NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Comparison of treatment satisfaction between patients with rheumatoid arthritis on tofacitinib citrate and adalimumab treatment
Protocol number	A3921304
Protocol version identifier	Version 3.2
Date of last version of protocol	10 December 2019
Active substance	Anatomical Therapeutic Chemical (ATC) code category: Selective immunosuppressant (L04AA29)
Medicinal product	Tofacitinib citrate
Research question and objectives	This study aims to compare treatment satisfaction and quality of life between patients who have been using tofacitinib citrate and those using adalimumab for 6 months or more and less than 2 years in the treatment of rheumatoid arthritis.
Author	PPD [redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
EULAR	The European League Against Rheumatism
RA	Rheumatoid Arthritis
TNF	Tumor Necrosis Factor
DMARD	Disease modifying antirheumaticdrug
MTX	Methotrexate
DAS	Disease Activity Score
CRP	C-reactive protein
PSM	Propensity Score Method
PS	Propensity Score
IPTW	Inverse Probability of Treatment Weighting
SMD	Standardized Mean Difference
TSQM	Treatment Satisfaction Questionnaire for Medication
QoL	Quality of Life
EQ-5D	EuroQoL-5Dimensions
EQ-VAS	EuroQoL-Visual Analogue Scale
PRO	Patient Reported Outcome

2. RESPONSIBLE PARTIES

Name, degree(s)	Title	Affiliation	Address
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3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	18.05.11	Substantial	P 4, 5	2. RESPONSIBLE PARTIES PPD -PPD removed and PPD added	PPD Change in author
			P 7, 8	6. Research Questions and Objectives 7.2.1. Inclusion Criteria - Inclusion criteria modified from more than 3 months and less than 2 years to more than 6 months and less than 2 years	Modified as subjects who have been taking tofacitinib citrate for 3 months and adalimumab for 6 months are more likely to be included in the study clinically. DAS28 from the clinical records was measured at 6 months, and this was applied.
			P 10	7.3. Variables Graph 1. Assessments [15, 20-21]: 2. Clinical characteristics - tofacitinib citrate or adalimumab added to DMARD - changed measuring units to the dose unit (mg/month)	To specify DMARD types, those in parenthesis have been added. Prescribing patterns are very different; therefore, the measuring unit was changed to include all variations.
			P 19	8.4. Ethical conduct of the study - Recent Declaration of Helsinki added	Most recent Declaration of Helsinki added
3.0	2019.01.31	Substantial	P 5	2. RESPONSIBLE PARTIES PPD 7.6.2. Data Collection Method - according to the included institutions, the number of institutions was changed to 23	According to the institutions added

			P 6 P 17	4. Milestones - End date of data collection changed to Sep 30, 2019 7.6.2. Data Collection Method - Data collected dates changed to September 30, 2019.	Followed data collection extension
			P 9–11	7.2.2. Exclusion criteria - Modified and added 7.3. Variables Graph 1. Assessments [15, 20-21]: 2. Clinical characteristics	Followed physician's advice that csDMARDs co-administered with bDMARDs can include items other than MTX and that there are no differences between csDMARD types.
			P 6, 14, 18	3. Amendments and Updates - reason for ver 2.0 modification: ~ patients who have been taking tofacitinib citrate for 3 months ~ 7.4 Data Sources - patients through a chart review and subject questionnaires 7.7.1 Outcome Comparisons Using PSMs - when the assumption for the parametric hypothesis is not satisfied- ~ when the assumptions for parametric hypothesis is not satisfied, non-parametric~	Changed to more appropriate term, and errors corrected.
			P 20	8. Study subject protection	Pfizer protocol template CCI [redacted]
3.1	2019.09.02	Administrative	P 9 P 18	4. Milestones - End date of data collection changed to December 31, 2019. 7.6.2. Data Collection Method - Data collected dates changed to December 31, 2019.	Followed data collection extension
3.2	2019.12.10	Administrative	P 9 P 18	4. Milestones	Followed data collection extension

				- End date of data collection changed to March 31, 2020. 7.6.2. Data Collection Method - Data collected dates changed to March 31, 2020.	

