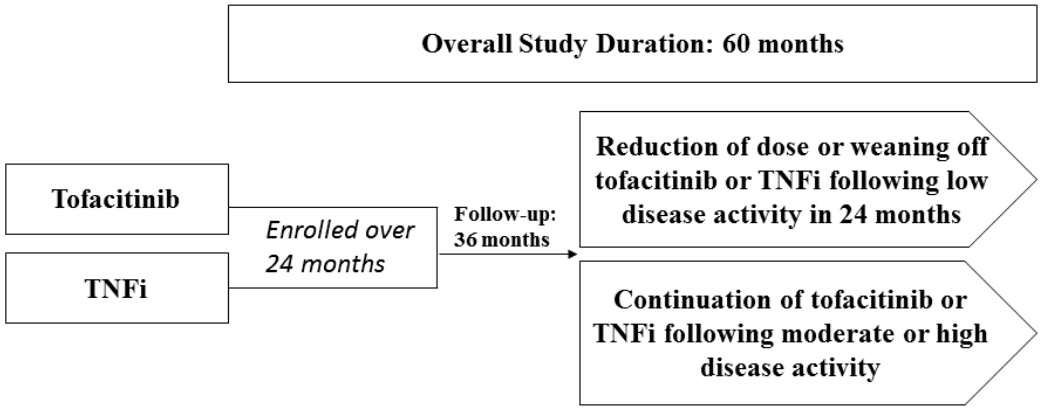
The study collected data on the short and long-term effectiveness, safety, treatment patterns and adherence for patients who were newly prescribed tofacitinib or a TNFi in routine practice by physicians in Taiwan. As this was an observational study, patients received care based on the standard of care for RA patients in Taiwan and per the judgment of the patient's treating physician. No drug was supplied for this study, but patients received treatment through standard local practice. The evaluation of study outcomes during follow-up was at the discretion of the treating physician. The study data collection and assessment schedule are described in Table 1.

Written informed consent was provided by the patients prior to being enrolled into the study. Patients who met all the inclusion and exclusion criteria were followed up for at least 36 months or death, withdrawal from study, or loss of follow-up, whichever occurred first.

A dose tapering policy of advanced therapy was introduced in the treatment guideline of RA since 2014 under the National Health Insurance (NHI) in Taiwan, which requests that patients achieving low disease activity after 24 months of treatment be tapered from the dose of tofacitinib or TNFi and discontinued from tofacitinib or TNFi in the following 12 months. However, the dose reduction due to low disease activity could occur at any time during the study. More detail is provided in Section 9.5.2.2.

The patients continued to be followed up in the study even if they discontinued treatment at any point during the study duration. Figure 1 shows a description of the study design.

Figure 1 Study Design



TNFi: Tumor Necrosis Factor inhibitor.

*Dose changes not mandated by the NHI at 24 months can occur at any time during follow-up.

Data were collected at baseline and at 6-month intervals (24 weeks) thereafter reflecting treatment outcomes over the previous 6 months, even if patient switched therapy according to routine clinical practice. Data from visits that occurred prior to a 6-month data collection point was documented in the medical charts. Baseline data included patient socio-demographic, clinical and treatment characteristics, summarized in more detail in Section 9.4 and Section 9.5. During follow-up, patient medical records were used to evaluate effectiveness and safety outcomes along with physician and patient questionnaires. The measurements of effectiveness and safety outcomes are described in more detail in Section 9.5.

Visits occurring outside of the 6-month (24 weeks) schedule included a one-week visit to assess short-term clinical effectiveness of tofacitinib and TNFi. At the 1-week visit, the HAQ-DI, the CDAI, and patient and physician administered global assessment of symptoms, were used to assess short-term effectiveness of the treatment and comparison groups. The HAQ-DI and CDAI are described in more detail in Section 9.5.1. Obtaining the assessments one-week after treatment also established a post treatment-baseline for long-term clinical effectiveness measurements.

There were 1-month (4-week) and 3-month (12-week) visits to assess the clinical effectiveness of tofacitinib and TNFi following a dose reduction in patients with low disease activity, in compliance with the NHI reimbursement guidelines. In order to ensure the uniform enrollment of patients in both the treatment and comparator arms, consecutive users of Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) were enrolled. Enrollment targets were implemented depending on pace of enrollment. The enrollment of patients at the sites is described in Section 9.2.

Table 1. Study Data Collection and Assessment Schedule

Data collection schedule:	1	2	3	4	5	6	7	8	9	10	11	12	Visit after Dose Down (Per NHI requirements)[a]	
Title	Enrollment/Baseline	Wk1	Wk24	Wk48	Wk72	Wk96	Wk120	Wk144	Wk168	Wk192	Wk216	Wk240	Wk4	Wk12
Visit Window (in days)[b]	0	+3	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographic Characteristics	X													
Medical History	X													
Smoking History	X													
Height	X													
Weight	X													
AEs/TAE/SAEs[c]	----------X----------													
Previous RA Treatment	X													
Concomitant Medication(s)	----------X----------													
RA Treatment during Study[d,e,f]	----------X----------													
Laboratory Data[g]	X		X	X	X	X	X	X	X	X	X	X	X	X
CDAI[h,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAS28-ESR[h,j]	X		X	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-RA[h]	X		X	X	X	X	X	X	X	X	X	X	X	X

Data collection schedule:	1	2	3	4	5	6	7	8	9	10	11	12	Visit after Dose Down (Per NHI requirements)[a]	
Title	Enrollment/Baseline	Wk1	Wk24	Wk48	Wk72	Wk96	Wk120	Wk144	Wk168	Wk192	Wk216	Wk240	Wk4	Wk12
Visit Window (in days)[b]	0	+3	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28	±28

a. Visits occurred 4 weeks and 12 weeks after mandatory dose reduction due to low disease activity per NHI requirement.

b. If patient could not be followed within the window period due to personal/special situation, data of the closest visiting date for that visit were collected.

c. AEs/TAE/SAEs were collected throughout the study starting from the date of the patient's informed consent signature until 28 days following the last administration of a drug under study.

d. Patients discontinuing from the initial study drug treatment were followed up through the end of the study.

e. Patients could have dose modifications at any time during the study. Reasons for dose change/interruption were collected as AE, per NHI requirements, lack of efficacy, and other.

f. Patients with low disease activity could have dose reductions (per NHI requirement) any time during the study.

g. Laboratory data included but was not limited to blood collection for ESR, CRP, AST, ALT, Total Bilirubin, Serum Creatinine, Lipid profile, CBC/Differential count. Collect laboratory data from the closest visit to data collection.

h. For patients changing treatment during follow-up, ideally baseline information were collected assuming they were conducted as routine practice.

i. The CDAI consisted of patient global assessment, physician global assessment, 28-swollen joint count, and 28-tender joint count.

j. The DAS28-ESR consisted of patient global assessment, 28-swollen joint count, 28-tender joint count, and the Erythrocyte Sedimentation Rate (ESR).

Abbreviations: AE: Adverse Event; CDAI: Clinical Disease Activity Index; DAS28-ESR: Disease Activity Score 28 - Erythrocyte Sedimentation Rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; RA: Rheumatoid Arthritis; SAE: Serious Adverse Event; TAE: Targeted Adverse Event; WPAI-RA: Work Productivity and Activity Impairment in RA; CRP: C-Reactive Protein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CBC: Complete Blood Count.

9.2. Setting

Patients were recruited from 7 sites in Taiwan with a specialty in rheumatology. Participating study sites were required to enroll into this study consecutive eligible patients who were either newly initiating tofacitinib, or were Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) initiators. If an eligible patient was approached and did not participate in the study, the reason for nonparticipation was documented in the enrollment log. Enrollment caps were placed on the sites to ensure that enrollment was uniform across sites and across the 2 arms.

Given that tofacitinib was a newly approved medication with slower anticipated enrollment rates compared to TNFi, it was important to monitor enrollment rates throughout the enrollment period to ensure that a 1:1 ratio of tofacitinib to TNFi was achieved. If for example the ratio of tofacitinib patients to TNFi patients was 1:3 at Month 9 (36 weeks), then a temporary cap was placed on the enrollment into the TNFi arm at the site until the 1:1 ratio was achieved. These measures were used to help minimize timing as a potential bias. No ratio between specific drugs was defined for patients on Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) in the comparison group.

Patients who were newly initiating tofacitinib, Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) for RA under routine clinical practice were eligible to participate in this study and were enrolled at the time of presentation of a routine clinic visit. Aside from the one-week visit for the completion of HAQ-DI and CDAI, and the one-month (4-week) and three-month (12-week) visits following mandatory dose reduction, no other clinic visits were required as part of participation in this study. All clinical assessments were intended to be performed at the time of a routine clinical encounter. PROs were completed by patients on paper at the time of a routine clinic visit and responses were entered into the Electronic Data Capture by the site. For patients not attending a one-week visit, data was reported as missing.

9.3. Subjects

Eligibility in the study is summarized below in Section 9.3.1 and Section 9.3.2. Eligible patients in the treatment group were naïve to tofacitinib, and in the comparison group to the drug they initiated (Enbrel® (etanercept), or Humira® (adalimumab), or Simponi® (golimumab)) at the time of enrollment but did not have to be naïve to other RA treatments. Users who had taken the same product before were not eligible for enrollment. Additionally, patients participating in other clinical studies were excluded due to protocol driven activities outside of normal practice and potential confounding in safety assessments.

9.3.1. Inclusion Criteria

The study patients met all of the following inclusion criteria at the time of enrollment:

1. Adults over 20 years of age.[1]
2. The patient had a clinical diagnosis of RA.
3. The patient was newly prescribed tofacitinib or a TNFi (ie, Enbrel® (etanercept), Humira® (adalimumab) or Simponi®(golimumab)) for RA at the time of enrollment. Patients switching from one TNFi to another or from one TNFi to tofacitinib were included as long as they were incident users of a given TNFi or of tofacitinib.
4. The patient had evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) had been informed of all pertinent aspects of the study.
5. The patient was able to read, write and reply to the study questionnaires.

9.3.2. Exclusion Criteria

1. Patient enrolled in any other clinical trial of an investigational product.

9.4. Variables

The list of exposures, outcomes, and other variables collected during the study including risk factors, comorbidities and concomitant medications are described in Protocol Table 2. Detailed definitions of the variables are described in Section 9.9.

9.5. Data Sources and Measurement

Data was collected from physician and patient questionnaires completed at enrollment (baseline) and during follow-up at approximately 6-month (24-week) intervals. Questionnaires did not contain personal identifiers. In the event of a switch to a new therapy during follow-up, baseline questionnaires were captured again.

Clinical effectiveness was measured using the HAQ-DI, CDAI, and the DAS28-ESR at baseline and every 6 months. Additionally, the HAQ-DI and CDAI scores were collected at 1-week after the treatment initiation. Additional clinical effectiveness assessments were conducted 1-month (4-week) and 3-months (12-week) after the mandatory dose reduction or treatment discontinuation. Thereafter, assessments continued at the standard 6-month intervals.

Adverse events (AEs) were collected at every visit.

[1] Patients between 18 and 20 were required to co-sign the consent from along with their legal guardian according to the local law.

The Work Productivity and Activity Impairment-rheumatoid arthritis (WPAI-RA) questionnaire was used to assess work productivity, activity impairment, presenteeism and absenteeism at work during study follow-up.

Prescriptions were used to calculate adherence and persistence to both the newly initiated treatment and comparison drugs during follow-up. Details on the calculation of adherence and persistence are provided in Section 9.9.5.

9.5.1. Patient-Reported Outcome (PRO) Measures

9.5.1.1. The Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI is a commonly used self-assessment instrument used in rheumatoid arthritis to measure functional disability in patients.[19] This validated tool is a generic instrument that contains 20 questions related to 8 functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The responses range from a scale of 0 (no functional disability) to 3 (severe functional disability). There are 3 steps to score the Health Assessment Questionnaire (HAQ): (1) Identify the highest subcategory score from each of the 8 categories. Adjust for use of aids/help by increasing the category score from 0 or 1 to a 2 if use of aids/help for that category (utilize table of companion aids/help for HAQ categories). If the category score is already a 2 or 3, no adjustment is made; (2) Sum the category scores; (3) Divide the final sum by the number of categories answered to obtain the final HAQ score rounded to the nearest value evenly divisible by 0.125. Requires a minimum of 6 categories answered, if less, do not score.

9.5.1.2. Work Productivity and Activity Index-Rheumatoid Arthritis (WPAI-RA)

The WPAI-RA, a self-administered tool to measure work productivity, was validated in patients with RA.[20] It consists of 6 questions on work productivity and activity impairment over the previous 7 days. Four main outcomes can be generated from the 6 questions: work productivity, activity impairment, absenteeism and presenteeism.

9.5.2. Physician-Reported Measures

9.5.2.1. Clinical Disease Activity Index (CDAI)

The CDAI is a composite measure of disease activity in RA patients which consists of patient global assessment, physician global assessment, 28-swollen joint count and 28-tender joint count with some minimum input provided by patients.[21] CDAI scores less than 2.8 are targeted for remission according to the American College of Rheumatology (ACR).[22]

9.5.2.2. Disease Activity Score 28 (DAS28-ESR)

The DAS28-ESR is a composite measure of disease activity in RA patients that consists of patient global assessment, 28-swollen joint count, 28-tender joint count, and the ESR.[21] DAS28-ESR scores less than 2.6 are targeted for remission according to the ACR. According to Taiwan NHI reimbursement guidelines, a reduction in dose is mandated when a patient has been treated with tofacitinib or a TNFi for 24 months and has low disease activity measured using the DAS28-ESR as (1) DAS28 ≤3.2 and (2) ESR≤25 MM/h and C-reactive Protein (CRP) ≤1 mg/dL.[23]

9.6. Bias

Given that this study compared effectiveness for patients on different treatments, patient characteristics directly related to the treatment were likely to influence physician prescribing behaviors. As a result, there would be confounding by indication when comparing effectiveness outcomes between the 2 treatment groups. Propensity score (PS) was used to control for this bias to the extent possible.

To minimize timing as a potential bias, enrollment caps were placed on the sites to ensure that enrollment is uniform across sites and the 2 arms. Given that tofacitinib is a newly approved medication with slower anticipated enrollment rates compared to TNFi, it is important to monitor enrollment rates throughout the enrollment period to ensure that a 1:1 ratio of tofacitinib to TNFi was achieving.

9.7. Study Size

The original plan was to enroll approximately 250 patients initiated on tofacitinib and approximately 250 patients initiated on TNFi [Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab)]. The target number of enrolled patients changed from 500 to 300 in December 2017. Finally, 267 patients in total were enrolled as the study population, including 145 tofacitinib users and 122 TNFi users. Patients were enrolled over the course of 24 months and followed for at least 36 months after enrollment.

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP) (Appendix 4).

9.9. Statistical Methods

Detailed methodology for summary and statistical analyses of data collected in this study was documented in a detailed SAP. The SAP might have modified the plans outlined in the protocol. Effectiveness and PROs were described for tofacitinib patients and for Enbrel® (etanercept), Humira® (adalimumab), or Simponi® (golimumab) separately and combined. The visit intervals were every 6 months unless indicated otherwise.

Statistical analysis and generation of all tables, listings and figures were performed by using SAS® (SAS Institute, North Carolina), version 9.2 or higher.

9.9.1. Analysis Sets

The Full Analysis Set (FAS) comprised of all enrolled patients providing informed consent in writing to participate in the study, where required by local regulation. If a patient withdrew consent, the patient's data collected before the consent withdrawal remained in the dataset. If a patient withdrew consent prior to treatment, the patient would not be included in the FAS. All analyses were performed on the FAS unless otherwise specified in the SAP.

The Effectiveness Analysis Set (EFF) was comprised of FAS patients who received tofacitinib or TNFi and did not switch during the study period. Effectiveness analyses were performed on the EFF unless otherwise specified.

The Drug Switching Analysis Set (DSS) comprised of those FAS patients who switched drugs from tofacitinib to TNFi or from TNFi to tofacitinib during the study period.

The Safety Analysis Set (SAF) consisted of all patients who received at least one dose of study drug (tofacitinib or TNFi) and allocated the patients into the index treatment arm. The SAF was used as the basis for most safety analyses.

9.9.2. Main Summary Measures

Continuous variables were summarized as mean, median, standard deviation, minimum and maximum. P-values from the two-sample t-test to evaluate the difference between 2 treatment groups were also reported for continuous variables. Categorical variables were summarized by counts and percentages. Unless otherwise stated, the calculation of percentages was based on the sample size of the treatment group in the analysis set of interest. P-values from the Chi-Square Test to evaluate the difference between 2 treatment groups were also reported for categorical variables. In case of cells with small frequencies (observed frequencies less than 5), the Fisher's Exact Test was used. Two-sided p-values <0.05 were considered statistically significant.

9.9.3. Main Statistical Methods

The effectiveness of tofacitinib was compared to TNFi by using mixed logistic regression models with dichotomous outcome variables for HAQ-DI, CDAI, DAS-ESR, and question 1 of WPAI-RA (currently employed or not). Separate models were built for each outcome variable, and included a dichotomous variable for treatment exposure, visit (as a categorical variable), adjusted for confounders (baseline socio-demographic, clinical and treatment characteristics), and considering subject as a random effect. Given the non-random assignment of treatment in this observational study setting, PS were included in this model to adjust for confounding by indication. The estimated odds ratio for the exposure effect (tofacitinib vs TNFi) along with its associated standard error and confidence limits were reported.

9.9.4. Primary Analysis

Baseline characteristics are summarized for RA patients separately by drug type and line of therapy as appropriate based on available sample size. Variables collected at baseline included patient socio-demographic, clinical, and treatment characteristics. Continuous variables were summarized as mean, median, standard deviation, minimum and maximum. Categorical variables were summarized as proportions with 95% confidence intervals. P-values were used to compare baseline characteristics of tofacitinib with TNFi.

The measure of effectiveness used after one-week of treatment from the incident dose is the HAQ-DI. CDAI scores were also be collected. The prevalence of disability using the HAQ-DI was summarized as the proportion of patients with an increase in the score from baseline to follow-up visits. Effectiveness was measured by using patient-reported HAQ-DI, CDAI, DAS28-ESR, and WPAI-RA. The CDAI was summarized as the proportion of patients with scores <2.8, ie, with remission at a given visit. The DAS28-ESR was summarized as the proportion of patients with scores <2.6, ie, with remission at a given visit. Additionally, descriptive comparisons were made at 6 months and 12 months.

The effectiveness of tofacitinib was compared to TNFi by using mixed logistic regression models with dichotomous outcome variables for HAQ-DI, CDAI and DAS-ESR. Three separate longitudinal models were built for each outcome variable, and each included a dichotomous variable for treatment exposure, adjusted for confounders (baseline socio-demographic, clinical and treatment characteristics). Given the non-random assignment of treatment in this observational study setting, PS were used to adjust for confounding by indication. The PS was defined as the probability of being exposed to tofacitinib conditioning on factors impacting the prescription of tofacitinib (baseline socio-demographic, clinical and treatment characteristics). The PS was either included in the model as a covariate, or a matching of the PS between the 2 exposure groups was performed to balance the baseline covariates between the 2 groups.

The mean and standard deviation of WPAI-RA scores were summarized at a given time point for each patient.

9.9.5. Secondary Analysis

AEs, TAEs and Serious Adverse Event (SAEs) were recorded at each occurrence and summarized as the proportion of patients with each safety event at a given point in time and descriptive in nature.

Treatment patterns were captured as the proportion of patients using a given treatment over a 12-month period including switching. Dose changes were summarized as appropriate for each treatment at every study visit.

Adherence to the treatment and comparison drugs were calculated from prescriptions over a 12-month period using the proportion of days covered (PDC) method. The 12-month time frame accounted for gaps in treatment and differences in frequency of administration of TNFi and tofacitinib. Adherence was calculated for both treatment and comparison groups using information obtained from prescriptions including medication name, dosage, unit, route, refill date and duration. Adherence values were calculated at the individual level and a 12-month period was defined as the time between 01 January and 31 December of a given year. Details regarding the computation of PDC was provided in the SAP.[24,25] Persistence was calculated as a continuous measure from prescriptions over the follow-up duration as total number of days between the first refill date and the last refill date (plus the days' supply of the last refill).[25,26] Persistence was also calculated as the proportion of patients who remained on therapy following 36 to 60 months of treatment.

Clinical and PROs were summarized following mandated reduction of dose or weaning off tofacitinib or TNFi in patients with low disease activity after 24 months per NHI requirements. The clinical and PROs of interest included effectiveness measured by using the HAQ-DI, CDAI, DAS28-ESR, and WPAI-RA, and they were summarized as described in Section 9.9.4.

9.9.6. Missing Values

RA diagnosis date (DD-MMM-YYYY) was imputed by the following algorithm:

- UNK-UNK-YYYY was imputed as 01-JUL-YYYY. In case the year of diagnosis was the same year as the year of enrollment, and subject was enrolled before 01-July, the RA diagnosis date was imputed as (Informed Consent Form [ICF] date-1 day).

- UNK-MMM-YYYY was imputed as 15-MMM-YYYY. In case the year and month of diagnosis was the same year and month as the year and month of enrollment, and subject was enrolled before the 15th, the RA diagnosis date was imputed as (ICF date-1 day).

Missing safety or effectiveness data was not imputed, and data was analyzed and presented as they were recorded in the database.

9.9.7. Sensitivity Analyses

None.

9.9.8. Change of Conduct of Study

The target number of enrolled patients changed from 500 to 300 in December 2017. In August 2021, 267 patients in total were enrolled as the study population.

9.10. Quality Control

Site training was performed to ensure that the data was collected by the staff in an organized and complete manner. Given that this was a non-interventional study, the data elements were aligned to information collected as part of routine care. Edit checks were performed and ongoing data review was conducted. Strategies for handling missing data were used at the data analysis stage.

9.11. Protection of Human Subjects

Subject information and consent

Written informed consent was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

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

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an IRB(s) and/or IEC(s) for each site participating in the study.

Ethical conduct of the study

The study was 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) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance

for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. RESULTS

10.1. Participants

Patient disposition is presented in Table 2. Individual data are presented in Listing 16.2.1-1.1.

A total of 267 patients comprised the FAS and safety analysis set, and 221 patients (82.8%) completed the study. Of 267 total study patients, 145 patients were prescribed tofacitinib (tofacitinib) and 122 patients were prescribed TNFi.

The effectiveness analysis set included 242 patients (90.6%) [tofacitinib 134 (92.4%), TNFi 108 (88.5%)] and the DSS included 25 patients (9.4%) [tofacitinib 11 (7.6%), TNFi 14 (11.5%)].

A total of 46 patients (17.2%) discontinued from the study due to withdrawal by subject [27 patients (10.1%)], lost to follow-up [11 patients (4.1%)], death [6 patients (2.2%)] and other reasons [2 patients (0.7%)].

Table 2. Patient Disposition-Full Analysis Set

Number of Patients	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Full Analysis Set (FAS)	145	122	267
Effectiveness Analysis Set (EFF)	134 (92.4)	108 (88.5)	242 (90.6)
Drug Switching Analysis Set (DSS)	11 (7.6)	14 (11.5)	25 (9.4)
Safety Analysis Set (SAF)	145 (100.0)	122 (100.0)	267 (100.0)
Patients Completed Study	119 (82.1)	102 (83.6)	221 (82.8)
Discontinuation from Study	26 (17.9)	20 (16.4)	46 (17.2)
Reasons for Discontinuation			
Lost to Follow-Up	7 (4.8)	4 (3.3)	11 (4.1)
Withdrawal by Patient	15 (10.3)	12 (9.8)	27 (10.1)
Death	2 (1.4)	4 (3.3)	6 (2.2)
Other	2 (1.4)	0	2 (0.7)

- SOURCE: Table 14.1-1.1.
  Percentages are based on the number of patients in FAS.
- Effectiveness Analysis Set is comprised of those FAS patients who received Tofacitinib or TNFi and do not switch to each other during the study period.
- Drug Switching Analysis Set is comprised of those patients who switched drugs from Tofacitinib to TNFi or from TNFi to Tofacitinib.
- Safety Analysis Set is comprised of those patients who received at least one dose of study drug (Tofacitinib or TNFi) and allocated into actual received treatment arm.

10.2. Descriptive Data

10.2.1. Demographic Characteristic

Socio-demographic characteristics are shown in Table 3. Individual data are presented in Listing 16.2.4-1.1.

Demographic characteristics were comparable in the 2 groups. The mean [standard deviation (SD)] age of study patients was 55.26 (12.678) years. More than 75% patients (n=204) in the study were less than 65 years of age. The majority (n=225, 84.3%) of patients were female. Patient's mean height and weight were comparable in the 2 groups. The majority of patients never smoked (n=194, 72.7%).

Table 3. Socio-Demographic Characteristics

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Age (years)				
n	145	122	267	0.8059
Mean	55.44	55.05	55.26	
SD	12.110	13.369	12.678	
Median	57.40	55.20	56.10	
Min, Max	21.5, 81.8	26.7, 84.9	21.5, 84.9	
Missing	0	0	0	
Age Category (years) n (%)				
n	145	122	267	0.7255
<65	112 (77.2)	92 (75.4)	204 (76.4)	
≥65	33 (22.8)	30 (24.6)	63 (23.6)	
Missing	0	0	0	
Sex n (%)				
n	145	122	267	0.5416
Male	21 (14.5)	21 (17.2)	42 (15.7)	
Female	124 (85.5)	101 (82.8)	225 (84.3)	
Missing	0	0	0	
Height (cm)				
n	111	88	199	0.7196
Mean	158.35	158.73	158.52	
SD	7.368	7.482	7.403	
Median	158.00	158.00	158.00	
Min, Max	138.7, 176.0	135.0, 180.0	135.0, 180.0	
Missing	34	34	68	
Weight (kg)				
n	113	90	203	0.8051
Mean	58.84	59.29	59.04	
SD	11.995	13.811	12.801	

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Median	58.00	57.05	57.10	
Min, Max	38.0, 93.0	34.0, 103.0	34.0, 103.0	
Missing	32	32	64	
Smoking Status n (%)				
n	120	92	212	0.4287
Never	111 (76.6)	83 (68.0)	194 (72.7)	
Former	5 (3.4)	6 (4.9)	11 (4.1)	
Current	4 (2.8)	3 (2.5)	7 (2.6)	
Missing	25 (17.2)	30 (24.6)	55 (20.6)	

- SOURCE: Table 14.1-2.1.
- Age was derived as the difference in years (without rounding or truncation) between the date of Informed Consent and the date of birth.
- Percentages and p-values are based on the number of patients in FAS.
- P-values from the two-sample t-test are reported for continuous variables. P-values from the Chi-square tests are reported for categorical variables.
- SD = Standard Deviation.

10.2.2. Clinical Characteristics at Baseline

Baseline RA characteristics are shown in Table 4. Individual data are presented in Listing 16.2.4-1.1.

The 2 groups differed by their time since diagnosis, with more recent diagnosis in TNFi initiators, the proportion of patients in high disease activity at baseline, and by their prior treatment exposure. The mean (SD) time since RA diagnosis was 7.95 (9.706) years in the tofacitinib initiators group, and 5.44 (6.692) years in the TNFi initiators group. Median time since RA diagnosis was 5.70 and 3.00 years in tofacitinib initiators group and TNFi initiators group, respectively.

At baseline, the overall mean (SD) HAQ-DI score was 0.9696 (0.76708) which indicates mild disability; it was consistent across the tofacitinib and TNFi initiators. The overall mean (SD) CDAI score was 31.25 (12.580) indicating high disease activity; it differed between the 2 groups, with 28.84 (12.627) in tofacitinib initiators, and 34.12 (11.955) in the TNFi initiators (p=0.0009). In the overall study population, the majority of patients reported high disease activity [177 (66.3%)], followed by moderate disease activity [55 (20.6%)] and low disease activity [14 (5.2%)]. The distribution of disease activity differed between the 2 groups, with a lower number proportion of tofacitinib patients in high disease activity (n=88, 60.7%) compared to TNFi patients (n=89, 73.0%; p=0.0139).

The mean (SD) DAS28-ESR score of the overall study population was 5.8245 (1.26163); it differed slightly between the 2 groups (tofacitinib 5.6259, vs TNFi 6.0627; p=0.0049). A total of 255 (95.5%) patients overall had a score of ≥ 3.2, indicating moderate disease activity.

The proportion of patients in the work force and percent impairment identified by the Work Productivity and Activity Index (WPAI) were comparable in the 2 groups. In total, 116 patients (43.4%) were employed during their participation in the study. The mean (SD) percent of work time missed due to RA was 4.46% (13.817). The mean (SD) percent impairment while working due to RA was 43.12% (26.447). The mean (SD) overall percent of work impairment due to RA was 44.71% (27.679) for overall study patients. The mean (SD) percent activity impairment due to RA for overall study patients was 50.00% (24.294).

At baseline, the mean (SD) tender joint count was slightly lower for tofacitinib patients (11.1 [6.67]) than for TNFi patients (13.5 [6.88]; p= 0.0046). The mean swollen joint count of TNFi patients was also lower among tofacitinib patients (5.8 [4.29]) compared to TNFi patients (7.1 [4.34]; p=0.0152).

Overall, 95.1% of patients had received 2 or more conventional DMARDs. However, the 2 groups differed by their prior exposure to biologic DMARDs: 95.1% (n=116) of TNFi initiators had no prior exposure to bDMARDS, and 98.4% (n=120) had not been exposed to TNFi. By contrast, only 65.5% (n=95) of 122 tofacitinib initiators were naïve to bDMARDs, and 70.3% (n=102) to TNFi, which means that 29.7% tofacitinib initiators had used TNFi in a prior treatment course. Furthermore, 11.0% (n=16) of tofacitinib initiators had been exposed to ≥2 prior bDMARDs.

Table 4. Baseline RA Characteristics

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Time since RA Diagnosis (years)				
n	125	107	232	0.0212
Mean	7.95	5.44	6.80	
SD	9.706	6.692	8.526	
Median	5.70	3.00	4.10	
Min, Max	0.1, 76.5	0.0, 40.3	0.0, 76.5	
Missing	20	15	35	
Baseline HAQ-DI				
n	145	122	267	0.7148
Mean	0.9853	0.9508	0.9696	
SD	0.76099	0.77699	0.76708	
Median	1.0000	0.8750	0.8750	
Min, Max	0.000, 3.000	0.000, 3.000	0.000, 3.000	
Missing	0	0	0	
Baseline CDAI				
n	134	112	246	0.0009
Mean	28.84	34.12	31.25	
SD	12.627	11.955	12.580	
Median	28.60	34.10	31.00	
Min, Max	4.0, 55.0	8.0, 65.0	4.0, 65.0	

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Missing	11	10	21	
Baseline CDAI Remission n (%)				
n	134	112	246	0.8535
≤2.8	0	0	0	
>2.8	134 (92.4)	112 (91.8)	246 (92.1)	
Missing	11 (7.6)	10 (8.2)	21 (7.9)	
Baseline CDAI LDA n (%)				
n	134	112	246	0.0120
≤10	13 (9.0)	1 (0.8)	14 (5.2)	
>10	121 (83.4)	111 (91.0)	232 (86.9)	
Missing	11 (7.6)	10 (8.2)	21 (7.9)	
Baseline CDAI (Disease Activity) n (%)				
n	134	112	246	0.0139
CDAI ≤2.8 (Remission)	0	0	0	
2.8< CDAI ≤10 (Low Disease Activity)	13 (9.0)	1 (0.8)	14 (5.2)	
10< CDAI ≤22 (Moderate Disease Activity)	33 (22.8)	22 (18.0)	55 (20.6)	
CDAI >22 (High Disease Activity)	88 (60.7)	89 (73.0)	177 (66.3)	
Missing	11 (7.6)	10 (8.2)	21 (7.9)	
Baseline DAS28-ESR				
n	144	120	264	0.0049
Mean	5.6259	6.0627	5.8245	
SD	1.33578	1.12635	1.26163	
Median	5.7440	6.0975	5.9740	
Min, Max	2.107, 8.045	2.533, 8.658	2.107, 8.658	
Missing	1	2	3	
Baseline DAS28-ESR Remission n (%)				
n	144	120	264	0.5426
<2.6	3 (2.1)	1 (0.8)	4 (1.5)	
≥2.6	141 (97.2)	119 (97.5)	260 (97.4)	
Missing	1 (0.7)	2 (1.6)	3 (1.1)	
Baseline DAS28-ESR LDA n (%)				
n	144	120	264	0.2774
<3.2	7 (4.8)	2 (1.6)	9 (3.4)	
≥3.2	137 (94.5)	118 (96.7)	255 (95.5)	
Missing	1 (0.7)	2 (1.6)	3 (1.1)	
Baseline WPAI-RA (%)				
Patient Currently Employed (Working for Pay) n (%)				
n	145	122	267	0.8035
Yes	64 (44.1)	52 (42.6)	116 (43.4)	
No	81 (55.9)	70 (57.4)	151 (56.6)	
Missing	0	0	0	

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Percent Work Time Missed Due to RA (%)				
n	59	46	105	0.2703
Mean	5.67	2.91	4.46	
SD	17.344	7.008	13.817	
Median	0.00	0.00	0.00	
Min, Max	0.0, 100.0	0.0, 40.0	0.0, 100.0	
Missing	5	6	11	
Percent Impairment while Working Due to RA (%)				
n	60	49	109	0.6271
Mean	42.00	44.49	43.12	
SD	25.697	27.542	26.447	
Median	50.00	50.00	50.00	
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	
Missing	4	3	7	
Percent Overall Work Impairment Due to RA (%)				
n	58	46	104	0.5857
Mean	43.38	46.38	44.71	
SD	27.464	28.160	27.679	
Median	50.00	50.00	50.00	
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	
Missing	6	6	12	
Percent Activity Impairment Due to RA (%)				
n	145	121	266	0.8005
Mean	49.66	50.41	50.00	
SD	23.612	25.179	24.294	
Median	50.00	50.00	50.00	
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	
Missing	0	1	1	
Baseline Tender Joint Count				
n	145	120	265	0.0046
Mean	11.1	13.5	12.2	
SD	6.67	6.88	6.86	
Median	11.0	13.0	12.0	
Min, Max	0, 25	1, 28	0, 28	
Missing	0	2	2	
Baseline Swollen Joint Count				
n	145	120	265	0.0152
Mean	5.8	7.1	6.4	
SD	4.29	4.34	4.35	
Median	5.0	7.0	6.0	
Min, Max	0, 18	0, 22	0, 22	

Characteristics	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)	p-value
Missing	0	2	2	
Previous TNFi n (%)				
n	145	122	267	<.0001
0	102 (70.3)	120 (98.4)	222 (83.1)	
1	35 (24.1)	2 (1.6)	37 (13.9)	
≥2	8 (5.5)	0	8 (3.0)	
Missing	0	0	0	
Patients receiving Prior bDMARDs n (%)				
n	145	122	267	<.0001
0	95 (65.5)	116 (95.1)	211 (79.0)	
1	34 (23.4)	6 (4.9)	40 (15.0)	
≥2	16 (11.0)	0	16 (6.0)	
Missing	0	0	0	
Patients receiving Prior cDMARDs n (%)				
n	145	122	267	0.3788
0	0	1 (0.8)	1 (0.4)	
1	8 (5.5)	4 (3.3)	12 (4.5)	
≥2	137 (94.5)	117 (95.9)	254 (95.1)	
Missing	0	0	0	

- SOURCE: Table 14.1-2.1.
- Percentages and p-values are based on the number of patients in FAS.
- P-values from the two-sample t-test are reported for continuous variables. P-values from the Chi-square test are reported for categorical variables.
- SD = Standard Deviation.
- Previous TNFi: including etanercept, adalimumab, and golimumab, which subject received 6 months prior to enrollment for RA disease and the route is injection and oral.
- Partial RA diagnosis date (YYYY-MM-DD) were imputed by the following algorithm: YYYY-UNK-UNK were imputed as YYYY-07-01; YYYY-MM-UNK were imputed as YYYY-MM-15. In case the ICF (Informed Consent Form) date is before the imputed date, (ICF date-1 day) were imputed. The details can be found in SAP Section 7.2.

10.2.3. Medical History

Selected medical history is shown in Table 5, including all the conditions that were reported by >5% of overall study patients.

A total of 246 patients (92.1%) reported some pre-specified or other significant medical history, [tofacitinib 133 (91.7%); TNFi 113 (92.6%)]. Pre-specified conditions reported by >5% of overall study patients included: Hypertension [65 (24.3%)], Hyperlipidemia [39 (14.6%)], Diabetes Mellitus [31 (11.6%)], Hepatitis B [28 (10.5%), Renal Insufficiency [20 (7.5%)], and Herpes Zoster [14 (5.2%)], and].

Medical history of TB is of special interest from the perspective of this study. Four patients (2.8%) from tofacitinib group presented a history of latent TB, while 3 (2.1%) and 1 (0.8%) patient from the tofacitinib and TNFi group, respectively, presented history of TB. In addition, 1 patient (0.8%) of TNFi group had Chickenpox. None of the study patient had received herpes zoster vaccination.

Overall, 25 patients (9.4%) presented with pre-specified condition of blood and lymphatic system disorders. Of these, majority of the patients [15 (5.6%)] reported iron deficiency anemia.

Additionally, 78 patients (29.2%) presented musculoskeletal and connective tissue disorders. Of these, majority of patients reported Sjogren's syndrome [42 (15.7%)], followed by Osteoarthritis [24 (9.0%)]. Furthermore, Psychiatric disorders were reported by 30 patients (11.2%), of which 27 patients (10.1%) reported Insomnia.

In addition to the pre-specified conditions, 204 patients (tofacitinib 104 + TNFi 100) underwent Hepatitis B surface antigen (HBsAg) test, of which 11 patients (5.4%) were positive. Hepatitis B surface antibody (Anti-HBs) was tested for 150 patients (tofacitinib 75 + TNFi 75), of which 55 tofacitinib patients (73.3%) and 42 TNFi patients (56.0%) were positive.

Rheumatoid factor was tested for 160 study patients, of which 110 patients (tofacitinib 57 + TNFi 53) were reported positive.

Table 5. Medical History-Full Analysis Set

Number of Subjects with	**Tofacitinib (N=145) n (%)**	**TNFi (N=122) n (%)**	**Total (N=267) n (%)**
Any Pre-Specified or Other Significant Medical Condition	133 (91.7)	113 (92.6)	246 (92.1)
Pre-Specified Medical Conditions			
Total	86 (59.3)	66 (54.1)	152 (56.9)
Hypertension	32 (22.1)	33 (27.0)	65 (24.3)
Hyperlipidemia	24 (16.6)	15 (12.3)	39 (14.6)
Diabetes Mellitus	12 (8.3)	19 (15.6)	31 (11.6)
Hepatitis B	17 (11.7)	11 (9.0)	28 (10.5)
Renal Insufficiency	12 (8.3)	8 (6.6)	20 (7.5)
Herpes Zoster	12 (8.3)	2 (1.6)	14 (5.2)
Latent TB	4 (2.8)	0	4 (1.5)
Tuberculosis (TB)	3 (2.1)	1 (0.8)	4 (1.5)
Chicken Pox	0	1 (0.8)	1 (0.4)
Other Significant Medical Conditions*			
Total	63 (43.4)	54 (44.3)	117 (43.8)
Blood and lymphatic system disorders			

Number of Subjects with	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Total	13 (9.0)	12 (9.8)	25 (9.4)
Iron deficiency anemia	7 (4.8)	8 (6.6)	15 (5.6)
Endocrine disorders			
Total	7 (4.8)	11 (9.0)	18 (6.7)
Eye disorders			
Total	14 (9.7)	6 (4.9)	20 (7.5)
Gastrointestinal disorders			
Total	25 (17.2)	17 (13.9)	42 (15.7)
Infections and infestations			
Total	21 (14.5)	14 (11.5)	35 (13.1)
Musculoskeletal and connective tissue disorders			
Total	42 (29.0)	36 (29.5)	78 (29.2)
Sjogren's syndrome	18 (12.4)	24 (19.7)	42 (15.7)
Osteoarthritis	12 (8.3)	12 (9.8)	24 (9.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)			
Total	6 (4.1)	8 (6.6)	14 (5.2)
Nervous system disorders			
Total	12 (8.3)	8 (6.6)	20 (7.5)
Psychiatric disorders			
Total	16 (11.0)	14 (11.5)	30 (11.2)
Insomnia	16 (11.0)	11 (9.0)	27 (10.1)
Reproductive system and breast disorders			
Total	12 (8.3)	6 (4.9)	18 (6.7)
Respiratory, thoracic, and mediastinal disorders			
Total	11 (7.6)	11 (9.0)	22 (8.2)
Skin and subcutaneous tissue disorders			
Total	12 (8.3)	6 (4.9)	18 (6.7)
Test Item			
HBsAg, total n, positive n (%)	104, 6 (5.8)	100, 5 (5.0)	204, 11 (5.4)
Rheumatoid Factor, total n, positive n (%)	84, 57 (67.9)	76, 53 (69.7)	160,110 (68.8)
Anti-HBs, total n, positive n (%)	75, 55 (73.3)	75, 42 (56.0)	150, 97 (64.7)
Anti-HBc, total n, positive n (%)	69, 47 (68.1)	58, 36 (62.1)	127, 83 (65.4)
Anti-CCP, total n, positive n (%)	62, 45 (72.6)	52, 36 (69.2)	114, 81 (71.1)
HBV DNA, total n, positive n (%)	17, 3 (17.6)	6, 0 (0.0)	23, 3 (13.0)

Redacted

Number of Subjects with	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
HBeAg, total n, positive n (%)	7, 1 (14.3)	7, 0 (0.0)	14, 1 (7.1)
HBeAb, total n, positive n (%)	1, 0 (0.0)	1, 1 (100.0)	2, 1 (50.0)

- SOURCE: Table 14.1-3.1.
- * Other significant medical conditions are coded using MedDRA version 24.0.
- The pre-specified medical conditions are listed in SAP. Other significant medical conditions: For serious infection in past 6 months prior to enrollment.
- System organ classes are presented alphabetically; preferred terms/ medical terms are sorted by descending frequency; multiple conditions of any SOC or preferred term/ medical term are counted only once.