4. MILESTONES

Milestone	Planned date
Study start-up	Request for proposal approval date
Completion of feasibility assessment	Participating institutions and investigators confirmation date
Start of data collection	Site visit training date
End of data collection	March 31, 2020
Final study report	12 months from the last patients

5. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes joint destruction and leads to loss of function, decreased quality of life [1], and ultimately death [2] from complications. It is characterized by an excessive increase in pro-inflammatory cytokines that causes abnormal inflammation [3]. Therefore, the American Arthritis Foundation has recommended early diagnosis and appropriate treatment targeting maintenance of low disease activity or remission of RA, prevention or delay of joint damage, and recovery of physical abilities and improvement in the quality of life [4].

According to the 2016 Update of the European League Against Rheumatism (EULAR) recommendation, the basic principle of the RA treatment goal is to provide the best care for the patients, and that treatment should be discussed and agreed between the two parties [5]. Therefore, patient evaluation of the treatment is an important factor for its success.

Recently, the development of new treatments with various mechanisms and diagnosis criteria for early detection have allowed diagnosis and treatments in earlier stages of RA than previously possible [6]. However, it is a chronic condition that is still difficult to cure, and various complications [7-10] and decreased quality of life [1] can occur with insufficient treatment or a prolonged disease presence. Within 2 years of diagnosis, irreversible bone erosion has been observed in more than 50% of patients [7], and it was shown that patients with prolonged disease period have a high risk for widespread complications, such as cardiovascular conditions [8], infection [9], and malignant tumor [10].

According to the 2015 American College of Rheumatology Guideline, patients who have insufficient response to or who do not have tolerance to the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) as the 1st line treatment are recommended to switch to biologic DMARDs (bDMARDs) or the small molecular target therapy JAK suppressor (tofacitinib citrate) to minimize disease activity or to expedite remission [11]. Most patients who receive csDMARDs suffer from a prolonged disease period, and it is important to assess quality of life and treatment satisfaction in this population.

bDMARDs are injectibles, and they have been reported to have low compliance [12] owing to invasive administrations and loss of therapeutic effects from immunogenic response [13, 14]. On the contrary, tofacitinib citrate, which has been developed recently and used as an antirheumatic drug, is reported to have similar efficacy [15] and safety [16-18] as those of the bDMARDs and has a higher patient preference owing to its oral route of administration [19].

In a comparison using a RCT, non-inferior effects [15] and safety [20] of tofacitinib citrate were shown when compared to commonly used the bDMARD adalimumab, and both agents showed a higher quality of life than the placebo [21]. However, most clinical treatment success reports compare bDMARDs [22-24], and there are few reports that compare JAK suppressors with bDMARDs and their effects on patient treatment satisfaction and quality of life.

Therefore, the purpose of this study is to compare the two most common clinically used antirheumatic agents, adalimumab and tofacitinib, in terms of treatment satisfaction and quality of life among Korean patients to assess treatment success from patients' perspectives.

6. RESEARCH QUESTION AND OBJECTIVES

This study aim to compare treatment satisfaction and quality of life between patients who have been using tofacitinib citrate and patients who have been using adalimumab for 6 months or more and less than 2 year in treatment of rheumatoid arthritis. The specific objectives are as follows:

Primary objective

To compare the treatment satisfaction between tofacitinib citrate users and adalimumab users.

Secondary objective

To compare the quality of life between tofacitinib citrate users and adalimumab users.

7. RESEARCH METHODS

7.1. Study design

This study is a multi-center, non-interventional cross-sectional study.

7.2. Setting

7.2.1. Study population

The study population is patients with RA who have been using tofacitinib citrate or adalimumab for 6 months or more and less than 2 years in RA treatment at the participating institutions.