10.2.4. Prior RA Treatment

Prior RA medication therapy of FAS is shown in Table 6. Individual data are presented in Listing 16.2.4-3.1.

Almost all study patients received cDMARDs as prior RA therapy, which is consistent with the NHI policies, in that RA patients must have failed two cDMARDs to be considered for reimbursement of bDMARDs and targeted synthetic DMARDs (including tofacitinib).[27] Majority of the patients [241 (90.3%)] received methotrexate for an average of 3.4 years, followed by hydroxychloroquine [213 (79.8%)] and sulfasalazine [165 (61.8%)]. The average years of hydroxychloroquine and sulfasalazine usage was 3.2 years and 3.9 years, respectively. Less than 35.0% patients received the other cDMARDS.

Besides cDMARDs, other prior RA therapies included NSAIDs and steroids, which were reported by an overall population of 221 (82.8%), and 196 (73.4%) patients, respectively.

Fifty (34.5%) tofacitinib initiators reported prior bDMARDs. Only 6 (4.9%) TNFi initiators reported prior bDMARDs (2 adalimumab, 1 tocilizumab, and 3 abatacept; no patients reported prior etanercept, golimumab, or rituximab exposure). The most common bDMARDs in the tofacitinib group were etanercept [21 (14.5%)] and adalimumab [20 (13.8%)].

Tofacitinib as a prior RA therapy was reported by 3 (2.5%) TNFi initiators, for an average of 1.4 years.

Table 6. Prior RA Medication Therapy-Full Analysis Set

Parameter	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Number of Subjects with at Least One Prior RA Medication Therapy	145 (100.0)	122 (100.0)	267 (100.0)
bDMARDs	50 (34.5)	6 (4.9)	56 (21.0)
Adalimumab	20 (13.8)	2 (1.6)	22 (8.2)
Average years using Adalimumab	1.8	2.6	1.8
Etanercept	21 (14.5)	0	21 (7.9)
Average years using Etanercept	4.1	0	4.1
Golimumab	10 (6.9)	0	10 (3.7)
Average years using Golimumab	1.6	0	1.6
Tocilizumab	9 (6.2)	1 (0.8)	10 (3.7)
Average years using Tocilizumab	0.5	3.6	0.6
Abatacept	6 (4.1)	3 (2.5)	9 (3.4)
Average years using Abatacept	1.3	0.4	1.0
Rituximab	6 (4.1)	0	6 (2.2)
Average years using Rituximab	3.4	0	3.4
cDMARDs	145 (100.0)	121 (99.2)	266 (99.6)
Methotrexate	131 (90.3)	110 (90.2)	241 (90.3)
Average years using Methotrexate	3.7	3.1	3.4
Hydroxychloroquine	112 (77.2)	101 (82.8)	213 (79.8)
Average years using Hydroxychloroquine	3.4	3.0	3.2
Sulfasalazine	95 (65.5)	70 (57.4)	165 (61.8)
Average years using Sulfasalazine	3.9	3.7	3.9
Leflunomide	51 (35.2)	37 (30.3)	88 (33.0)
Average years using Leflunomide	2.3	2.0	2.2
Cyclosporine	21 (14.5)	11 (9.0)	32 (12.0)
Average years using Cyclosporine	2.4	1.4	2.0
Azathioprine	5 (3.4)	8 (6.6)	13 (4.9)
Average years using Azathioprine	2.2	2.6	2.5
Cyclophosphamide	1 (0.7)	3 (2.5)	4 (1.5)
Average years using Cyclophosphamide	3.5	1.0	1.6
Chloroquine	3 (2.1)	0	3 (1.1)
Average years using Chloroquine	7.1	0	7.1
NSAIDs	119 (82.1)	102 (83.6)	221 (82.8)
Meloxicam	8 (5.5)	7 (5.7)	15 (5.6)
Average years using Meloxicam	0.7	1.0	0.8
Diclofenac sodium	3 (2.1)	0	3 (1.1)
Average years using Diclofenac sodium	0.4	0	0.4
Indomethacin	1 (0.7)	0	1 (0.4)
Average years using Indomethacin	0.1	0	0.1
Ketoprofen	1 (0.7)	0	1 (0.4)
Average years using Ketoprofen	0	0	0
Other	113 (77.9)	96 (78.7)	209 (78.3)

Parameter	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Average years using Other	1.2	1.0	1.1
Steroid	107 (73.8)	89 (73.0)	196 (73.4)
Prednisone	50 (34.5)	42 (34.4)	92 (34.5)
Average years using Prednisone	0.6	0.6	0.6
Methylprednisolone	23 (15.9)	11 (9.0)	34 (12.7)
Average years using Methylprednisolone	1.2	0.3	0.9
Other	55 (37.9)	51 (41.8)	106 (39.7)
Average years using Other	0.9	1.0	0.9
Tofacitinib	0	3 (2.5)	3 (1.1)
Average years using Tofacitinib	0	1.4	1.4
Other	27 (18.6)	16 (13.1)	43 (16.1)
Folic acid	21 (14.5)	12 (9.8)	33 (12.4)
Average years using Folic acid	2.6	1.9	2.4
Paracetamol; tramadol	6 (4.1)	2 (1.6)	8 (3.0)
Average years using Paracetamol; tramadol	0.9	0.3	0.8
Colchicine	1 (0.7)	2 (1.6)	3 (1.1)
Average years using Colchicine	1.7	2.1	2.0
Cevimeline	0	2 (1.6)	2 (0.7)
Average years using Cevimeline	0	6.0	6.0
Paracetamol	0	1 (0.8)	1 (0.4)
Average years using Paracetamol	0	0.1	0.1

- SOURCE: Table 14.1-4.1.
- 'Other' is based on WHO Drugs Preferred Terms.
- Prior RA medications were coded using WHO Drug Dictionary Global version 202103_B3.

10.2.5. Concomitant Medication

Concomitant medications of FAS are shown in Table 7. Individual data are presented in Listing 16.2.4-4.1.

All the study patients received concomitant medications. Medications received by >25% patients mostly included methotrexate [199 (74.5%)], celecoxib [160 (59.9%)], hydroxychloroquine [159 (59.6%)], prednisolone [147 (55.1%)], sulfasalazine [104 (39.0%)] and etoricoxib [90 (33.7%)].

Table 7. Concomitant Medications-Full Analysis Set

WHO Drug Preferred Term	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Number of Subjects with Any WHO Drug Preferred Term	145 (100.0)	122 (100.0)	267 (100.0)
Methotrexate	104 (71.7)	95 (77.9)	199 (74.5)
Folic acid	104 (71.7)	92 (75.4)	196 (73.4)
Celecoxib	86 (59.3)	74 (60.7)	160 (59.9)
Hydroxychloroquine	81 (55.9)	78 (63.9)	159 (59.6)
Prednisolone	77 (53.1)	70 (57.4)	147 (55.1)
Sulfasalazine	54 (37.2)	50 (41.0)	104 (39.0)
Etoricoxib	51 (35.2)	39 (32.0)	90 (33.7)

- SOURCE: Table 14.1-5.1.
- Concomitant Medications were coded using WHO Drug Dictionary Global version 202103_B3.
- WHO Drug Preferred Terms are sorted by descending frequency; multiple conditions of any preferred term are counted only once.

10.3. Outcome Data

A total of 242 patients (90.6%) were included in the EFF set, 134 patients (92.4%) in the tofacitinib group and 108 patients (88.5%) in the TNFi group. A total of 25 patients (9.4%) were included in the DSS set, 11 patients (7.6%) in the tofacitinib group and 14 patients (11.5%) in the TNFi group. A total of 267 patients (100%) were included in the SAF set, 145 patients (100%) in the tofacitinib group and 122 patients (100%) in the TNFi group. (Source: Table 14.1-1.1).

10.4. Main Results

10.4.1. Short-term Effectiveness of Tofacitinib and TNFi

10.4.1.1. HAQ-DI Core

Short-term effectiveness of tofacitinib and TNFi after one-week was measured in terms of HAQ-DI score as shown in Table 8.

Patients (n=134) of tofacitinib group had a Mean (SD) HAQ-DI score of 0.9729 (0.76418) at baseline. Fifty-three patients (39.6%) were evaluated after one-week of treatment by tofacitinib and showed a mean (SD) change from baseline of -0.1769 (0.47182), with 40 patients (29.9%) showing no increase in the HAQ-DI score after one week of tofacitinib treatment compared to baseline.

The mean (SD) baseline HAQ-DI score of the 108 patients in the TNFi group was 0.9838 (0.78148). Fifty-five (50.9%) patients were evaluated at Week 1 and had a mean change from baseline of -0.1568 (0.35044), with 46 patients (42.6%) showing no increase in the HAQ-DI score after one-week of TNFi treatment compared to baseline.

Table 8. HAQ-DI Score, Summary Statistics over Time-Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: All Visits					
Baseline	HAQ-DI Score	n	134	108	242
		Mean	0.9729	0.9838	0.9778
		SD	0.76418	0.78148	0.77036
		Median	0.9375	0.8750	0.8750
		Min, Max	0.000, 3.000	0.000, 3.000	0.000, 3.000
Week 1	HAQ-DI Score	n*	53	55	108
		Mean	0.7995	0.7682	0.7836
		SD	0.76521	0.74629	0.75226
		Median	0.6250	0.6250	0.6250
		Min, Max	0.000, 2.875	0.000, 3.000	0.000, 3.000
	Increased from Baseline	n (%)	13 (9.7)	9 (8.3)	22 (9.1)
	Not Increased from Baseline	n (%)	40 (29.9)	46 (42.6)	86 (35.5)
	Change from Baseline (Week 1-Baseline)	n	53	55	108
		Mean	-0.1769	-0.1568	-0.1667
		SD	0.47182	0.35044	0.41264
		Median	0.0000	0.0000	0.0000
		Min, Max	-1.500, 1.000	-1.125, 0.625	-1.500, 1.000

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)

- SOURCE: Table 14.2-1.1.2.
- SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.
- * Not all patients came back to be assessed at Week 1. As a non-interventional study, all clinical assessments were intended to be performed at routine clinical encounter and the missing visits were not considered as protocol deviations.

10.4.1.2. CDAI Score

Summary statistics of CDAI score over time is shown in Table 9.

After one-week of treatment, the mean change from baseline, evaluated in 47 (35.1%) tofacitinib patients and 49 (45.4%) TNFi patients, was -6.82 and -11.1, respectively. Bearing in mind that less than half the patients were assessed at that time point, 22 (16.4%) tofacitinib initiators and 27 (25.0%) TNFi initiators showed a significant improvement at Week 1 (defined as a ≥6.5 points decrease of CDAI score).

Table 9. CDAI Score, Summary Statistics over Time- Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: All Visits					
Baseline	CDAI Score	n	125	101	226
		Mean	28.35	34.61	31.15
		SD	12.395	11.819	12.510
		Median	28.50	34.50	31.00
		Min, Max	4.0, 55.0	12.0, 65.0	4.0, 65.0
	CDAI >2.8	n (%)*	125 (93.3)	101 (93.5)	226 (93.4)
	CDAI ≤10	n (%)*	13 (9.7)	0	13 (5.4)
	CDAI >10	n (%)*	112 (83.6)	101 (93.5)	213 (88.0)
Baseline	CDAI >22 (High Disease Activity)	n (%)*	80 (59.7)	81 (75.0)	161 (66.5)
	10< CDAI ≤22(Moderate Disease Activity)	n (%)*	32 (23.9)	20 (18.5)	52 (21.5)
	CDAI ≤10 (Low Disease Activity)	n (%)*	13 (9.7)	0	13 (5.4)
Week 1	CDAI Score	n[#]	48	51	99
		Mean	27.15	25.14	26.11
		SD	9.940	9.830	9.885
		Median	27.00	24.00	25.50
		Min, Max	8.5, 48.0	10.5, 48.0	8.5, 48.0

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	CDAI >2.8	n (%)*	48 (35.8)	51 (47.2)	99 (40.9)
	CDAI ≤10	n (%)*	4 (3.0)	0	4 (1.7)
	CDAI >10	n (%)*	44 (32.8)	51 (47.2)	95 (39.3)
	Change from Baseline (Week 1-Baseline)	n	47	49	96
		Mean	-6.82	-11.11	-9.01
		SD	6.652	10.828	9.236
		Median	-5.50	-7.60	-6.50
		Min, Max	-22.3, 4.0	-37.5, 2.0	-37.5, 4.0
	CDAI Significant Improvement (-6.5 points)	n (%)*	22 (16.4)	27 (25.0)	49 (20.2)
	CDAI Significant Deterioration (+6.5 points)	n (%)*	0	0	0
	MCID Improvement (Week 1-Baseline)				
	-12 points (Patients CDAI starting in >22)	n (%)^	10 (12.5)	20 (24.7)	30 (18.6)
	-6 points (Patients CDAI starting in 10< CDAI ≤22)	n (%)^	0	0	0
	-1 points (Patients CDAI starting in ≤10)	n (%)^	0	0	0

- SOURCE: Table 14.2-1.3.2.
- SD = Standard Deviation; MCID = Minimally Clinically Important Differences.
- * Percentages are based on the number of patients in Effectiveness Analysis Set.
- ^ Percentages of MCID improvement are based on the number of each CDAI starting point groups (high, moderate, and low disease activity at baseline).
- # Not all patients came back to be assessed at Week 1. As a non-interventional study, all clinical assessments were intended to be performed at routine clinical encounter and the missing visits were not considered as protocol deviations.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.4.2. Long-term Effectiveness of Tofacitinib and TNFi

10.4.2.1. HAQ-DI Score

Long-term effectiveness after 6 months (Week 24) and 12 months (Week 48) of tofacitinib and TNFi treatment as measured by HAQ-DI score is shown in Table 10.

The Mean (SD) change in HAQ-DI score from baseline after 24 weeks of treatment for overall study patients, tofacitinib patients and TNFi patients was -0.2034 (0.53078), -0.1817 (0.53536), and -0.2300 (0.52643), respectively. Improvement was shown by 96 (71.6%) of tofacitinib initiators, 84 (77.8%) of TNFi initiators, and 180 (74.4%) patients overall. The MCID for HAQ-DI has been described as a reduction of at least 0.22.[28] The Mean (SD) change in HAQ-DI score from baseline after 48 weeks of treatment for overall study patients, tofacitinib and TNFi patients was -0.2155 (0.58463), -0.2392 (0.57886), and -0.1856 (0.59335), respectively. Improvement was shown by 95 (70.9%) of tofacitinib initiators, 74 (68.5%) of TNFi initiators, and 169 (69.8%) patients overall.

Table 10. HAQ-DI Score, Summary Statistics over Time-Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Week 24	HAQ-DI Score	n	130	106	236
		Mean	0.7817	0.7217	0.7548
		SD	0.75872	0.79288	0.77316
		Median	0.6250	0.3750	0.5000
		Min, Max	0.000, 3.000	0.000, 3.000	0.000, 3.000
	Increased from Baseline	n (%)*	34 (25.4)	22 (20.4)	56 (23.1)
	Not Increased from Baseline	n (%)*	96 (71.6)	84 (77.8)	180 (74.4)
	Change from Baseline (Week 24-Baseline)	n	130	106	236
		Mean	-0.1817	-0.2300	-0.2034
		SD	0.53536	0.52643	0.53078
		Median	0.0000	-0.1250	-0.1250
		Min, Max	-2.000, 1.250	-2.125, 1.000	-2.125, 1.250
Week 48	HAQ-DI Score	n	127	101	228
		Mean	0.7431	0.7240	0.7346
		SD	0.72105	0.78964	0.75058
		Median	0.6250	0.5000	0.5000
		Min, Max	0.000, 2.625	0.000, 2.875	0.000, 2.875
	Increased from Baseline	n (%)*	32 (23.9)	27 (25.0)	59 (24.4)
	Not Increased from Baseline	n (%)*	95 (70.9)	74 (68.5)	169 (69.8)

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	Change from Baseline (Week 48-Baseline)	n	127	101	228
		Mean	-0.2392	-0.1856	-0.2155
		SD	0.57886	0.59335	0.58463
		Median	-0.1250	-0.1250	-0.1250
		Min, Max	-1.875, 1.375	-2.250, 1.000	-2.250, 1.375

- SOURCE: Table 14.2-1.1.2.
- SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.4.2.2. CDAI Score

Long-term effectiveness of tofacitinib and TNFi as measured by CDAI score is shown in Table 11.

The Mean (SD) change in CDAI score from baseline after 24 weeks of treatment for overall study patients, tofacitinib patients and TNFi patients was -15.84 (12.241), -12.85 (10.258), and -19.43 (13.466), respectively.

Significant improvement in CDAI score (reduction from baseline by ≥6.5 points) at 24 weeks were recorded for 80 tofacitinib patients (59.7%) and 80 TNFi patients (74.1%). Significant deterioration (increase from baseline by ≥6.5 points) was recorded for 2 tofacitinib treated patients (1.5%) and 3 TNFi treated patient (2.8%). The minimal clinically important difference was reached by 82 tofacitinib treated patients and 79 TNFi treated patients after 24 weeks of treatment.

The Mean (SD) change in CDAI score from baseline after 48 weeks of treatment for overall study patients, tofacitinib patients and TNFi patients was -17.76 (12.900), -14.56 (12.113), and -21.74 (12.799) respectively.

Significant improvement in CDAI score at 48 weeks was reported for 81 tofacitinib treated patients (60.4%) and 78 TNFi treated patients (72.2%). Deterioration of CDAI score was reported for 2 tofacitinib treated patients (1.5%) and 1 TNFi treated patient (0.9%). The minimal clinically important difference was reached by 77 tofacitinib treated patients and 75 TNFi treated patients after 48 weeks of treatment.

Overall, a score ≤10, indicating a low disease activity, was observed for 43 (32.1%) and 47 (35.1%) tofacitinib users at Week 24 and Week 48, respectively, and for 22 (20.4%) and 39 (36.1%) TNFi users, at Week 24 and Week 48, respectively. Remission (CDAI score <2.8) was observed for 5 (3.7%) tofacitinib users at Week 24, and 6 (4.5%) tofacitinib users and 2 (1.9%) TNFi users at Week 48.

Table 11. CDAI Score, Summary Statistics over Time- Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Week 24	CDAI Score	n	126	105	231
		Mean	15.38	15.43	15.40
		SD	9.455	7.936	8.778
		Median	13.95	14.50	14.00
		Min, Max	1.0, 54.0	3.0, 52.5	1.0, 54.0
	CDAI ≤2.8	n (%)*	5 (3.7)	0	5 (2.1)
	CDAI >2.8	n (%)*	121 (90.3)	105 (97.2)	226 (93.4)
	CDAI ≤10	n (%)*	43 (32.1)	22 (20.4)	65 (26.9)
	CDAI >10	n (%)*	83 (61.9)	83 (76.9)	166 (68.6)
	Change from Baseline (Week 24-Baseline)	n	118	98	216
		Mean	-12.85	-19.43	-15.84
		SD	10.258	13.466	12.241
		Median	-13.25	-22.00	-16.25
		Min, Max	-38.5, 12.0	-54.0, 16.0	-54.0, 16.0
	CDAI Significant Improvement (-6.5 points)	n (%)*	80 (59.7)	80 (74.1)	160 (66.1)
	CDAI Significant Deterioration (+6.5 points)	n (%)*	2 (1.5)	3 (2.8)	5 (2.1)
MCID Improvement (Week 24-Baseline)					
	-12 points (Patients CDAI starting in >22)	n (%)^	55 (68.8)	67 (82.7)	122 (75.8)
	-6 points (Patients CDAI starting in 10< CDAI ≤22)	n (%)^	18 (56.3)	12 (60.0)	30 (57.7)
	-1 points (Patients CDAI starting in ≤10)	n (%)^	9 (69.2)	0	9 (69.2)
Week 48	CDAI Score	n	121	97	218
		Mean	13.24	13.81	13.49
		SD	7.890	7.904	7.883
		Median	11.50	12.00	11.50
		Min, Max	1.0, 52.0	2.0, 52.0	1.0, 52.0
	CDAI ≤2.8	n (%)*	6 (4.5)	2 (1.9)	8 (3.3)
	CDAI >2.8	n (%)*	115 (85.8)	95 (88.0)	210 (86.8)

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	CDAI ≤10	n (%)*	47 (35.1)	39 (36.1)	86 (35.5)
	CDAI >10	n (%)*	74 (55.2)	58 (53.7)	132 (54.5)
	Change from Baseline (Week 48-Baseline)	n	114	92	206
		Mean	-14.56	-21.74	-17.76
		SD	12.113	12.799	12.900
		Median	-13.50	-23.25	-16.85
		Min, Max	-47.0, 14.0	-54.0, 10.0	-54.0, 14.0
	CDAI Significant Improvement (-6.5 points)	n (%)*	81 (60.4)	78 (72.2)	159 (65.7)
	CDAI Significant Deterioration (+6.5 points)	n (%)*	2 (1.5)	1 (0.9)	3 (1.2)
MCID Improvement (Week 48-Baseline)					
	-12 points (Patients CDAI starting in >22)	n (%)^	54 (67.5)	66 (81.5)	120 (74.5)
	-6 points (Patients CDAI starting in 10< CDAI ≤22)	n (%)^	19 (59.4)	9 (45.0)	28 (53.8)
	-1 points (Patients CDAI starting in ≤10)	n (%)^	4 (30.8)	0	4 (30.8)

- SOURCE: Table 14.2-1.3.2.
- SD = Standard Deviation; MCID = Minimally Clinically Important Differences.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- ^ Percentages of MCID improvement are based on the number of each CDAI starting point groups (high, moderate, and low disease activity at baseline).
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.4.2.3. DAS28-ESR Score

DAS28-ESR score is shown in Table 12.

Overall, 232 patients (95.9%) had a baseline DAS28-ESR score of ≥3.2, indicating a moderate disease activity. After 24 and 48 weeks of treatment, 177 patients (73.1%) and 166 patients (68.6%), respectively, presented a score of ≥3.2. The Mean (SD) change from baseline of DAS28-ESR score after 24 and 48 weeks of treatment was -1.7236 (1.27115) and -1.9274 (1.33509) in the total cohort, respectively.

At Week 24, the mean (SD) change from baseline of DAS28-ESR score was -1.3989 (1.25953) for tofacitinib users and -2.1159 (1.17621) for TNFi users. At Week 48, the mean (SD) change from baseline was -1.6116 (1.37288) for tofacitinib users and -2.3340 (1.17163) for TNFi users.

Overall, a score <3.2, indicating a low disease activity, was observed for 28 (20.9%) and 30 (22.4%) tofacitinib users at Week 24 and Week 48, respectively, and for 19 (17.6%) and 20 (18.5%) TNFi users at Week 24 and Week 48, respectively. Remission (DAS28-ESR score <2.6) was observed for 15 (11.2%) tofacitinib users at Week 24, and 12 (9.0%) tofacitinib users at Week 48. In the TNFi group, remission was observed for 8 (7.4%) and 4 (3.7%) patients at Week 24 and Week 48, respectively.

Table 12. DAS28-ESR Score, Summary Statistics over Time-Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Baseline	DAS28-ESR Results	n	133	107	240
		Mean	5.5812	6.1065	5.8154
		SD	1.33041	1.07431	1.24817
		Median	5.7010	6.1210	5.9740
		Min, Max	2.107, 8.045	2.999, 8.658	2.107, 8.658
	DAS28-ESR <2.6	n (%)*	3 (2.2)	0	3 (1.2)
	DAS28-ESR ≥2.6	n (%)*	130 (97.0)	107 (99.1)	237 (97.9)
	DAS28-ESR <3.2	n (%)*	7 (5.2)	1 (0.9)	8 (3.3)
	DAS28-ESR ≥3.2	n (%)*	126 (94.0)	106 (98.1)	232 (95.9)
Week 24	DAS28-ESR Results	n	122	102	224
		Mean	4.0948	3.9946	4.0492
		SD	1.30311	0.95187	1.15510
		Median	4.0980	4.0380	4.0760
		Min, Max	0.485, 8.103	1.417, 7.530	0.485, 8.103
	DAS28-ESR <2.6	n (%)*	15 (11.2)	8 (7.4)	23 (9.5)
	DAS28-ESR ≥2.6	n (%)*	107 (79.9)	94 (87.0)	201 (83.1)
	DAS28-ESR <3.2	n (%)*	28 (20.9)	19 (17.6)	47 (19.4)
	DAS28-ESR ≥3.2	n (%)*	94 (70.1)	83 (76.9)	177 (73.1)
	Change from Baseline (Week 24-Baseline)	n	122	101	223
		Mean	-1.3989	-2.1159	-1.7236
		SD	1.25953	1.17621	1.27115
		Median	-1.5235	-2.2080	-1.9150
		Min, Max	-5.541, 1.297	-4.706, 1.755	-5.541, 1.755
Week 48	DAS28-ESR Results	n	121	95	216
		Mean	3.8654	3.8003	3.8368
		SD	1.10889	0.93104	1.03264
		Median	3.8920	3.8450	3.8595
		Min, Max	0.769, 8.020	0.485, 7.140	0.485, 8.020
	DAS28-ESR <2.6	n (%)*	12 (9.0)	4 (3.7)	16 (6.6)
	DAS28-ESR ≥2.6	n (%)*	109 (81.3)	91 (84.3)	200 (82.6)
	DAS28-ESR <3.2	n (%)*	30 (22.4)	20 (18.5)	50 (20.7)
	DAS28-ESR ≥3.2	n (%)*	91 (67.9)	75 (69.4)	166 (68.6)

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	Change from Baseline (Week 48-Baseline)	n	121	94	215
		Mean	-1.6116	-2.3340	-1.9274
		SD	1.37288	1.17163	1.33509
		Median	-1.6360	-2.3560	-2.0430
		Min, Max	-5.257, 2.150	-5.125, 0.349	-5.257, 2.150

- SOURCE: Table 14.2-1.4.2.
  SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.4.2.4. WPAI

Long-term effectiveness of Tofacitinib and TNFi as measured by WPAI score is shown in Table 13.

A total of 59 tofacitinib patients and 46 TNFi patients of the EFF set were in the working force at baseline.

The Mean (SD) change from baseline in percent work time missed due to RA at Week 24 for overall study patients, tofacitinib treated patients and TNFi treated patients was -0.74 (10.139), -1.70 (11.871), and 0.49 (7.347), respectively.

The Mean (SD) change from baseline in percent impairment while working due to RA at Week 24 for overall study patients, tofacitinib treated patients and TNFi treated patients was -10.23 (23.211), -7.66 (24.602) and -13.33 (21.316), respectively.

The Mean (SD) change from baseline in overall percent work impairment due to RA at Week 24 for overall study patients, tofacitinib treated patients and TNFi treated patients was -9.66 (23.905), -8.14 (25.433) and - 11.60 (21.997), respectively.

The Mean (SD) change from baseline in percent activity impairment due to RA at Week 24 was comparable among overall study patients, tofacitinib treated patients and TNFi treated patients, and was -10.64 (22.834), -9.69 (22.027) and -11.81 (23.850), respectively.

Table 13. WPAI-RA Score, Summary Statistics over Time- Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: All Visits					
Baseline	Patient Currently Employed (Working for Pay)	Yes, n (%)*	59 (44.0)	46 (42.6)	105 (43.4)
		No, n (%)*	75 (56.0)	62 (57.4)	137 (56.6)
	Percent Work Time Missed Due to RA	n	55	40	95
		Mean	6.08	2.12	4.41
		SD	17.904	4.347	13.995
		Median	0.00	0.00	0.00
		Min, Max	0.0, 100.0	0.0, 16.7	0.0, 100.0
	Percent Impairment While Working Due to RA	n	55	43	98
		Mean	42.73	43.49	43.06
		SD	26.419	28.359	27.146
		Median	50.00	40.00	50.00
		Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0
	Percent Overall Work Impairment Due to RA	n	54	40	94
		Mean	44.19	45.13	44.59
		SD	28.020	28.924	28.257
		Median	50.00	45.00	50.00
		Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0
	Percent Activity Impairment Due to RA	n	134	107	241
		Mean	50.00	51.59	50.71
		SD	23.683	25.519	24.476
		Median	50.00	50.00	50.00
		Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0
Week 24	Patient Currently Employed (Working for Pay)	Yes, n (%)*	54 (40.3)	43 (39.8)	97 (40.1)
		No, n (%)*	76 (56.7)	62 (57.4)	138 (57.0)
	Percent Work Time Missed Due to RA	n	51	41	92
		Mean	2.53	2.03	2.31
		SD	6.844	6.522	6.670
		Median	0.00	0.00	0.00
		Min, Max	0.0, 28.6	0.0, 33.3	0.0, 33.3

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	Percent Impairment While Working Due to RA	n	52	42	94
		Mean	34.04	26.90	30.85
		SD	23.285	23.529	23.539
		Median	30.00	20.00	30.00
		Min, Max	0.0, 90.0	0.0, 70.0	0.0, 90.0
	Percent Overall Work Impairment Due to RA	n	51	41	92
		Mean	35.22	28.63	32.28
		SD	24.367	24.306	24.429
		Median	30.00	20.00	30.00
		Min, Max	0.0, 90.0	0.0, 73.3	0.0, 90.0
	Percent Activity Impairment Due to RA	n	130	106	236
		Mean	40.00	39.25	39.66
		SD	23.756	25.698	24.597
		Median	40.00	40.00	40.00
		Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0
Change from Baseline (Week 24-Baseline)	Percent Work Time Missed Due to RA	n	46	36	82
		Mean	-1.70	0.49	-0.74
		SD	11.871	7.347	10.139
		Median	0.00	0.00	0.00
		Min, Max	-54.5, 22.2	-12.5, 33.3	-54.5, 33.3
	Percent Impairment While Working Due to RA	n	47	39	86
		Mean	-7.66	-13.33	-10.23
		SD	24.602	21.316	23.211
		Median	-10.00	-10.00	-10.00
		Min, Max	-80.0, 50.0	-60.0, 40.0	-80.0, 50.0
	Percent Overall Work Impairment Due to RA	n	46	36	82
		Mean	-8.14	-11.60	-9.66
		SD	25.433	21.997	23.905
		Median	-7.38	-9.04	-9.04
		Min, Max	-80.0, 54.4	-60.0, 40.0	-80.0, 54.4
	Percent Activity Impairment Due to RA	n	130	105	235
		Mean	-9.69	-11.81	-10.64
		SD	22.027	23.850	22.834

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
		Median	-10.00	-10.00	-10.00
		Min, Max	-90.0, 30.0	-80.0, 60.0	-90.0, 60.0

- SOURCE: Table 14.2-1.2.2.
- SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last visit with non-missing value of "Are you currently employed (working for pay)?" before the post-dose down visit.

10.4.3. Effectiveness Outcomes From Mixed Logistic Models

Effectiveness of tofacitinib vs. TNFi is shown in Table 14. Two ORs are presented for each variable, firstly the OR adjusted on PS (baseline sociodemographic, clinical and treatment characteristics), and secondly the unadjusted (crude) OR.

The mixed logistic regression model did not evidence a significant difference between tofacitinib and TNFi for any of the effectiveness variables in the study population.

Table 14. Logistic Regression Model-Effectiveness Analysis Set

Parameter	Statistics	PS-adjusted, Tofacitinib vs. TNFi	Unadjusted, Tofacitinib vs. TNFi[d]
All Visits			
HAQ-DI Outcome for Improvement[a]	Odds Ratio (SE)	2.4 (0.5)[b]	1.1 (0.4)
	95% CI Odds Ratio	(0.9 - 6.3)	(0.5 - 2.5)
	P-Value	0.0848	0.7312
CDAI Outcome for Remission	Odds Ratio (SE)	1.4 (1.0)[c]	2.7 (0.7)
	95% CI Odds Ratio	(0.2 - 9.7)	(0.7 - 9.9)
	P-Value	0.7549	0.1405
DAS28-ESR Outcome for Remission	Odds Ratio (SE)	1.9 (0.6)[c]	2.0 (0.5)
	95% CI Odds Ratio	(0.6 - 6.3)	(0.8 - 5.1)
	P-Value	0.3092	0.1312
CDAI Outcome for LDA	Odds Ratio (SE)	1.2 (0.4)[c]	1.2 (0.3)
	95% CI Odds Ratio	(0.6 - 2.5)	(0.7 - 2.3)
	P-Value	0.5859	0.4825
DAS28-ESR Outcome for LDA	Odds Ratio (SE)	1.3 (0.4)[c]	1.2 (0.3)
	95% CI Odds Ratio	(0.6 - 2.9)	(0.6 - 2.4)
	P-Value	0.5297	0.5450
WPAI-RA Outcome (Currently employed)	Odds Ratio (SE)	8.5 (2.2)[c]	2.4 (1.8)
	95% CI Odds Ratio	(0.1 - 645.0)	(0.1 - 89.9)

Parameter	Statistics	PS-adjusted, Tofacitinib vs. TNFi	Unadjusted, Tofacitinib vs. TNFi[d]
All Visits			
	P-Value	0.3341	0.6277
• SOURCE: Table 14.2-1.2.2. a. The HAQ-DI outcome for improvement is defined as whether there was a decrease of the HAQ-DI score from baseline or not. b. The analysis is conducted by including treatment group, visit, baseline HAQ-DI score, and PS score as covariates for adjustment. The SE is the estimation of ln(OR). c. The analysis is conducted by including treatment group, visit, and PS score as covariates for adjustment. d. The crude odds ratio and corresponding 95% CI is generated by original model with excluding the propensity score.			

10.5. Other Analyses

10.5.1. Treatment Patterns of Tofacitinib and TNFi

Treatment patterns of tofacitinib and TNFi, assessed for the for FAS, are displayed in Table 15.

A total of 45 (31.0%) tofacitinib users and 41 (33.6%) TNFi users had an event of treatment discontinuation or switch, after a Mean (SD) time of 17.378 (12.7808) months for tofacitinib users and 16.706 (11.9836) months for TNFi users, respectively.

The Kaplan-Meier curves are presented in Figure 2 and Figure 3. The 25th percentile time to discontinuation or treatment switch was 27.630 months for tofacitinib users and 21.191 months for TNFi patients.

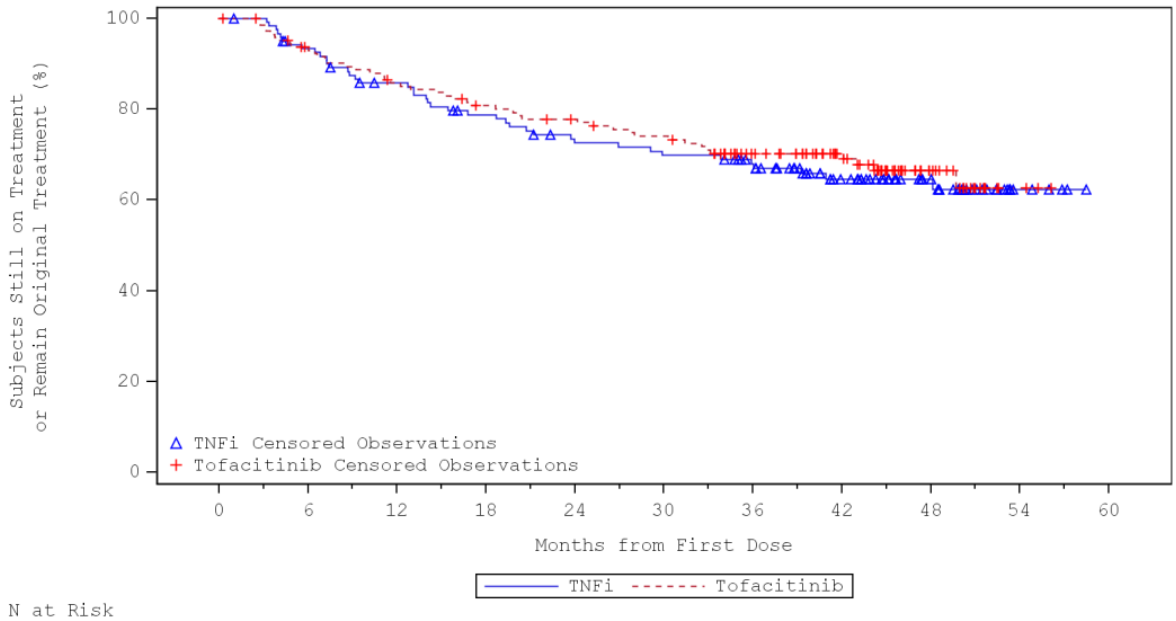
The hazard ratio of treatment discontinuation or switch was 0.886 (95% CI: 0.544, 1441) for tofacitinib over the TNFi group.

Table 15. Treatment Patterns-Full Analysis Set

Characteristic	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)
Time to Event (Discontinuation or Treatment Switch) (Month)			
n	45	41	86
Mean	17.378	16.706	17.058
SD	12.7808	11.9836	12.3390
Median	14.752	13.963	14.012
Min, Max	2.79, 49.68	3.24, 48.13	2.79, 49.68
K-M Estimation of Time to Event (Discontinuation or Treatment Switch) (Month)			
25th percentile	27.630	21.191	25.068
Median (95% CI@)	-(-, -)	-(-, -)	-(-, -)
75th percentile	-	-	-
Hazard Ratio estimation for Tofacitinib over TNFi group #			
Hazard Ratio	0.886		
95% CI	0.544, 1.441		

- SOURCE: Table 14.1-7.1
- * Other advanced RA treatment type can be generally divided into below category: Non-TNFi type (Generic name in Abatacept, Tocilizumab, Baricitinib, Rituximab); TNFi (non-study observed) type (Generic name in Certolizumab pegol, Opinercept).
- Due to the similar mechanism of action, if subjects using TNFi (study observed) type and then switch to the TNFi (non-study observed) type, it is not viewed as treatment switch in the analysis.
- @ The confidence intervals are estimated by Brookmeyer and Crowley method.
- # Hazard Ratio is estimated by Cox regression model by adjusting for: age, sex, previous bDMARDs use, previous cDMARDs use, baseline DAS28-ESR score, baseline WPAI-RA, and comorbidity (CCI score). For details refer to SAP Section 16.