7.2.2. Inclusion criteria

Study populations must satisfy the following inclusion criteria for enrollment:

1. ≥ 19 years of age

2. Patients who satisfy the 2010 American College of Rheumatology/European League Against Rheumatism diagnosis criteria [a)]

3. Treatment groups:

    1) Tofacitinib citrate users: patients who have been taking tofacitinib citrate for more than 6 months

    2) Adalimumab users: patients who have been taking adalimumab for more than 6 months

4. Patients who can read and write the questionnaire forms in Korean

7.2.3. Exclusion criteria

Study population who satisfy the exclusion criteria listed below will be excluded from the study:

1 Patients who are taking tofacitinib citrate or adalimumab for more than 2 years

2 Patients who are taking tofacitinib citrate or adalimumab along with azathioprine or cyclosporine

3 Patients who are participating in clinical research with other investigational products

4. Patients who are taking bDMARDs for diseases other than RA

a)

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A-D;	
a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2—10 large joints	1
1—3 small joints (with or without involvement of large joints)**	2
4—10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)††	5
B. Serology (at least 1 test result is needed for classification)‡‡	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)§§	
Normal CRP *and* normal ESR 0	0
Abnormal CRP *or* normal ESR 1	1
D. Duration of symptoms¶¶	
<6 weeks	0
≥6 weeks	1

*The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfilment of the 2010 criteria should be classified as having RA.
Patients with long-standing disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

†Differential diagnoses differ in patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡Although patients with a score of less than 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶'Large joints' refers to shoulders, elbows, hips, knees and ankles.

**'Small joints' refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists.

††In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular, etc.).

‡‡Negative refers to international unit (IU) values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but three of less times the ULN for the laboratory and assay; high-positive refers to IU values that are more than three times the ULN for the laboratory and assay. When rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF.

§§Normal/abnormal is determined by local laboratory standards.

¶¶Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.
ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

7.3. Variables

The information detailed below will be collected from medical records and patient questionnaires during the study from those who satisfy the inclusion criteria.

Table 1. Evaluation Criteria [15,20-21]

Evaluation Criteria	Information	Evaluation Method
1. Demographics	• Age • Gender	Medical Chart
	• Educational level • Financial status • Employment status	Patient Questionnaire
2. Clinical Characteristics	• Body mass index • Comorbidities • Initial RA diagnosis date • DMARD types used previously • Current use of DMARD (tofacitinib citrate or adalimumab), treatment numbers/duration/doses (mg/month) Co-administered drug types, numbers, dosage (csDMARDs/NSAIDs/steroid; mg/month) • DAS28 components	Medical Chart
3. Treatment Satisfaction	• Treatment satisfaction questionnaire for medication, (TSQM)	Patient Questionnaire

4. Quality of Life	• EuroQoL-Visual Analogue Scale, EQ-VAS • EuroQoL-5 Dimensions index, EQ-5D index	Patient Questionnaire

7.3.1. Propensity score methods

The purpose of the propensity score is to create conditions similar to those of randomized trials by balancing the covariates in subjects between the groups. The propensity score adjustment method reduces multidimensional covariates into a one-dimensional score, or the propensity score. The computed propensity score can be used for bias reduction through restriction, matching, stratification, covariate adjustment, and weighted methods. It can also be used to estimate the mean treatment effect of two groups or the mean treatment effects of the active group compared to those of the control group.

- **Propensity score use of the propensity score in the cross-sectional studies** [26-30]

The propensity score is used in the cross-sectional studies to remove or minimize effects from the disturbance variable. Analytical methods using propensity scores are considered superior to the average covariate analysis method of the one-dimensional study. Therefore, the analytical method using propensity score will be used in this study.

1) ***Propensity score matching*** [25]

- Propensity score matching can restrict variations between the covariates by matching subjects with similar propensity scores from groups 1 and 2.
- Duplicates not allowed: Once a subject from group 2 is matched with a subject from group 1, he/she cannot be considered for a match to a subject from another group, and therefore, the subject from group 2 can be matched for a maximum of one time.
- Greedy matching (nearest matching method): Subject from group 1 is randomly selected; then the subject with the closest propensity score is selected from group 2 (caliper matching is also an option), and 1:1 matching will be considered.
- If too many subjects are eliminated from the analysis after matching, this method will not be considered as the analytical method, and only the methods described below will be considered and reported. Standards for the decision will be described in the SAP in detail.