Figure 2 Time to Events (Discontinuation/Switch)-Crude Survival Curve-Full Analysis Set

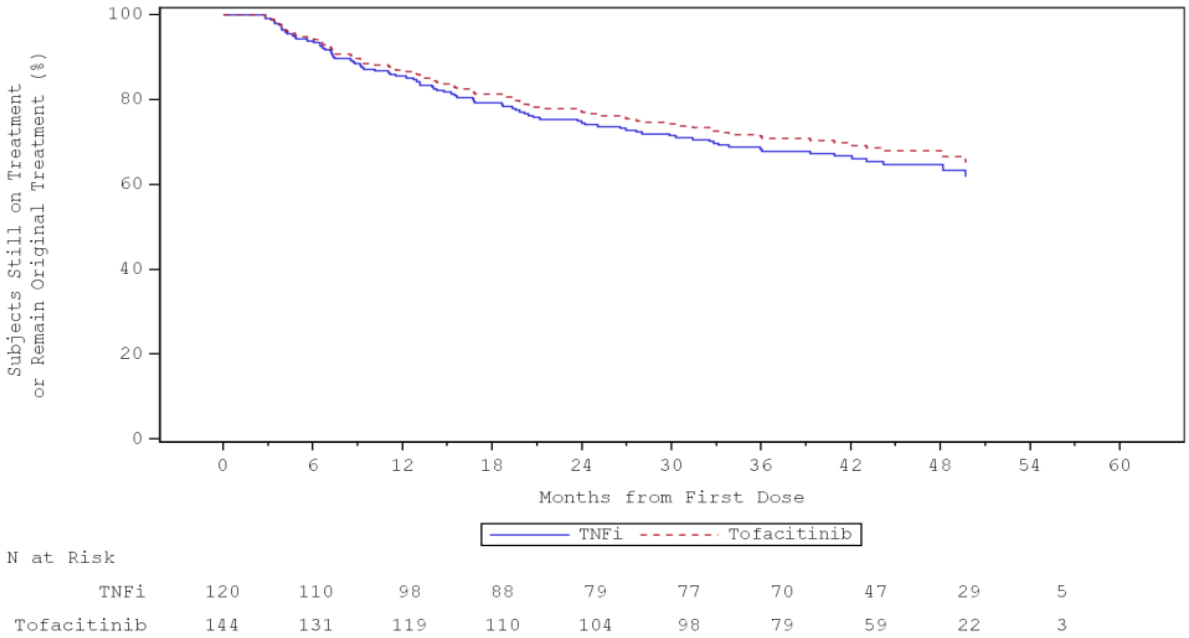


N at Risk

TNFi	122	111	99	89	80	77	70	47	29	5
Tofacitinib	145	131	119	110	104	98	79	59	22	3

Source: Figure 14.1-7.1.2.

Figure 3 Time to Events (Discontinuation/Switch)-Adjusted Survival Curve-Full Analysis Set



The adjusted survival curve is estimated by Cox regression model, by adjusting for age, sex, previous bDMARDs use, previous cDMARDs use, baseline DAS28-ESR score, baseline WPAI-RA, and comorbidity (CCI score). For details, refer to SAP section 16.

Source: Figure 14.1-7.1.3.

10.5.1.1. Dose Changes for Tofacitinib and TNFi

Details of dose changes for tofacitinib and TNFi are shown in Table 16.

In the total study population, 173 patients (64.8%) required dose change or dose interruption during the study. The reasons reported in the eCRF for dose change or dose interruption (as described in Table 1) included: AE (49 patients (18.4%)); NHI requirement (as described in Section 9.1) for 39 (14.6%) patients, and lack of efficacy for 29 patients (10.9%), respectively. The other patients reported other reasons. Patients might have more than one dose change, and then more than one reason for dose change, and in that case, the patient was counted once for each type of reason.

Dose change or interruption was more frequent in the tofacitinib users, compared to TNFi users. There were 113 (77.9%) tofacitinib users and 60 (49.2%) TNFi users with doses changed or interrupted during the study. In the tofacitinib group, 59.3% of patients (vs 28.7% of TNFi users) had dose changes or interruptions unrelated to AE, NHI requirement or lack of efficacy. Dose change or interruption due to an AE was slightly more frequent in tofacitinib users (n=31, 21.4%) than in TNFi users (n=18, 14.8%).

Table 16 Dose Change-Full Analysis Set

Characteristic	Tofacitinib (N=145) n (%)	TNFi (N=122) n (%)	Total (N=267) n (%)
Dose(s) Changed /Interrupted*	113 (77.9)	60 (49.2)	173 (64.8)
Reason			
AE	31 (21.4)	18 (14.8)	49 (18.4)
Per NHI Requirements	23 (15.9)	16 (13.1)	39 (14.6)
Lack of Efficacy	18 (12.4)	11 (9.0)	29 (10.9)
Other	86 (59.3)	35 (28.7)	121 (45.3)

- SOURCE: Table 14.1-6.3
- * The reasons of dose(s) changed or interrupted were summarized only for index treatment. For subjects who had more than one reason of dose change or interrupted, subject was counted once for each type of reason.

10.5.1.2. Proportion of Patients using Tofacitinib and TNFi Each Year

Proportion of patients using tofacitinib and TNFi each year are shown in Table 17. All patients were followed up for the first year of treatment (including switching); approximately 80% of patients were followed up for the second year, 70% for the third year, and 60% for the fourth treatment year. Approximately 20% of patients overall were followed up to the fifth treatment year. Overall, 86 patients (32.2%) either discontinued the index medication [31 (11.6%)] or switched to another medication [55 (20.6%)]; these proportions were similar among tofacitinib and TNFi users. A total of 181 (67.8%) patients were censored, of which 156 patients (58.4%) received the index treatment continuously and 25 patients (9.4%) withdrew from the study without experiencing the events of interest.

Table 17. Treatment Patterns-Full Analysis Set

Characteristic	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)
Proportion of subjects using a given treatment over a 12-month period including switching			
1st year period	145 (100.0)	122 (100.0)	267 (100.0)
2nd year period	119 (82.1)	97 (79.5)	216 (80.9)
3rd year period	106 (73.1)	81 (66.4)	187 (70.0)
4th year period	82 (56.6)	72 (59.0)	154 (57.7)
5th year period	21 (14.5)	31 (25.4)	52 (19.5)
Subjects with Event	45 (31.0)	41 (33.6)	86 (32.2)
Subjects Discontinue Index Treatment	16 (11.0)	15 (12.3)	31 (11.6)
Subjects Switched from Index Study Medication to Other Advanced RA Treatment*	29 (20.0)	26 (21.3)	55 (20.6)
Subjects Censored	100 (69.0)	81 (66.4)	181 (67.8)
Subjects Received Index Treatment Continuously	86 (59.3)	70 (57.4)	156 (58.4)

Characteristic	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)
Subjects are Early Withdrawal with Any Reason before Events Occurred	14 (9.7)	11 (9.0)	25 (9.4)

- SOURCE: Table 14.1-7.1.
- * Other advanced RA treatment type can be generally divided into below category: Non-TNFi type (Generic name in Abatacept, Tocilizumab, Baricitinib, Rituximab); TNFi (non-study observed) type (Generic name in Certolizumab pegol, Opinercept).
- Due to the similar mechanism of action, if subjects using TNFi (study observed) type and then switch to the TNFi (non-study observed) type, it is not viewed as treatment switch in the analysis.

10.5.2. Adherence and Persistence to Tofacitinib and TNFi

Data is presented in Table 18. Individual data is presented in Listing 16.2.5-1.2.

Persistence and adherence to therapy were comparable for tofacitinib and TNFi users (Table 18).

The number of patients who remained on tofacitinib therapy was 117 patients (80.7%) at the end of first year, 104 patients (71.7%) at the end of the second year, and 79 patients (54.5%) at the end of the third year. The mean (SD) persistence over the whole study period was 996.2 (498.30) days for the tofacitinib users.

The number of patients who remained on TNFi therapy was 96 (78.7%) at the end of first year, 80 patients (65.6%) at the end of the second year, and 70 patients (57.4%) at the end of the third year. The mean (SD) persistence over whole study period was 986.0 (537.19) days for the TNFi users.

The mean (SD) PDC in the whole study period patients was 80.4784% (30.30124) for the 145 tofacitinib initiators. A total of 103 patients (71.0%) were found to be adherent.

The mean (SD) PDC in the whole study period was 78.4178% (33.17959) for the 122 TNFi initiators. A total of 87 patients (71.3%) were found to be adherent.

Table 18. Study Medication Exposure-Full Analysis Set

Time Interval	Characteristic	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)
1st year period	Persistence (days)			
	n	145	122	267
	Mean	327.7	322.9	325.5
	SD	92.23	93.35	92.60
	Median	365.0	365.0	365.0
	Min, Max	7, 365	5, 365	5, 365
	Number of Patients who Remain on Therapy at the End of This Period*	117 (80.7)	96 (78.7)	213 (79.8)
2nd year period	Persistence (days)			
	n	117	96	213
	Mean	342.1	333.4	338.2
	SD	72.91	82.87	77.49
	Median	365.0	365.0	365.0
	Min, Max	6, 365	34, 365	6, 365
	Number of Patients who Remain on Therapy at the End of This Period*	104 (71.7)	80 (65.6)	184 (68.9)
3rd year period	Persistence (days)			
	n	104	80	184
	Mean	330.5	352.4	340.1
	SD	82.68	51.20	71.40
	Median	365.0	365.0	365.0
	Min, Max	5, 365	52, 365	5, 365
	Number of Patients who Remain on Therapy at the End of This Period*	79 (54.5)	70 (57.4)	149 (55.8)
4th year period	Persistence (days)			
	n	79	70	149
	Mean	257.7	247.5	252.9
	SD	104.17	126.15	114.73
	Median	274.0	285.5	278.0
	Min, Max	5, 365	1, 365	1, 365
5th year period	Persistence (days)			
	n	21	28	49
	Mean	96.0	120.0	109.7
	SD	65.13	84.92	77.25
	Median	88.0	101.0	91.0
	Min, Max	4, 248	1, 320	1, 320

Time Interval	Characteristic	Tofacitinib (N=145)	TNFi (N=122)	Total (N=267)
Whole study period	Persistence (days)			
	n	145	122	267
	Mean	996.2	986.0	991.5
	SD	498.30	537.19	515.47
	Median	1184.0	1175.0	1181.0
	Min, Max	7, 1708	5, 1780	5, 1780
Whole study period	PDC (%)			
	n	145	122	267
	Mean	80.4784	78.4178	79.5368
	SD	30.30124	33.17959	31.60519
	Median	98.1663	99.9080	98.2869
	Min, Max	0.508, 100.000	0.361, 100.000	0.361, 100.000
	PDC (%)			
	n	145	122	267
	<80%#	42 (29.0)	35 (28.7)	77 (28.8)
	≥80%#	103 (71.0)	87 (71.3)	190 (71.2)

- SOURCE: Table 14.1-6.1.
- SD = Standard Deviation. PDC = Proportion of days covered.
- 1st Year period = From the date of the first dose of index study medication to (the date of the first dose of index study medication + 364 days).
- Nth Year period = From (the end date of N-1 year period +1 day) to (the date of the first dose of index study medication + 365*N-1 days).
- PDC of Nth Year period: Given the target date = min (cut-off date, the date of completing the study or discontinuation from the study), if the date of first dose to the target date <N*365 days, then the PDC of Nth Year period = Proportion of days taking index medication divided by (the target date – start date of N year period +1). If the date of first dose to the target date > N*365 days, then the PDC of Nth Year period = Proportion of days taking index medication divided by 365 days.
- Whole study period = From the date of the first dose of index study medication to the date of completing the study or discontinuation from the study or to the date of cut-off date for those patients who still remain on the treatment.
- Patients who switched drug during the period or who discontinued the index treatment are excluded.
- # The percentages are based on the number of subjects for each period (n).

10.5.3. Clinical and Patient-reported Outcomes Following Tofacitinib or TNFi Dose Reduction or Weaning Off

10.5.3.1. HAQ-DI Score

The change of HAQ-DI score after dose reduction of tofacitinib and TNFi is shown in Table 19.

Twenty-four tofacitinib users and 16 TNFi users underwent a dose reduction or weaning off.

The mean (SD) HAQ-DI score at the time of dose reduction was 0.5938 (0.70927) for tofacitinib users, and 0.7188 (0.88682) for TNFi users.

An increase of functional disability index as assessed by the HAQ-DI was seen for 6 and 9 of the 24 tofacitinib users 4 and 12 weeks after tapering, respectively. In the TNFi group, 5 and 6 patients had an increase of functional disability index 4 and 12 weeks after tapering, respectively.

Table 19. HAQ-DI Score, Summary Statistics over Time-Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Dose Down Baseline	HAQ-DI Score	n	24	16	40
		Mean	0.5938	0.7188	0.6438
		SD	0.70927	0.88682	0.77653
		Median	0.4375	0.3750	0.3750
		Min, Max	0.000, 2.250	0.000, 2.750	0.000, 2.750
Week 4 Post Treatment	HAQ-DI Score	n	22	13	35
		Mean	0.5966	0.7308	0.6464
		SD	0.78578	0.73571	0.75943
		Median	0.2500	0.5000	0.3750
		Min, Max	0.000, 2.375	0.000, 2.250	0.000, 2.375
	Increased from Baseline	n (%)*	6 (4.5)	5 (4.6)	11 (4.5)
	Not Increased from Baseline	n (%)*	16 (11.9)	8 (7.4)	24 (9.9)
	Change from Baseline (Week 4 Post Treatment-Baseline)	n	22	13	35
		Mean	0.0625	-0.0673	0.0143
		SD	0.26656	0.51945	0.37838
		Median	0.0000	0.0000	0.0000
		Min, Max	-0.375, 0.750	-1.375, 0.875	-1.375, 0.875

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Week 12 Post Treatment	HAQ-DI Score	n	22	13	35
		Mean	0.7216	0.7981	0.7500
		SD	0.92737	0.78152	0.86496
		Median	0.2500	0.5000	0.3750
		Min, Max	0.000, 2.625	0.000, 2.125	0.000, 2.625
	Increased from Baseline	n (%)*	9 (6.7)	6 (5.6)	15 (6.2)
	Not Increased from Baseline	n (%)*	13 (9.7)	7 (6.5)	20 (8.3)
	Change from Baseline (Week 12 Post Treatment-Baseline)	n	22	13	35
		Mean	0.1080	0.0000	0.0679
		SD	0.30690	0.57054	0.41936
		Median	0.0000	0.0000	0.0000
		Min, Max	-0.500, 0.875	-1.125, 1.000	-1.125, 1.000

- SOURCE: Table 14.2-1.1.2.
- SD = Standard Deviation.
- * Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.5.3.2. CDAI Score

The effect of dose reduction on the CDAI score was evaluated during the study as shown in Table 20.

In the tofacitinib group, according to the CDAI score before the time of dose reduction, 18 patients (13.4%) had low disease activity, 5 patients (3.7%) moderate disease activity and 1 patient (0.7%) had high disease activity. Of the 24 patients with dose reduction, 22 were assessed 4 weeks and 12 weeks after tapering. Two patients presented a CDAI deterioration 4 weeks and 2 patients 12 weeks after dose reduction.

In the TNFi group, according to the CDAI score at the time of dose reduction, 9 patients had low disease activity, 4 patients moderate disease activity and 3 patients had high disease activity. Of the 16 patients with dose reduction, 13 were assessed 4 weeks and 12 weeks after tapering. Three patients presented a CDAI deterioration 4 weeks after dose reduction, and one patient 12 weeks after dose reduction.

Four weeks after the dose reduction, the mean change of CDAI was 1.75 (3.621) for 22 tofacitinib users and 1.18 (6.099) for 13 TNFi users. Twelve weeks after the dose reduction, the mean change of CDAI was 1.90 (3.138) for tofacitinib users and -0.12 (5.687) for TNFi users.

Table 20. CDAI Score, Summary Statistics over Time- Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Dose Down Baseline	CDAI >22 (High Disease Activity)	n (%)*	1 (0.7)	3 (2.8)	4 (1.7)
	10< CDAI ≤22(Moderate Disease Activity)	n (%)*	5 (3.7)	4 (3.7)	9 (3.7)
	CDAI ≤10 (Low Disease Activity)	n (%)*	18 (13.4)	9 (8.3)	27 (11.2)
Week 4 Post Treatment	CDAI Score	n	22	13	35
		Mean	8.58	12.00	9.85
		SD	5.785	6.955	6.368
		Median	7.50	10.00	9.40
		Min, Max	2.0, 19.0	3.0, 26.0	2.0, 26.0
	CDAI ≤2.8	n (%)*	5 (3.7)	0	5 (2.1)
	CDAI >2.8	n (%)*	17 (12.7)	13 (12.0)	30 (12.4)
	CDAI ≤10	n (%)*	14 (10.4)	7 (6.5)	21 (8.7)
	CDAI >10	n (%)*	8 (6.0)	6 (5.6)	14 (5.8)
	Change from Baseline (Week 4 Post Treatment-Baseline)	n	22	13	35
		Mean	1.75	1.18	1.54
		SD	3.621	6.099	4.616
		Median	1.00	3.20	2.00
		Min, Max	-4.0, 7.7	-8.8, 8.0	-8.8, 8.0
	CDAI Significant Improvement (-6.5 points)	n (%)*	0	2 (1.9)	2 (0.8)
	CDAI Significant Deterioration (+6.5 points)	n (%)*	2 (1.5)	3 (2.8)	5 (2.1)
	MCID Improvement (Week 4 Post Treatment-Baseline)				
	-12 points (Patients CDAI starting in >22)	n (%)^	0	0	0
	-6 points (Patients CDAI starting in 10< CDAI ≤22)	n (%)^	0	1 (25.0)	1 (11.1)
	-1 points (Patients CDAI starting in ≤10)	n (%)^	4 (22.2)	0	4 (14.8)
Week 12 Post Treatment	CDAI Score	n	22	13	35
		Mean	10.44	10.70	10.53
		SD	8.526	6.126	7.626
		Median	9.50	11.00	10.00
		Min, Max	1.0, 40.0	3.0, 24.0	1.0, 40.0

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	CDAI ≤2.8	n (%)*	3 (2.2)	0	3 (1.2)
	CDAI >2.8	n (%)*	19 (14.2)	13 (12.0)	32 (13.2)
	CDAI ≤10	n (%)*	12 (9.0)	6 (5.6)	18 (7.4)
	CDAI >10	n (%)*	10 (7.5)	7 (6.5)	17 (7.0)
	Change from Baseline (Week 12 Post Treatment-Baseline)	n	22	13	35
		Mean	1.90	-0.12	1.15
		SD	3.138	5.687	4.299
		Median	1.00	2.00	1.00
		Min, Max	-3.0, 9.0	-13.0, 8.0	-13.0, 9.0
	CDAI Significant Improvement (-6.5 points)	n (%)*	0	2 (1.9)	2 (0.8)
	CDAI Significant Deterioration (+6.5 points)	n (%)*	2 (1.5)	1 (0.9)	3 (1.2)
	MCID Improvement (Week 12 Post Treatment-Baseline)				
	-12 points (Patients CDAI starting in >22)	n (%)^	0	1 (33.3)	1 (25.0)
	-6 points (Patients CDAI starting in 10< CDAI ≤22)	n (%)^	0	0	0
	-1 points (Patients CDAI starting in ≤10)	n (%)^	1 (5.6)	2 (22.2)	3 (11.1)

- SOURCE: Table 14.2-1.3.2
  SD = Standard Deviation; MCID = Minimally Clinically Important Differences.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- # Percentages are based on the number of patients per time point.
- ^ Percentages of MCID improvement are based on the number of each CDAI starting point groups (high, moderate, and low disease activity at baseline).
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.5.3.3. DAS28-ESR

The DAS28-ESR score after dose reduction is shown in Table 21.

In the tofacitinib group, according to the DAS28-ESR score before the time of dose reduction, 18 patients (13.4%) had a DAS28-ESR score <3.2, of which 14 (10.4%) were in remission (score <2.6). Of the 24 patients with dose reduction, 21 were assessed 4 weeks after tapering, and 22 12 weeks after tapering. Four weeks and 12 weeks after tapering, an increase of the mean DAS28-ESR score (by 0.60 and 0.55 points, respectively) and of the number of patients with DAS28-ESR score ≥3.2 was observed (6 patients before dose reduction, 8 at Week 4, and 11 patients at Week 12).

In the TNFi group, according to the CDAI score before the time of dose reduction, 10 patients (9.3%) had a DAS28-ESR score <3.2, of which 6 (5.6%) were in remission (score <2.6). Of the 16 patients with dose reduction, 13 were assessed 4 weeks and 12 were assessed 12 weeks after tapering. Four weeks and 12 weeks after tapering, an increase of the mean DAS28-ESR score (by 0.40 and 0.27 points, respectively) and of the number of patients with DAS28-ESR score ≥3.2 was observed (6 patients before dose reduction, 7 at Week 4, and 8 patients at Week 12).

Table 21. DAS28-ESR Score, Summary Statistics over Time-Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Dose Down Baseline	DAS28-ESR Results	n	24	16	40
		Mean	2.6204	3.0811	2.8047
		SD	1.28244	1.29747	1.29214
		Median	2.5360	2.9200	2.7005
		Min, Max	0.970, 5.630	0.555, 5.477	0.555, 5.630
	DAS28-ESR <2.6	n (%)*	14 (10.4)	6 (5.6)	20 (8.3)
	DAS28-ESR ≥2.6	n (%)*	10 (7.5)	10 (9.3)	20 (8.3)
	DAS28-ESR <3.2	n (%)*	18 (13.4)	10 (9.3)	28 (11.6)
	DAS28-ESR ≥3.2	n (%)*	6 (4.5)	6 (5.6)	12 (5.0)
Week 4 Post Treatment	DAS28-ESR Results	n	21	13	34
		Mean	2.9157	3.4547	3.1218
		SD	1.13761	1.06590	1.12613
		Median	2.8940	3.3840	3.0850
		Min, Max	1.127, 4.888	1.337, 5.002	1.127, 5.002
	DAS28-ESR <2.6	n (%)*	9 (6.7)	2 (1.9)	11 (4.5)
	DAS28-ESR ≥2.6	n (%)*	12 (9.0)	11 (10.2)	23 (9.5)
	DAS28-ESR <3.2	n (%)*	13 (9.7)	6 (5.6)	19 (7.9)
	DAS28-ESR ≥3.2	n (%)*	8 (6.0)	7 (6.5)	15 (6.2)
	Change from Baseline (Week 4 Post Treatment-Baseline)	n	21	13	34
		Mean	0.6083	0.4016	0.5293
		SD	0.74449	0.97085	0.83009
		Median	0.5230	0.7510	0.5835
		Min, Max	-1.215, 1.748	-1.894, 1.622	-1.894, 1.748
Week 12 Post Treatment	DAS28-ESR Results	n	22	12	34
		Mean	3.1559	3.3679	3.2307
		SD	1.35645	1.09483	1.25738
		Median	3.1815	3.6460	3.3395
		Min, Max	1.127, 5.606	0.695, 5.023	0.695, 5.606
	DAS28-ESR <2.6	n (%)*	9 (6.7)	2 (1.9)	11 (4.5)
	DAS28-ESR ≥2.6	n (%)*	13 (9.7)	10 (9.3)	23 (9.5)

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
	DAS28-ESR <3.2	n (%)*	11 (8.2)	4 (3.7)	15 (6.2)
	DAS28-ESR ≥3.2	n (%)*	11 (8.2)	8 (7.4)	19 (7.9)
	Change from Baseline (Week 12 Post Treatment-Baseline)	n	22	12	34
		Mean	0.5514	0.2749	0.4538
		SD	0.66556	0.90745	0.75787
		Median	0.5765	0.2595	0.4310
		Min, Max	-0.579, 1.969	-1.289, 1.648	-1.289, 1.969

- SOURCE: Table 14.2-1.4.2.
- SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last non-missing value before the post-dose down visit.

10.5.3.4. WPAI-RA Score

The effect of dose reduction on WPAI-RA score is shown in Table 22.

Overall, 15 study patients were employed at the time of study experienced dose reduction, of these 8 patients (6.0%) were from tofacitinib group and 7 patients (6.5%) were from TNFi group. Conversely, 25 patients (16 from the tofacitinib group and 9 from the TNFi group) who experienced dose reduction were not employed at the time of study.

Among the few patients in employment, mean changes in percent of work time missed, percent impairment while working, and percent overall work impairment deteriorated slightly, with absolute changes ranging from 2.86% to 7.71% in the tofacitinib group, and from -8.33% to 3.85% in the TNFi group at Week 4. At Week 12, the absolute changes of these 3 scores compared to the last assessment before dose reduction ranged between 0 and 2.50% for the tofacitinib group, and between 1.67% and 8.33% in the TNFi group, in the direction of a slight deterioration.

Percent activity impairment due to RA followed the same trend; the mean change in this score was +1.36% at Week 4 and +0.45% at Week 12 (both n=22) after dose reduction for the tofacitinib group and +3.85% at Week 4 and Week 12 in the TNFi group (both n=13).

Table 22. WPAI-RA Score, Summary Statistics over Time- Effectiveness Analysis Set

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: After Dose Down (including Dose Down Visit)					
Dose Down Baseline	Patient Currently Employed (Working for Pay)	Yes, n (%)*	8 (6.0)	7 (6.5)	15 (6.2)
		No, n (%)*	16 (11.9)	9 (8.3)	25 (10.3)
	Percent Work Time Missed Due to RA	n	8	7	15
		Mean	0.00	7.14	3.33
		SD	0.000	18.898	12.910
		Median	0.00	0.00	0.00
		Min, Max	0.0, 0.0	0.0, 50.0	0.0, 50.0
	Percent Impairment While Working Due to RA	n	8	7	15
		Mean	15.00	22.86	18.67
		SD	20.000	30.938	25.033
		Median	10.00	10.00	10.00
		Min, Max	0.0, 60.0	0.0, 80.0	0.0, 80.0
	Percent Overall Work Impairment Due to RA	n	8	7	15
		Mean	15.00	24.29	19.33
		SD	20.000	34.087	26.851
		Median	10.00	10.00	10.00
		Min, Max	0.0, 60.0	0.0, 90.0	0.0, 90.0
	Percent Activity Impairment Due to RA	n	24	16	40
		Mean	31.67	30.63	31.25
		SD	25.988	27.681	26.330
		Median	25.00	30.00	30.00
		Min, Max	0.0, 100.0	0.0, 90.0	0.0, 100.0
Week 4 Post Treatment	Patient Currently Employed (Working for Pay)	Yes, n (%)*	7 (5.2)	6 (5.6)	13 (5.4)
		No, n (%)*	15 (11.2)	7 (6.5)	22 (9.1)
	Percent Work Time Missed Due to RA	n	7	6	13
		Mean	2.86	0.00	1.54
		SD	7.559	0.000	5.547
		Median	0.00	0.00	0.00
		Min, Max	0.0, 20.0	0.0, 0.0	0.0, 20.0
	Percent Impairment While Working Due to RA	n	7	6	13

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: After Dose Down (including Dose Down Visit)					
		Mean	21.43	28.33	24.62
		SD	27.343	33.116	29.045
		Median	20.00	10.00	10.00
		Min, Max	0.0, 80.0	0.0, 80.0	0.0, 80.0
	Percent Overall Work Impairment Due to RA	n	7	6	13
		Mean	22.00	28.33	24.92
		SD	28.775	33.116	29.694
		Median	20.00	10.00	10.00
		Min, Max	0.0, 84.0	0.0, 80.0	0.0, 84.0
	Percent Activity Impairment Due to RA	n	22	13	35
		Mean	32.27	39.23	34.86
		SD	25.991	23.616	25.014
		Median	25.00	30.00	30.00
		Min, Max	0.0, 80.0	10.0, 80.0	0.0, 80.0
Change from Baseline (Week 4 Post Treatment-Baseline)	Percent Work Time Missed Due to RA	n	7	6	13
		Mean	2.86	-8.33	-2.31
		SD	7.559	20.412	15.359
		Median	0.00	0.00	0.00
		Min, Max	0.0, 20.0	-50.0, 0.0	-50.0, 20.0
	Percent Impairment While Working Due to RA	n	7	6	13
		Mean	7.14	1.67	4.62
		SD	11.127	7.528	9.674
		Median	10.00	0.00	0.00
		Min, Max	-10.0, 20.0	-10.0, 10.0	-10.0, 20.0
	Percent Overall Work Impairment Due to RA	n	7	6	13
		Mean	7.71	0.00	4.15
		SD	11.968	8.944	10.999
		Median	10.00	0.00	0.00
		Min, Max	-10.0, 24.0	-10.0, 10.0	-10.0, 24.0
	Percent Activity Impairment Due to RA	n	22	13	35
		Mean	1.36	3.85	2.29
		SD	13.903	11.209	12.853
		Median	0.00	10.00	0.00
		Min, Max	-30.0, 40.0	-10.0, 20.0	-30.0, 40.0

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: After Dose Down (including Dose Down Visit)					
Week 12 Post Treatment	Patient Currently Employed (Working for Pay)	Yes, n (%)*	8 (6.0)	6 (5.6)	14 (5.8)
		No, n (%)*	14 (10.4)	7 (6.5)	21 (8.7)
	Percent Work Time Missed Due to RA	n	8	6	14
		Mean	0.00	0.00	0.00
		SD	0.000	0.000	0.000
		Median	0.00	0.00	0.00
		Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0
	Percent Impairment While Working Due to RA	n	8	6	14
		Mean	17.50	30.00	22.86
		SD	26.592	34.059	29.464
		Median	10.00	15.00	10.00
		Min, Max	0.0, 80.0	0.0, 90.0	0.0, 90.0
	Percent Overall Work Impairment Due to RA	n	8	6	14
		Mean	17.50	30.00	22.86
		SD	26.592	34.059	29.464
		Median	10.00	15.00	10.00
		Min, Max	0.0, 80.0	0.0, 90.0	0.0, 90.0
	Percent Activity Impairment Due to RA	n	22	13	35
		Mean	33.18	39.23	35.43
		SD	23.174	25.318	23.806
		Median	30.00	30.00	30.00
		Min, Max	0.0, 80.0	0.0, 90.0	0.0, 90.0
Change from Baseline (Week 12 Post Treatment-Baseline)	Percent Work Time Missed Due to RA	n	8	6	14
		Mean	0.00	-8.33	-3.57
		SD	0.000	20.412	13.363
		Median	0.00	0.00	0.00
		Min, Max	0.0, 0.0	-50.0, 0.0	-50.0, 0.0
	Percent Impairment While Working Due to RA	n	8	6	14
		Mean	2.50	3.33	2.86
		SD	11.650	8.165	9.945
		Median	0.00	5.00	0.00
		Min, Max	-10.0, 20.0	-10.0, 10.0	-10.0, 20.0

Visit	Parameter	Statistics	Tofacitinib (N=134)	TNFi (N=108)	Total (N=242)
Visits: After Dose Down (including Dose Down Visit)					
	Percent Overall Work Impairment Due to RA	n	8	6	14
		Mean	2.50	1.67	2.14
		SD	11.650	7.528	9.750
		Median	0.00	0.00	0.00
		Min, Max	-10.0, 20.0	-10.0, 10.0	-10.0, 20.0
	Percent Activity Impairment Due to RA	n	22	13	35
		Mean	0.45	3.85	1.71
		SD	16.177	17.097	16.357
		Median	0.00	0.00	0.00
		Min, Max	-60.0, 20.0	-20.0, 40.0	-60.0, 40.0

- SOURCE: Table 14.2-1.2.2.
- SD = Standard Deviation.
- Percentages are based on the number of patients in Effectiveness Analysis Set.
- The baseline for dose down visits is the measurements at the dose down visit or the last visit with non-missing value of "Are you currently employed (working for pay)?" before the post-dose down visit.

10.6. Adverse Events/Adverse Reactions

10.6.1. All Adverse Events

Summary of all AEs of safety analysis set is shown in Table 23. Individual data are presented in Listing 16.2.7-1.1.

No AEs were reported for 63 tofacitinib patients (43.4%) and 54 TNFi patients (44.3%).

A total of 82 tofacitinib patients (56.6%) reported one or several AEs, and 24 patients (16.6%) reported AEs considered by the investigators as related to the use of tofacitinib. In the TNFi group, 68 patients (55.7%) presented any AE, and 11 patients (9.0%) had AEs considered by the investigators as related to use of a specific TNFi.

Targeted AEs (refer to Section 7) were observed in 36 patients (24.8%) in the tofacitinib group, with 16 patients (11.0%) having TAEs considered related by the investigators. In the TNFi group, 16 patients (13.1%) reported TAEs, with 4 patients (3.3%) having TAEs considered related.

In the tofacitinib group 29 patients (20.0%) experienced serious AEs (SAEs), with 13 patients (9.0%) having SAEs which were considered related to use of tofacitinib by the investigators. In the TNFi group, 26 patients (21.3%) experienced SAEs, with 3 (2.5%) having SAEs considered related.

In the tofacitinib and TNFi users, the incidence rates (IR) per 100 patient years were the following:

- Any AE: 12.9 per 100 patient years, and 14.0 per 100 patient years, respectively;
- Any TAE: 13.7 per 100 patient years, and 7.0 per 100 patient years, respectively.

Any SAE: 10.6 per 100 patient years, and 8.9 per 100 patient years, respectively

Table 23. Summary of All Adverse Events-Safety Analysis Set

Number of Patients Experiencing	Tofacitinib (N=145) n (%) IR	TNFi (N=122) n (%) IR
No Adverse Events	63 (43.4)	54 (44.3)
One or More Adverse Events (AEs)	82 (56.6) 12.9	68 (55.7) 14.0
Related	24 (16.6) 10.8	11 (9.0) 5.9
One or More Targeted Adverse Events (TAEs)	36 (24.8) 13.7	16 (13.1) 7.0
Related	16 (11.0) 7.4	4 (3.3) 2.2
One or More Serious Adverse Events (SAEs)	29 (20.0) 10.6	26 (21.3) 8.9
Related	13 (9.0) 6.0	3 (2.5) 1.7

- SOURCE: Table 14.3.1-1.1.
- IR = Incidence Rate (per 100 patient years).
- Incidence rate (per 100 patient years) = (100*Number of patients with AE) / [Sum of time at risk (days)of all patients in treatment group/365.25].
- Patients with partial or missing first AE start date are not contributed to the incidence rate.
- Percentage is (n divided by N)*100.
- If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event To calculate IR, the first AE start date was used for calculation if the same AE occurred more than once in a patient.
- Targeted adverse events are listed in SAP Section 18.1.3.

10.6.1.1. All Adverse Events by System Organ Class and Preferred Term

All AEs are presented in Table 24 by system organ class (SOC) and preferred term (PT).

The majority of AEs were of mild or moderate severity. Of the 267 study patients, 150 patients (56.2%) reported at least one AE. In the tofacitinib group, 82 patients (56.6%) reported at least one AE, of which 23 patients (15.9%) had mild AEs, 17 patients (11.7%) had moderate AEs and 3 patients (2.1%) had severe AEs. In the TNFi group, 68 patients (55.7%) reported at least one AE, of which 22 (18.0%) had mild AEs, 12 patients (9.8%) had moderate AEs and 7 patients (5.7%) had severe AEs.

Adverse events presented by > 5% of total study patients are shown in Table 24.

The SOCs for the AEs assessed as severe included: Gastrointestinal disorders, reported by 2 TNFi patients (1.6%), Infections and infestations, reported by 3 tofacitinib patients (2.1%) and 2 TNFi patients (1.6%), Nervous system disorders, reported by 1 patient each from the tofacitinib and TNFi groups, and Respiratory, thoracic and mediastinal disorders, reported by 1 patient (0.7%) in the tofacitinib group.

Table 24 All Adverse Events by System Organ Class and Preferred Term-Whole study period-Safety Analysis Set

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
System Organ Class Preferred Term	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Subjects with At Least One AE	23 (15.9)	17 (11.7)	3 (2.1)	39 (26.9)	82 (56.6)	22 (18.0)	12 (9.8)	7 (5.7)	27 (22.1)	68 (55.7)	150 (56.2)
Gastrointestinal disorders	4 (2.8)	1 (0.7)	0	16 (11.0)	21 (14.5)	2 (1.6)	1 (0.8)	2 (1.6)	4 (3.3)	9 (7.4)	30 (11.2)
General disorders and administration site conditions	2 (1.4)	2 (1.4)	0	8 (5.5)	12 (8.3)	0	3 (2.5)	0	5 (4.1)	8 (6.6)	20 (7.5)
Infections and infestations	11 (7.6)	7 (4.8)	3 (2.1)	31 (21.4)	52 (35.9)	13 (10.7)	4 (3.3)	2 (1.6)	18 (14.8)	37 (30.3)	89 (33.3)
Herpes zoster	3 (2.1)	2 (1.4)	0	13 (9.0)	18 (12.4)	1 (0.8)	0	0	3 (2.5)	4 (3.3)	22 (8.2)
Upper respiratory tract infection	5 (3.4)	1 (0.7)	0	1 (0.7)	7 (4.8)	5 (4.1)	0	0	5 (4.1)	10 (8.2)	17 (6.4)

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
System Organ Class Preferred Term	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Injury, poisoning and procedural complications	1 (0.7)	1 (0.7)	0	9 (6.2)	11 (7.6)	2 (1.6)	1 (0.8)	0	5 (4.1)	8 (6.6)	19 (7.1)
Investigations	6 (4.1)	1 (0.7)	0	3 (2.1)	10 (6.9)	3 (2.5)	0	0	4 (3.3)	7 (5.7)	17 (6.4)
Musculoskeletal and connective tissue disorders	2 (1.4)	3 (2.1)	0	18 (12.4)	23 (15.9)	2 (1.6)	2 (1.6)	0	11 (9.0)	15 (12.3)	38 (14.2)
Nervous system disorders	0	2 (1.4)	1 (0.7)	11 (7.6)	14 (9.7)	4 (3.3)	0	1 (0.8)	6 (4.9)	11 (9.0)	25 (9.4)
Respiratory, thoracic and mediastinal disorders	3 (2.1)	1 (0.7)	1 (0.7)	19 (13.1)	24 (16.6)	2 (1.6)	2 (1.6)	0	8 (6.6)	12 (9.8)	36 (13.5)
Skin and subcutaneous tissue disorders	3 (2.1)	0	0	6 (4.1)	9 (6.2)	3 (2.5)	2 (1.6)	0	7 (5.7)	12 (9.8)	21 (7.9)

- SOURCE: Table 14.3.1-2.1.4 “unknown” column added to Table 24.
- Adverse events were coded to system organ class and preferred term using the MedDRA Version 24.0 coding dictionary.
- Percentage is (n divided by N)*100.
- For subjects with the same AEs occurred more than once, only one is counted for each SOC and PT.
- In cases where a subject had events with missing and non-missing severities, the maximum of the non-missing severities is displayed.
- * The total subject number of each SOC and PT includes both missing and non-missing severities.

10.6.1.2. Serious Adverse Events

SAEs presented by ≥2 patients are displayed by SOC and PT in

Table 25. Individual data are presented in Listing 16.2.7-1.2.

A total of 55 study patients (20.6%) presented SAEs, of which 29 patients (20.0%) were tofacitinib users and 26 patients (21.3%) were TNFi users. Most of these patients [n=31 (11.6%)] presented SAEs contained in the Infections and infestations SOC, followed by Musculoskeletal and connective tissue disorders [9 (3.4%)], Respiratory, thoracic and mediastinal disorders [7 (2.6%)], Nervous system disorders [6 (2.2%)] and General disorders and administration site conditions [5 (1.9%)].

Pneumonia (n=5, 1.9%), herpes zoster and urinary tract infection (n=4,1.5%) each, were the most frequent SAEs in the study population.