2) ***Propensity score adjustment*** [28]

This method uses all patients enrolled in the study,

- ***Propensity score adjustment***: A method for including the treatment variable and the PS itself as a covariate in a multiple model estimating a treatment effect.

3) ***Propensity score based weighing*** [28]

This method also uses all patient data.

- ***Propensity score weighting***: A method of using IPTW (inverse probability of treatment weighting) method to estimate a mean treatment effect of the two drug groups. The weight makes the characteristics of treatment groups similar to the target population.

4) ***Propensity score based stratification*** [28]

This method also uses all patient data.

- ***Propensity score stratification***: A method of stratifying patients according to the quintiles or deciles of their propensity score, and evaluate a treatment effect within each stratum. A pooled treatment effect will then be obtained across strata.

7.3.2. Treatment satisfaction questionnaire for medication version 1.4

TSQM version 1.4 is a self-report questionnaire for investigating treatment satisfaction. TSQM version 1.4 is the original version created with domain scoring for effectiveness, convenience, global satisfaction, and side effects with 14 items. Then each domain is scored by formula. The formula for TSQM scoring will be stated in Statistical Analysis Plan. TSQM scores range from 0 to 100 by each domain, higher scores indicate that the patient is in a greater satisfaction.

7.3.3. EuroQoL-5 dimension-3 level index and EuroQoL-visual analogue scale

EuroQoL-5 dimension (EQ-5D) is a standardized measure of health status, such as quality of life. The EuroQoL-5 dimension-3 level (EQ-5D-3L) essentially consists of 2 pages – the EQ-5D descriptive system and EuroQoL-visual analogue scale (EQ-VAS).

The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. The scale is 0 to 100, higher scores imply that the patient is in a better health state.

The formula for EQ-5D scoring will be stated in Statistical Analysis Plan.

7.4. Data sources

Once a subject satisfies the inclusion criteria and voluntarily consents to participate in the study, subject data will be collected through review of medical records and patient questionnaires. Variables collected from the medical chart include demographic and clinical characteristics. Educational status, total income for the past year, and the current employment status will be collected from the questionnaires. Treatment satisfaction and the quality of life questions will be collected using the TSQM questionnaires and EQ-5D measurements, and the subject will self-record these.

7.5. Study sample size

The purpose of this study is to compare treatment satisfaction and quality of life in patients with RA who are receiving adalimumab or tofacitinib citrate. It is essential to identify the minimum sample size required to obtain statistically significant differences between the two groups. The equation below was used to calculate the sample size in this study [31].

$$N = \frac{2\sigma^2}{(\mu_1 - \mu_2)^2}\left[z_{1-\alpha/2} + z_{1-\beta}\right]^2$$

- σ: Standard deviation from the overall satisfaction pooled ≈ 14.58 (SD1: 16 [18], SD2: 13 [24])

$$\sigma = \sqrt{(\sigma_1{}^2 + \sigma_2{}^2)/2}$$

- μ_1: Average of the overall satisfaction measured (larger) = 83 [24]
- μ_2: Average of the overall satisfaction measured (smaller) = 79 [24]
- $z_{1-\alpha/2}$: 95% confidence interval (double-sided) significance = 1.96
- $z_{1-\beta}$: 80% power threshold = 0.842

Sample size was calculated based on literature that compared the median general satisfaction number between two drugs from the TSQM and the EQ-5D index score [24].