Table 25. Serious Adverse Events by System Organ Class and Preferred Term-Safety Analysis Set

	Tofacitinib (N=145) n (%)					**TNFi (N=122) n (%)**					**Overall (N=267) n (%)**
System Organ Class **Preferred Term**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Subjects with At Least One SAE	1 (0.7)	10 (6.9)	3 (2.1)	15 (10.3)	29 (20.0)	3 (2.5)	8 (6.6)	7 (5.7)	8 (6.6)	26 (21.3)	55 (20.6)
Gastrointestinal disorders	0	0	0	0	0	0	0	2 (1.6)	0	2 (1.6)	2 (0.7)
General disorders and administration site conditions	1 (0.7)	2 (1.4)	0	0	3 (2.1)	0	1 (0.8)	0	1 (0.8)	2 (1.6)	5 (1.9)
Condition aggravated	0	1 (0.7)	0	0	1 (0.7)	0	1 (0.8)	0	0	1 (0.8)	2 (0.7)
Pyrexia	1 (0.7)	0	0	0	1 (0.7)	0	0	0	0	1 (0.8)	2 (0.7)
Infections and infestations	0	5 (3.4)	3 (2.1)	12 (8.3)	20 (13.8)	2 (1.6)	4 (3.3)	2 (1.6)	3 (2.5)	11 (9.0)	31 (11.6)

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
System Organ Class **Preferred Term**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Pneumonia	0	1 (0.7)	0	2 (1.4)	3 (2.1)	0	1 (0.8)	0	1 (0.8)	2 (1.6)	5 (1.9)
Herpes zoster	0	1 (0.7)	0	3 (2.1)	4 (2.8)	0	0	0	0	0	4 (1.5)
Urinary tract infection	1 (0.7)	0	1 (0.7)	0	2 (1.4)	0	1 (0.8)	0	1 (0.8)	2 (1.6)	4 (1.5)
Arthritis bacterial	0	2 (1.4)	0	0	2 (1.4)	0	0	0	1 (0.8)	1 (0.8)	3 (1.1)
Pyelonephritis acute	0	0	0	2 (1.4)	2 (1.4)	1 (0.8)	0	0	0	1 (0.8)	3 (1.1)
Septic shock	0	0	0	2 (1.4)	2 (1.4)	0	0	1 (0.8)	0	1 (0.8)	3 (1.1)
Cellulitis	0	0	0	0	0	0	2 (1.6)	0	0	2 (1.6)	2 (0.7)
Otitis media	1 (0.7)	0	0	1 (0.7)	2 (1.4)	0	0	0	0	0	2 (0.7)
Injury, poisoning and procedural complications	0	1 (0.7)	0	0	1 (0.7)	0	0	0	1 (0.8)	1 (0.8)	2 (0.7)
Metabolism and nutrition disorders	0	0	1 (0.7)	0	1 (0.7)	0	0	0	1 (0.8)	1 (0.8)	2 (0.7)
Musculoskeletal and connective tissue disorders	0	2 (1.4)	0	3 (2.1)	5 (3.4)	0	2 (1.6)	0	2 (1.6)	4 (3.3)	9 (3.4)
Osteoarthritis	0	1 (0.7)	0	1 (0.7)	2 (1.4)	0	0	0	1 (0.8)	1 (0.8)	3 (1.1)
Rotator cuff syndrome	0	0	0	1 (0.7)	1 (0.7)	0	2 (1.6)	0	0	2 (1.6)	3 (1.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	1 (0.7)	2 (1.4)	3 (2.1)	0	0	1 (0.8)	0	1 (0.8)	4 (1.5)
Nervous system disorders	0	2 (1.4)	1 (0.7)	0	3 (2.1)	1 (0.8)	0	1 (0.8)	1 (0.8)	3 (2.5)	6 (2.2)
Renal and urinary disorders	0	0	1 (0.7)	1 (0.7)	2 (1.4)	0	1 (0.8)	0	0	1 (0.8)	3 (1.1)
Acute kidney injury	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.8)	0	0	1 (0.8)	2 (0.7)

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
System Organ Class **Preferred Term**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Respiratory, thoracic and mediastinal disorders	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.4)	5 (3.4)	0	2 (1.6)	0	0	2 (1.6)	7 (2.6)
Pulmonary oedema	0	0	0	1 (0.7)	1 (0.7)	0	1 (0.8)	0	0	1 (0.8)	2 (0.7)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.7)	1 (0.7)	0	1 (0.8)	0	1 (0.8)	2 (1.6)	3 (1.1)

- SOURCE: Table 14.3.1-3.1 "unknown" column was added for Table 25.
- SAE = Serious Adverse Events.
- Adverse events were coded to system organ class and preferred term, using the MedDRA Version 24.0 coding dictionary.
- Percentage is (n divided by N)*100.
- For subjects with the same AEs occurred more than once, only one is counted for each SOC and PT.
- In cases where a subject had events with missing and non-missing severities, the maximum of the non-missing severities is displayed.
- * The total subject number of each SOC and PT includes both missing and non-missing severities.

10.6.1.3. Targeted Adverse Events

TAEs by safety analysis set are presented in Table 26. Individual data are presented in Listing 16.2.7-1.3.

A total of 52 study patients (19.5%) reported at least one TAE, of which 36 patients (24.8%) were tofacitinib users and 16 patients (13.1%) were TNFi users.

In the tofacitinib group, 5 patients (3.4%) reported mild TAEs, 7 patients (4.8%) reported moderate TAEs, and 2 patients (1.4%) reported severe TAEs. In the TNFi group, 2 patients (1.6%) each reported mild and moderate TAEs, while 5 patients (4.1%) reported severe TAEs.

In the tofacitinib group, in the TAE category infection the TAE subcategory for severe TAEs were serious infection by 2 patients (1.4%), opportunistic infection and septicemia presented by 1 patient (0.7%) each. In the TAE category tumor/malignancy was one event with the TAE subcategory other cancer reported by 1 patient (0.7%).

In the TNFi group for the TAE category Infection the TAE subcategory for severe TAEs were serious infection for 2 patients (1.4%), septicemia and hepatitis B reactivation reported for 1 patient (0.8%) each. In addition, 1 patient (0.8%) presented liver enzyme abnormality. In the TAE category major adverse cardiovascular event (MACE), nonfatal events of myocardial infarction (MI) were reported for 1 patient (0.8%). In the tumor/malignancy category one severe event of other cancer was reported for one patient (0.8%).

Table 26 Targeted Adverse Events-Safety Analysis Set

	Tofacitinib (N=145) n (%)					**TNFi (N=122) n (%)**					**Overall (N=267) n (%)**
TAE Category **TAE Subcategory**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Subjects with At Least One TAE	5 (3.4)	7 (4.8)	2 (1.4)	22 (15.2)	36 (24.8)	2 (1.6)	2 (1.6)	5 (4.1)	7 (5.7)	16 (13.1)	52 (19.5)
Infection	5 (3.4)	6 (4.1)	2 (1.4)	20 (13.8)	33 (22.8)	2 (1.6)	2 (1.6)	2 (1.6)	6 (4.9)	12 (9.8)	45 (16.9)
Herpes Zoster Infection	3 (2.1)	2 (1.4)	0	13 (9.0)	18 (12.4)	1 (0.8)	0	0	2 (1.6)	3 (2.5)	21 (7.9)
Other serious infection	1 (0.7)	3 (2.1)	0	7 (4.8)	11 (7.6)	1 (0.8)	1 (0.8)	0	2 (1.6)	4 (3.3)	15 (5.6)
Pneumonia	1 (0.7)	2 (1.4)	0	3 (2.1)	6 (4.1)	0	2 (1.6)	0	4 (3.3)	6 (4.9)	12 (4.5)
Bone Joint infection	0	1 (0.7)	0	2 (1.4)	3 (2.1)	0	0	0	1 (0.8)	1 (0.8)	4 (1.5)
Cellulitis	0	0	0	1 (0.7)	1 (0.7)	0	0	0	3 (2.5)	3 (2.5)	4 (1.5)
Bronchitis	1 (0.7)	1 (0.7)	0	0	2 (1.4)	0	0	0	0	0	2 (0.7)
Opportunistic infection	0	0	1 (0.7)	0	1 (0.7)	0	0	0	1 (0.8)	1 (0.8)	2 (0.7)
Septicemia	0	0	1 (0.7)	0	1 (0.7)	0	0	1 (0.8)	0	1 (0.8)	2 (0.7)
Gastroenteritis	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	1 (0.4)
Hepatitis B reactivation	0	0	0	0	0	0	0	1 (0.8)	0	1 (0.8)	1 (0.4)
Serious Infection (hospitalization/parenteral antibiotics)	0	5 (3.4)	2 (1.4)	12 (8.3)	19 (13.1)	1 (0.8)	2 (1.6)	2 (1.6)	5 (4.1)	10 (8.2)	29 (10.9)

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
TAE Category **TAE Subcategory**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Liver enzyme abnormality	0	1 (0.7)	0	1 (0.7)	2 (1.4)	1 (0.8)	0	1 (0.8)	1 (0.8)	3 (2.5)	5 (1.9)
MACE	0	0	0	0	0	0	0	1 (0.8)	0	1 (0.8)	1 (0.4)
Nonfatal events of myocardial infarction (MI)	0	0	0	0	0	0	0	1 (0.8)	0	1 (0.8)	1 (0.4)
Tumor/Malignancy	0	0	1 (0.7)	2 (1.4)	3 (2.1)	0	0	1 (0.8)	0	1 (0.8)	4 (1.5)
Other cancer	0	0	1 (0.7)	1 (0.7)	2 (1.4)	0	0	1 (0.8)	0	1 (0.8)	3 (1.1)
Breast cancer	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	1 (0.4)

- SOURCE: Table 14.3.1-4.1
  TAE = Targeted Adverse Events.
- Percentage is (n divided by N)*100.
- For subjects with the same AEs occurred more than once, only one is counted for each SOC and PT.
- In cases where a subject had events with missing and non-missing severities, the maximum of the non-missing severities is displayed.
- * The total subject number of each SOC and PT includes both missing and non-missing severities.

10.6.1.4. Related Targeted Adverse Events

The targeted AEs related to the treatment are shown in Table 27.

A total of 20 study patients (7.5%) presented with at least one related TAE, of which 16 patients (11.0%) were tofacitinib users and 4 patients (3.3%) were TNFi users. None of the related AEs were assessed as severe.

In the tofacitinib in the TAEs category infection related events were reported for the TAE subcategory serious infection for 12 patients (8.3%), herpes zoster infection for 8 patients (5.5%), other serious infection for 4 patients (2.8%), pneumonia for 3 patients (2.1%),

bone joint infection for 1 patient (0.7%), and gastroenteritis for 1 patient (0.7%). In the TAE category tumor/malignancy were 2 events reported for 1 patient (0.7%) in the TAE subcategory other cancer.

In the TNFi group in the TAEs category infection, related events were reported for the TAE subcategory serious infections for 3 patients (2.5%), pneumonia for 2 patients (1.8%), herpes zoster infection, other serious infection, bone joint infection, cellulitis and opportunistic infection for 1 patient (0.8%) in each TAE subcategory.

Table 27. Related Targeted Adverse Events-Safety Analysis Set

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
TAE Category TAE Subcategory	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**
Subjects with At Least One Related TAE	2 (1.4)	3 (2.1)	0	11 (7.6)	16 (11.0)	1 (0.8)	1 (0.8)	0	2 (1.6)	4 (3.3)	20 (7.5)
Infection	2 (1.4)	3 (2.1)	0	11 (7.6)	16 (11.0)	1 (0.8)	1 (0.8)	0	2 (1.6)	4 (3.3)	20 (7.5)
Herpes Zoster Infection	2 (1.4)	2 (1.4)	0	4 (2.8)	8 (5.5)	1 (0.8)	0	0	0	1 (0.8)	9 (3.4)
Other serious infection	0	0	0	4 (2.8)	4 (2.8)	0	0	0	1 (0.8)	1 (0.8)	5 (1.9)
Pneumonia	0	1 (0.7)	0	2 (1.4)	3 (2.1)	0	1 (0.8)	0	1 (0.8)	2 (1.6)	5 (1.9)
Bone Joint infection	0	0	0	1 (0.7)	1 (0.7)	0	0	0	1 (0.8)	1 (0.8)	2 (0.7)
Cellulitis	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.8)	1 (0.4)
Gastroenteritis	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	1 (0.4)
Opportunistic infection	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.8)	1 (0.4)
Serious Infection (hospitalization/parenteral antibiotics)	0	2 (1.4)	0	10 (6.9)	12 (8.3)	0	1 (0.8)	0	2 (1.6)	3 (2.5)	15 (5.6)
Tumor/Malignancy	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	1 (0.4)
Other cancer	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	1 (0.4)

	Tofacitinib (N=145) n (%)					TNFi (N=122) n (%)					Overall (N=267) n (%)
TAE Category **TAE Subcategory**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Mild**	**Moderate**	**Severe**	**Unknown**	**Total***	**Total**

- SOURCE: Table 14.3.1-4.2.
- TAE = Targeted Adverse Events.
- Percentage is (n divided by N)*100.
- For subjects with the same AEs occurred more than once, only one is counted for each SOC and PT.
- In cases where a subject had events with missing and non-missing severities, the maximum of the non-missing severities is displayed.
- * The total subject number of each SOC and PT includes both missing and non-missing severities.

11. DISCUSSION

11.1. Key Results and Interpretation

From 2016 to 2021, Pfizer conducted a prospective cohort study for tofacitinib users and TNFi users with RA from 7 sites in Taiwan. The study enrolled initiators of tofacitinib or TNFi treatment over the course of 24 months and followed for at least 36 months after enrolment. Data was collected at baseline and at six-month intervals thereafter, even if patient switched therapy according to routine clinical practice. Among the 267 eligible patients (FAS), 145 were tofacitinib initiators and 122 were TNFi initiators. The mean age of the study population was 55.3 years and 84.3% were female. The mean weight was 59.0 kg and 2.6% were current smokers. These characteristics were similar for tofacitinib users and TNFi users. An earlier study describing RA patients using Taiwan NHI Research Database showed that the mean age at RA diagnosis was 53.7 years, and 77.7% were women.[29] In our study, tofacitinib users had longer RA history (mean years since RA diagnosis: 8.0 years) versus TNFi users (5.4 years). This difference in RA history is consistent with Taiwan's NHI reimbursement policies, in that RA patients who demonstrate a poor response to a biologic treatment should switch to another biologics with an alternative mode of action or to tofacitinib.[27] Thus, when patients started with tofacitinib treatment, they had a longer RA history and were more likely to be later in their treatment course.

There were 29.6% tofacitinib initiators with prior exposure to TNFi, whereas most patients in the TNFi group (98.4%) have never taken any other TNFi treatment before. Similarly, 34.5% tofacitinib initiators priorly used bDMARDs while that proportion for TNFi group was only 4.9%. The most common prior bDMARDs were the TNFi treatments adalimumab and etanercept. All tofacitinib users (100%) and almost all TNFi users (99.2%) had used cDMARDs previously, which is consistent with the NHI policies, in that RA patients must have failed two cDMARDs to be considered for reimbursement of bDMARDs and targeted synthetic DMARDs (including tofacitinib).[27] Regarding the most common cDMARDs, for both groups, around 90% users had been prescribed methotrexate and around 80% users had been prescribed hydroxychloroquine. NSAIDs were taken by more than 80% of patients in both groups, and steroid by more than 70% in both groups. In 2019, a study in Taiwan showed that NSAIDs were the most frequently used drugs for RA from 2003 to 2010, followed by cDMARDs, for which the utilization doubled during the same time period, and then followed by steroids for which the prescription also doubled during that time.[30] These previous findings are consistent with the current study in that NSAIDs and steroids were broadly prescribed to RA patients in Taiwan.

The most frequently reported baseline medical comorbidities included hypertension (24.3%), hyperlipidemia (14.6%), diabetes (11.6%), and hepatitis B (10.5%). Prevalence of other baseline conditions was less than 10%. Hyperlipidemia was more prevalent in tofacitinib users, while TNFi users were more likely to have baseline hypertension and diabetes. Previous studies have reported that RA patients were more likely to have these comorbidities (hypertension, hyperlipidemia, diabetes, and hepatitis B).[31,32] Baseline rheumatoid factor was similar between the groups with 67.9% tofacitinib users and 69.7% TNFi users having

positive rheumatoid factor. This result was consistent with the clinical consensus that around 70% RA patients were seropositive.[33]

In the current study, the baseline CDAI score, and relevant joint counts implied slightly more severe RA conditions for TNFi users. According to baseline CDAI, more TNFi users had high disease activity (73.0%) than tofacitinib users (60.7%). The mean number of tender joints was 13.5 for TNFi users versus 11.1 for tofacitinib users; and the mean number of swollen joints was 7.1 for TNFi users versus 5.8 for tofacitinib users. However, the baseline HAQ-DI score and DAS28-ESR score were similar between the groups. The mean HAQ-DI was 0.99 for tofacitinib users and 0.95 for TNFi users. The proportion of patients with DAS28-ESR score ≥3.2 was 94.5% for tofacitinib users and 96.7% for TNFi users. The 2 groups presented no significant difference in terms of WPAI-RA components. Overall, the disease activity of the study population was not mild and was consistent with the indication of tofacitinib, which is the treatment to moderate or severe RA.

During the follow-up, cDMARDs was used concomitantly for most patients. There were 71.7% tofacitinib users taking methotrexate concomitantly and the proportion was slightly higher, at 77.9% among TNFi users. Hydroxychloroquine and sulfasalazine had also higher proportion of users in TNFi group than in tofacitinib group, although the differences in terms of proportion of users were 8% and 4%, respectively. Other frequently used concomitant medications included celecoxib and prednisolone, which were taken by more than half of the study population. The somewhat different proportions in concomitant medications between tofacitinib users and TNFi users may add to the difficulty in comparing their effectiveness.

For short-term effectiveness, only 53 tofacitinib users (36.6%) and 55 TNFi users (45.1%) had HAQ-DI measured at Week 1, and 48 tofacitinib users (33.1%) and 51 TNFi users (41.8%) had their CDAI measured at the same time. Thus, about 40% of patients only were assessed at Week 1. Patients prescribed TNFi were bDMARd naïve, whereas 30% of tofacitinib patients were previously exposed to bDMARDs, this may have influenced the request by the caregiver HCP and the patient's willingness to have a visit and an assessment at Week 1 in routine practice. Bearing in mind this limitation and potential bias, there was no drastic difference between the 2 groups in the mean change of HAQ-DI since baseline, but TNFi users seemed to have a numerically larger proportion of improvement in HAQ-DI and CDAI (with no statistical testing). For HAQ-DI, the proportion of improvement was 83.6% for TNFi users and 75.5% for tofacitinib users, but the mean change from baseline was similar (-0.16 for TNFi users and -0.18 for tofacitinib users, while a reduction of ≥0.22 is usually used as MCID). For CDAI, the proportion of significant improvement was 55.1% for TNFi users and 46.8% for tofacitinib users. The mean change from baseline was -11.1 for TNFi users and -6.8 for tofacitinib users. These were crude comparisons and could be confounded by factors such as baseline characteristics. TNFi users had shorter history of RA and had more concomitant medications, which could also be confounders. Furthermore, as mentioned, patients in TNFi group might have more severe RA at baseline, and thus may be easier to get a larger extent of improvement.

Prior real-world studies have investigated the effectiveness of tofacitinib. The ORAL (Oral Rheumatoid Arthritis triaL) Strategy, a one-year randomized controlled trial of more than a thousand patients from 25 countries, showed no significant difference between tofacitinib monotherapy versus combination therapies (either adalimumab plus methotrexate or tofacitinib plus methotrexate), regarding the percentage of participants achieving the American College of Rheumatology response criteria for 50% improvement (ACR50) at Month 6.[34] The ORAL Standard trial also showed that among RA patients receiving background methotrexate, tofacitinib was numerically similar to adalimumab in efficacy, and the mean change of HAQ-DI at Month 3 was -0.55 for tofacitinib (5 mg) users and -0.49 for adalimumab users.[35] The ORAL Surveillance trial showed that the mean change of HAQ-DI from baseline was -0.50 for tofacitinib (0.5 mg) users and -0.46 for TNFi users at Month 6.[36] A prospective study based on the Swiss Clinical Quality Management in Rheumatoid Arthritis (SCQM-RA) cohort found no significant difference between tofacitinib and TNFi in reaching LDA at 12 months, measured by CDAI; and they found an approximately 50% increased risk of discontinuations due to ineffectiveness for TNFi compared with tofacitinib [hazard ratio: 1.59 (95% CI: 1.33, 1.89)].[37] A study in the United States (US) published in 2020 showed no difference between TNFi and non-TNFi (including tofacitinib) users in the effectiveness measured by CDAI and HAQ-DI scores.[38] A meta-analysis of 45 clinical trials evidenced similar efficacy between tofacitinib and bDMARDs,[39] so did a retrospective study conducted in Australia in 2020.[40]

The current study shows generally consistent evidence with the above-mentioned prior studies. In our study, the long-term effectiveness was measured by HAQ-DI, WPAI-RA, CDAI, and DAS28-ESR every 6 months during follow-up. For CDAI and DAS28-ESR, TNFi users had consistently greater improvement in terms of mean score change from baseline, except at the last time point (240 week), where there was an important attrition. In the mixed logistic regressions, tofacitinib users and TNFi users did not have significant differences in the 6 outcomes, whether before or after applying the PS adjustment (6 outcomes: HAQ-DI outcome for improvement, CDAI outcome for remission/LDA, DAS28-ESR outcome for remission/LDA, and WPAI-RA for currently employed). All the point estimates were greater than 1.0, for which the direction favored tofacitinib. The descriptive effectiveness was not entirely consistent by using different RA scores. Not only does each score focus on different aspects, but they are also different in that some were reported by patients, and some were reported by physicians. Studies have reported a discordance between patients' and physicians' perception of RA severity.[41-43] DAS28 and CDAI cut-offs do not translate into the same clinical information, either.[44]

The multiple years of follow-up and the repeated visits allowed a more comprehensive assessment of the treatment patterns for both study medications. Patients were meant to be followed up for 36 months after initiation of tofacitinib or TNFi, and patients switching therapies remained in follow-up. All patients were followed up for the first year of treatment (including switching); approximately 80% of patients were followed up for the second year, 70% for the third year, and 60% for the fourth treatment year. Approximately 20% of patients overall, enrolled early in the recruitment period, were followed up to the fifth

treatment year. The mean time to discontinuation or switch was similar for users of either medication (tofacitinib: 17.4 months; TNFi: 16.7 months). The hazard ratio of treatment discontinuation/switch was 0.89 (0.54, 1.44) for tofacitinib users over TNFi users. An analysis using Taiwan National Healthcare Insurance Claims and the Death Registry between 2012 and 2017 found that, compared to etanercept users, adalimumab users were more likely to discontinue/switch, whereas users of tocilizumab, abatacept, tofacitinib, and golimumab were similarly less likely to discontinue/switch the treatment.[27] In this study, compared to TNFi users followed over time, tofacitinib users were more likely have a dose change or interruption, overall and at each time point. The overall proportion of dose change was 77.9% for tofacitinib users and 49.2% for TNFi users. Noted that tofacitinib is an oral drug and 59.3% of the dose change/interruption reasons listed in the eCRF were not related to AE, NHI requirement, or lack of efficiency. During the whole study period, the mean PDC for tofacitinib and TNFi were 0.80 and 0.78, respectively, indicating similar adherence. The proportion of PDC ≥0.8 were also highly comparable between the groups (tofacitinib: 71.0%; TNFi: 71.3%). Persistence was also similar, which was averagely 996 days for tofacitinib users and 986 days for TNFi users. Studies from some other geographic regions have shown poorer adherence and persistence. In a systematic review of observational studies from 2018 to 2020,[40,45] the proportion of tofacitinib users with 12-month PDC ≥0.8 in the US was only 48.2% (in our study it was 85.5%); in Canada, the persistence at one-year and 2 years was 62.7% and 49.6%, respectively (vs 71.7% and 54.5% in the present study); and in Japan, the one-year discontinuation rate was 32% (in our study 80% users remained on tofacitinib at year one). However, from the same review, the median drug maintenance in Switzerland (25 months) was longer than our study (14.75 months). The difference in the adherence and persistence by geographic regions might be relevant to the difference in patient characteristics and reimbursement policies.

Clinical response and PROs were also measured after the dose reduction of tofacitinib or TNFi. Patients could have their dose reduced due to other reasons than the NHI reimbursement guideline, so this population is heterogeneous. At the time of dose reduction, TNFi users were generally at higher disease activity than tofacitinib users: the proportion of CDAI >10 was 10.48% for TNFi users versus 8.37% for tofacitinib users; the proportion of DAS28-ESR ≥3.2 was 37.5% versus 25.0%; and the mean HAQ-DI was 0.72 versus 0.59. After 4 weeks following the dose reduction, the proportion of CDAI >10 was 46.2% for TNFi users versus 36.4% for tofacitinib users; the proportion of DAS28-ESR ≥3.2 was 53.8% versus 38.1%; and the mean HAQ-DI was 0.73 versus 0.60. After 12 weeks following the dose reduction, the proportion of CDAI >10 was 53.8% for TNFi users versus 45.5% for tofacitinib users; the proportion of DAS28-ESR ≥3.2 was 66.7% versus 50.0%; and the mean HAQ-DI was 0.80 versus 0.72. Therefore, after the dose reduction, RA severity generally increased gradually for both groups, and the severity was consistently higher for TNFi users. Only a few deteriorations were observed after the dose reduction.

During the study, more than half of the study population experienced AEs (56.6% tofacitinib users and 55.7% TNFi users). While the proportions of patients experiencing AEs and SAEs were similar between the 2 groups, more tofacitinib users had related AEs and related SAEs. The proportion of patients experiencing TAEs was higher for tofacitinib users, whether related (16 patients (11.0%) in the tofacitinib group versus 4 patients (3.3%) in the TNFi group) or non-related (20 patients (13.8 %) in the tofacitinib group versus 12 patients (9.8%) in the TNFi group). The most frequent AEs pertained to the infections and infestations SOC, followed by Musculoskeletal and connective tissue disorders, respiratory thoracic or mediastinal disorders, and gastrointestinal disorders. For 19 patients in the tofacitinib group and for 10 patients in the TNFi group was at least one event reported in the infection TAE subcategory serious infections, defined as infections requiring hospitalization or use of parenteral antibiotics. There were 18 tofacitinib users and 3 TNFi users who had a TAE of herpes zoster. One patient had hepatitis B reactivation in the TNFi group. No patient ever had hepatitis C reactivation or TB during the study. Overall, in the current study, tofacitinib users were more likely to experience a TAE in the category infection than TNFi users. One patient in the TNFi group experienced a MACE. Two tofacitinib users and 3 TNFi users had liver enzyme abnormalities. Three patients with tofacitinib treatment and 1 patient with TNFi treatment had at least one event in the category cancer/malignancy.

A systematic review and meta-analysis for interventional studies in 2015 showed a comparable risk of serious infection between tofacitinib users and bDMARDs users with moderate to severe RA.[46] A multi-database cohort study in the US using data till 2018 found that the risk of serious infection associated with tofacitinib was significantly higher than etanercept, numerically higher than abatacept, golimumab, and tocilizumab, similar to adalimumab and certolizumab, and significantly lower than infliximab; and that tofacitinib was associated with a 2-fold higher risk of herpes zoster comparing to all the bDMARDs.[46] A registry study spanning the years 2012 to 2019 in the US found that tofacitinib users and bDMARDs users had similar rates for MACE, serious infections, malignancy, death, and venous thromboembolism; while herpes zoster rates were higher for tofacitinib initiators than for bDMARDs initiators.[48] The proportion of patients experienced herpes zoster in our study was 12.4%, and that proportion was 5.6% in a prior study in Taiwan, but that prior study was much shorter (from 2015 to 2017).[49] Our study is consistent with prior findings in that tofacitinib users were more likely to develop herpes zoster than TNFi users. Further, although there were more tofacitinib users who experienced serious infections than TNFi users, the sample size was limited in both groups.

11.2. Limitations

One of the study objectives is to compare the effectiveness of bDMARDs for patients on tofacitinib versus TNFi. In the absence of randomization, confounding by indication could be an issue, and patient characteristics directly related to the treatment were likely to influence physician prescribing behaviors. The analysis PS applied and included baseline socio-demographic, clinical, and treatment characteristics to the PS model. However, PS can only address known and measured confounders. As an observational study, residual confounding

cannot be fully ruled out for the comparison of the effectiveness between tofacitinib and TNFi.
Further, the measurements of effectiveness included HAQ-DI, WPAI-RA, CDAI, and DAS28-ESR. These measurements were patient-reported or physician-reported outcomes and were subjected to information bias. In the study, the instruments used had relatively short recall periods, limits the potential recall bias.

No study visits were scheduled for this study; however, update of data collection was requested at 24-week intervals. Rather, all clinical assessments were performed at the time of a routine clinical encounter or obtained by referencing the medical record within an allowable time window (±28 days). The median [interquartile range (IQR)] days between actual visits were 168 (159.5, 175) days, showing a visit interval of approximately 6 months.

In addition, there could be potential selection bias. Consented patients could drop out from the study, and whether these dropped out patients would develop similar outcomes and have similar treatment patterns to the patients who remained on the study is not known. However, during follow-up, only a small proportion of patients withdrew their consent (15 tofacitinib users and 12 TNFi users), and most of the patients remained in follow-up. Besides, selection bias arising from the lack of complete enrolment of potential eligible patients was reduced by maintaining screening logs at sites.

Although, the study population was not large, the follow-up was for a relatively long time and was able to assess the long-term effectiveness, safety, adherence, and treatment patterns of the 2 therapies of interest. Statistical power to detect potential difference in the effectiveness between tofacitinib and TNFi was however limited by the sample size. The odds ratios of the 6 outcomes (HAQ-DI outcome for improvement, CDAI outcome for remission/LDA, DAS28-ESR outcome for remission/LDA, and WPAI-RA for currently employed), did not show any statistically significant difference between the 2 bDMARDs in the study population. However, all the adjusted and unadjusted odds ratios had their point estimates greater than 1, and there is possibly a trend for tofacitinib outperforming TNFi in these aspects. Future studies on whether tofacitinib users obtain significantly better clinical results would help inform the comparative effectiveness.

11.3. Generalizability

The study included patients newly prescribed tofacitinib or a TNFi in routine practice by physicians from 7 centers in Taiwan. Therefore, the population was limited to patients going to these specific centers and who gave their consent. The studied patients differ by disease activity or other characteristics from patients not seeking medical care or not treated at these 7 sites. Our study population may not be representative of the general new users of bDMARDs in Taiwan.

It is not clear whether being enrolled in the study would affect patients' behavior and thus impact the outcomes of interest, for instance, whether being in the research study is associated with better adherence. Therefore, it is possible that the adherence in the study population does not fully reflect the adherence of the overall initiators of tofacitinib and TNFi in the general clinical practice.

As mentioned in the Key Results and Interpretation section, RA patients using tofacitinib or TNFi in Taiwan may differ from patients in other countries and regions. Thus, the study result may not be generalized to the patients worldwide. Besides, it is possible that clinical guidelines, treatments, or reimbursement policies will evolve in the future. Therefore, the results from the current study might only be applicable in recent years.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

After the approval of tofacitinib in 2014 in Taiwan, Pfizer conducted a multicentered prospective cohort study of 267 RA patients who used tofacitinib or TNFi. Tofacitinib users and TNFi users were generally similar for baseline characteristics, whereas tofacitinib users had longer history of RA and TNFi users might have slightly more higher baseline RA severity. No significant difference was found in the long-term effectiveness between the 2 therapies. Tofacitinib users and TNFi users evidenced comparable persistence and adherence. The majority of AEs were of mild or moderate severity, in users of either drug. The overall SAE rates were similar between tofacitinib users and TNFi users. The proportions of patients who experienced any serious infection, defined as infections requiring hospitalization or use of parenteral antibiotics was higher in the tofacitinib group compared to the TNFi group, so was the number of targeted adverse events of herpes zosters.

14. REFERENCES

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet*. Sep 15 2001;358(9285):903-11. doi:10.1016/s0140-6736(01)06075-5.

2. Sullivan PW, Ghushchyan V, Huang XY, Globe DR. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. *J Rheumatol*. Mar 2010;37(3):544-9. doi:10.3899/jrheum.081306.

3. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am*. May 2001;27(2):269-81. doi:10.1016/s0889-857x(05)70201-5.

4. Rudan I, Sidhu S, Papana A, et al. Prevalence of rheumatoid arthritis in low- and middle-income countries: A systematic review and analysis. *J Glob Health*. Jun 2015;5(1):010409. doi:10.7189/jogh.05.010409.

5. Lee YH, Tsou HK, Kao SL, et al. Patients With Rheumatoid Arthritis Increased Risk of Developing Osteoarthritis: A Nationwide Population-Based Cohort Study in Taiwan. *Front Med (Lausanne)*. 2020;7:392. doi:10.3389/fmed.2020.00392.

6. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int*. May 2021;41(5):863-877. doi:10.1007/s00296-020-04731-0.

7. Köhler BM, Günther J, Kaudewitz D, Lorenz HM. Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. *J Clin Med*. Jun 28 2019;8(7)doi:10.3390/jcm8070938.

8. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis*. Apr 2010;69(4):638-643. doi:10.1136/ard.2009.123976.

9. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med*. Mar 20 2007;146(6):406-15. doi:10.7326/0003-4819-146-6-200703200-00005.

10. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. Nov 2005;52(11):3381-90. doi:10.1002/art.21405.

11. Kari Puolakka HK, Timo Möttönen,Pekka Hannonen,Markku Korpela,Heikki Julkunen,Reijo Luukkainen,Kaisa Vuori,Leena Paimela,Harri Blåfield,Markku Hakala,Marjatta Leirisalo-Repo. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis Rheum*. 2004;50(1):55-62.

12. Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet*. May 8 1999;353(9164):1568-73. doi:10.1016/s0140-6736(98)08513-4.

13. Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum*. May 2009;60(5):1222-31. doi:10.1002/art.24447.

14. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis*. Nov 2007;66(11):1443-9. doi:10.1136/ard.2007.071092.

15. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet*. Jul 17-23 2004;364(9430):263-9. doi:10.1016/s0140-6736(04)16676-2.

16. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum*. Jan 2000;43(1):22-9. doi:10.1002/1529-0131(200001)43:1<22::Aid-anr4>3.0.Co;2-9.

17. Lundquist LM, Cole SW, Sikes ML. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. *World J Orthop*. Sep 18 2014;5(4):504-11. doi:10.5312/wjo.v5.i4.504.

18. Benucci M, Li Gobbi F, Meacci F, et al. Antidrug antibodies against TNF-blocking agents: correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. *Biologics*. 2015;9:7-12. doi:10.2147/btt.S69606.

19. Krishnan E, Sokka T, Häkkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. *Arthritis Rheum*. Mar 2004;50(3):953-60. doi:10.1002/art.20048.

20. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2010;12(5):R177. doi:10.1186/ar3141.

21. Salaffi F, Cimmino MA, Leardini G, Gasparini S, Grassi W. Disease activity assessment of rheumatoid arthritis in daily practice: validity, internal consistency, reliability and congruency of the Disease Activity Score including 28 joints (DAS28) compared with the Clinical Disease Activity Index (CDAI). *Clin Exp Rheumatol*. Jul-Aug 2009;27(4):552-9.

22. van der Helm-van Mil AH, Breedveld FC, Huizinga TW. Aspects of early arthritis. Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res Ther*. 2006;8(4):216. doi:10.1186/ar1983.

23. Xeljanz Film-Coated Tablets. Center for Drug Evaluation. Available at: http://www.nhi.gov.tw/Resource/webdata/26686_1_Xeljanz%20Film-Coated%20Tablets%E8%A9%95%E4%BC%B0%E5%A0%B1%E5%91%8A.pdf. Accessed: November 2015. (Article in Chinese).

24. Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence.

25. RS L. Calculating Medication Compliance, Adherence, and Persistence in Administrative Pharmacy Claims Databases.

26. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. Jan 1997;50(1):105-16. doi:10.1016/s0895-4356(96)00268-5.

27. Li, K. J., Chang, C. L., Hsin, C. Y., & Tang, C. H. (2021). Switching and Discontinuation Pattern of Biologic Disease-Modifying Antirheumatic Drugs and Tofacitinib for Patients With Rheumatoid Arthritis in Taiwan. *Frontiers in pharmacology*, 1848.

28. Behrens, F., Koehm, M., Schwaneck, E. C., Schmalzing, M., Gnann, H., Greger, G., ... & Burkhardt, H. (2019). Use of a “critical difference” statistical criterion improves the predictive utility of the Health Assessment Questionnaire-Disability Index score in patients with rheumatoid arthritis. *BMC rheumatology*, 3(1), 1-9.

29. Kuo, C. F., Luo, S. F., See, L. C., Chou, I. J., Chang, H. C., & Yu, K. H. (2013). Rheumatoid arthritis prevalence, incidence, and mortality rates: a nationwide population study in Taiwan. *Rheumatology International*, *33*(2), 355-360.

30. Lee, C. Y., Tai, C. J., Tsai, Y. F., Kuan, Y. H., Lee, C. H., & Huang, K. H. (2019). Prescribing trend of antirheumatic drugs in taiwan and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. *BioMed research international*, *2019*.

31. Ramos, A. L., Redeker, I., Hoffmann, F., Callhoff, J., Zink, A., & Albrecht, K. (2019). Comorbidities in patients with rheumatoid arthritis and their association with patient-reported outcomes: results of claims data linked to questionnaire survey. *The Journal of rheumatology*, *46*(6), 564-571.

32. Hsu, C. S., Lang, H. C., Huang, K. Y., Lin, H. H., & Chen, C. L. (2016). Association of rheumatoid arthritis and hepatitis B infection: a nationwide nested case-control study from 1999 to 2009 in Taiwan. *Medicine*, *95*(18).

33. Wilson, D. (2006). Rheumatoid factors in patients with rheumatoid arthritis. *Canadian Family Physician*, *52*(2), 180.; WebMD "What type of RA do you have?" https://www.webmd.com/rheumatoid-arthritis/rheumatoid-arthritis-types accessed Nov 2021.

34. Fleischmann, R., Mysler, E., Hall, S., Kivitz, A. J., Moots, R. J., Luo, Z., ... & Calmes, J. M. (2017). 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. *The Lancet*, 390(10093), 457-468.

35. Van Vollenhoven, R. F., Fleischmann, R., Cohen, S., Lee, E. B., García Meijide, J. A., Wagner, S., ... & Wilkinson, B. (2012). Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *New England Journal of Medicine*, 367(6), 508-519.

36. Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis. *ClinicalTrials.gov*. https://clinicaltrials.gov/ct2/show/results/NCT02092467 accessed Nov 2021.

37. Finckh, A., Tellenbach, C., Herzog, L., Scherer, A., Moeller, B., Ciurea, A., ... & Zufferey, P. (2020). Comparative effectiveness of antitumour necrosis factor agents, biologics with an alternative mode of action and tofacitinib in an observational cohort of patients with rheumatoid arthritis in Switzerland. *RMD open*, 6(1), e001174.

38. Pappas, D. A., St John, G., Etzel, C. J., Fiore, S., Blachley, T., Kimura, T.,... & Kremer, J. M. (2021). 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. *Annals of the Rheumatic Diseases*, *80*(1), 96-102.

39. Bergrath, E., Gerber, R. A., Gruben, D., Lukic, T., Makin, C., & Wallenstein, G. (2017). Tofacitinib versus biologic treatments in moderate-to-severe rheumatoid arthritis patients who have had an inadequate response to nonbiologic DMARDs: systematic literature review and network meta-analysis. *International journal of rheumatology*, *2017*.

40. Bird, P., Littlejohn, G., Butcher, B., Smith, T., da Fonseca Pereira, C., Witcombe, D., & Griffiths, H. (2020). Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia. *Clinical rheumatology*, *39*(9).

41. Barton, J. L., Imboden, J., Graf, J., Glidden, D., Yelin, E. H., & Schillinger, D. (2010). Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis care & research*, *62*(6), 857-864.

42. Studenic, P., Radner, H., Smolen, J. S., & Aletaha, D. (2012). Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis & Rheumatism*, *64*(9), 2814-2823.

43. Nicolau, G., Yogui, M. M., Vallochi, T. L., Gianini, R. J., Laurindo, I. M., & Novaes, G. S. (2004). Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. *The Journal of Rheumatology*, *31*(7), 1293-1296.

44. Martins, F. M., da Silva, J. A. P., Santos, M. J., Vieira-Sousa, E., Duarte, C., Santos, H.,... & Canhão, H. (2015). DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma. pt. *Rheumatology*, *54*(2), 286-291.

45. Bertoldi, I., & Caporali, R. (2021). Tofacitinib: Real-World Data and Treatment Persistence in Rheumatoid Arthritis. *Open Access Rheumatology: Research and Reviews*, *13*, 221.

46. Strand, V., Ahadieh, S., French, J., Geier, J., Krishnaswami, S., Menon, S.,... & Gómez-Reino, J. J. (2015). Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis research & therapy*, *17*(1), 1-9.

47. Pawar, A., Desai, R. J., Gautam, N., & Kim, S. C. (2020). Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study. *The Lancet Rheumatology*, 2(2), e84-e98.

48. Kremer, J. M., Bingham III, C. O., Cappelli, L. C., Greenberg, J. D., Madsen, A. M., Geier, J.,... & Kavanaugh, A. (2021). Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States–Based Rheumatoid Arthritis Registry. *ACR open rheumatology*, *3*(3), 173-184

49. Chen, Y. J., Chen, Y. M., Huang, W. N., Chen, H. H., Liao, T. L., Chen, J. P., ... & Chen, D. Y. (2020). Herpes Zoster in rheumatoid arthritis patients receiving tofacitinib, a single center experience from Taiwan. *Medicine, 99*(41).

15. LIST OF SOURCE TABLES AND FIGURES

Document Approval Record

Document Name:	A3921275 Non Interventional Study Report 25 March 2022
Document Title:	An Observational Study of Xeljanz® (tofacitinib citrate) and Biologic Rheumatoid Arthritis Treatments to Characterize their General Treatment Patterns, Effectiveness and Safety in a Real World Taiwanese Population

Signed By:	Date(GMT)	Signing Capacity
Redacted	30-Mar-2022 11:54:56	Redacted
Redacted	01-Apr-2022 07:49:59	Redacted
Redacted	01-Apr-2022 11:29:01	Redacted