Jobanputra P et al. (2010) reported that the median EQ-5D index score and the median overall satisfaction score from TSQM (interquartile range) at 3 months after taking the medication in the adalimumab group were 0.62 (0.59–0.76) and 83 (67–100), respectively. In contrast, these scores were 0.62 (0.52–0.76) and 79 (58–92), respectively, in the etanercept group. Based on the sample number calculated in this study, we assumed that the average scores for the EQ-5D index or TSQM would be similar to the median scores from this measurement tool. This is because the interquartile ranges were almost symmetrical to the median value. We also assumed that the difference between the 3rd interquartile and median values (or the difference between the median and the 1st interquartile values) would replace the deviation from the general EQ-5D index or TSQM scores. This is because approximately 67% of the normal distribution data falls within the average ± 1 standard deviation, whereas 50% of uniform distribution data falls within median ± interquartile (in other words, within the interquartile range: Q1–Q3) values. Based on these assumptions, the standard deviations for the EQ-5D index scores were from 0.03 (= 0.62–0.59) to 0.14 (= 0.76–0.62) in adalimumab and from 0.1 (= 0.62–0.52) to 0.14 (=0.76–0.62) in etanercept. Under the same assumption, the standard deviations for the TSQM scores were from 16 (= 83–67) to 17 (= 100–83) in adalimumab and from 13 (= 92–79) to 21 (= 79–58) in etanercept.

We assumed 0 (= 0.62–0.62) and 4 (= 83–79) points as the difference in the average EQ-5D and TSQM scores between patients receiving adalimumab and tofacitinib citrate. We also assumed the standard deviations as 0.03–0.14 and 16–17 points for the EQ-5D index and TSQM, respectively, in patients receiving adalimumab and in patients receiving tofacitinib citrate, the EQ-5D index and TSQM as 0.1–0.4 points and 13–21 points, respectively. Through various combinations of standard deviations, we assumed that the minimum pooled standard deviation is 0.07 (= $\sqrt{(0.03^2 + 0.1^2)/2}$ and 14.58 (= $\sqrt{(16^2 + 13^2)/2}$), and the maximum pooled standard deviation is 0.14 (= $\sqrt{(0.14^2 + 0.14^2)/2}$) and 19.1 (= $\sqrt{(17^2 + 21^2)/2}$) in the EQ-5D index and TSQM, respectively.

It was calculated that a total of 32 subjects in each group will be needed to detect the average difference of 0.05 points in EQ-5D with an 80% power at 5% significance, and a standard deviation of 0.07. The average difference of EQ-5D between the groups from a previous study was 0, which could not be used to calculate the sample size. Therefore, we voluntarily selected a small number, 0.05, as the average difference for the calculation. If 0.14 is used as the pooled standard deviation, a total of 125 per group will be needed.

When 14.58 is set as the pooled standard deviation for TSQM, a total of 209 subjects will be needed for each group for an 80% power with 5% significance. If 19.1 is set as the pooled standard deviation, a total of 359 subjects will be needed for each group.

Based on the above calculations of the range of sample sizes for each group, the most number needed for each group, conservatively, is 360 subjects. Considering 10–20% of subjects not consenting, the actual sample size would be 400–450 subjects per group. Therefore,

approximately 420 subjects will be identified from each group from the total of 840 subjects in this study.

Considering the geographic distribution and the number of patients as well as the clinical experiences and the academic success of the physicians, institutions participating in this study are deemed representative hospitals to care for patients with RA in Korea. Therefore, we believe that subjects who are screened from these institutions and undergo inclusion/exclusion criteria and the consent process are representative of Korea's patients with rheumatoid arthritis who either use tofacitinib citrate or adalimumab.

7.6. Data management

7.6.1. Data collection

As used in this study protocol, the term case report form should be considered a paper docu ment record in accordance with the data collection method used in this study. A case report form should be prepared for each patient included in the study. The original case record form should not be disclosed in any form to Pfizer's authorized representative or any third party ex cept the regulatory authority without the written consent of Pfizer.

The investigators should collect and report all clinical and laboratory data entered in the cas e report form and other data collection forms (evidence documents). And the researcher have ultimate responsibility for ensuring their accuracy, authenticity / originality, attributability, co mpleteness, consistency, readability, timely collection (concurrency), continuity and, where n ecessary, availability. In order to verify accuracy of the information contained in the case rec ord, the case report form should be signed by the researcher or a delegated researcher. All mo difications to the case report form and the grounds document should include the date and initi als, the reason (if necessary), and do not cover the original content.

In most cases, the supporting documentation is the patient's medical chart record. In this cas e, the data collected in the case report form should match the data recorded in the chart.

In some cases, the case report form or part of the case report form may also be the evidence document. In this case, the document should be kept in the investigator's center and Pfizer, an d clearly stated in the documentation that the case report from, along with the data recorded i n the case report form, is the basis document.

7.6.2. Data collection method

Data will be collected based on the study timeline. The study will be conducted at a total of 23 institutions from the start date until March 31, 2020 according to the treatment timelines in patients with RA. Patients who satisfy inclusion and exclusion criteria and voluntarily consent to participate in the study will be enrolled. Patient information will be retrieved from medical charts. Information that cannot be obtained from medical charts will be collected from patient

questionnaires, and treatment satisfaction and quality of life will be self-reported using authorized tools (TSQM and EQ-5D-3L).

7.6.3. Data management

Data management will be performed concurrently with data collection. A questionnaire will be issued to the researcher in charge of the research institute regarding the contents that are collected by mistake. Repeat this process until the final database is confirmed by reviewing the contents of the questionnaire that has been resolved by the researchers in charge of each research institute. The range of invalid values of each question will be fully described in data management plan.

After the completion of data collection, de-identified data will be aggregated in central database. Database lock will be conducted prior to the statistical analyses.

7.7. Data analysis

Data analysis will be undertaken using SAS software, version 9.4 of the SAS® system for Windows (Cary, NC, USA).

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan, which will be dated, filed and maintained by the sponsor. The Statistical Analysis Plan may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The subjects of this study are as follows.

- All patients enrolled as study subjects who were eligible for two treatment groups.

The general principles of statistical analysis in this study are as follows:

- Complete statistical analysis plan before DB lock is done. The details of the data analysis methodology of this study are specified in the statistical analysis plan.
- If a statistical test is required, it should be carried out at the two-side significant level 5%.
- When multivariable analysis is performed, independent variables used for actual analysis can be added or subtracted considering the structure of collected data and general charac teristics of study subjects.
- In the case of data that do not have a bias in the interpretation of the results, the analysis i s carried out based on only the observed data without adjusting the missing values. If it i s deemed that significant bias is imposed on the interpretation of the results when the an alysis is carried out with only the observed data, the analysis is carried out by statisticall y adjusting the missing values using the following appropriate missing value imputation method. As a method of replacing missing values, methods such as mean imputation, me

dian imputation, probability imputation, regression imputation, ratio imputation, or mult iple imputation are used depending on the pattern of missing values.
- Other inconsistent data may be excluded from the analysis under the responsibility of the investigator.

7.7.1. Patient's characteristics and outcomes in total patients

For data on the demographic and clinical characteristics, the continuous data will provide mean, standard deviation, median, and range (min, max). If the form of the data is not normally distributed, the median, range, and quartile range are suggested. Categorical data will provide frequency and percentages. Comparison between groups will be performed by the Student's t-test. If normality assumption is not met, a nonparametric method is used. At this time, as a review of the assumption of normality, the histogram of each continuous variable will be evaluated based on the results of the parametric tests. If the form of the data is not normally distributed, the logarithm transformed data will be used for comparison between the groups. Categorical variables will be tested using the chi-square test, but Fisher's exact test will be used when the assumptions required for parametric testing are not met.

The score of each domain in generic tools (TSQM and EQ-5D) will be presented by the mean and standard deviation. The difference of score at each domain according to the patient's characteristics will be evaluated by Student t-test or ANOVA. If the score does not satisfy the assumptions required for the parametric test, nonparametric method will be used.

7.7.2. Outcomes comparison using propensity score methods

Differences in treatment satisfaction and quality of life between the two groups will be compared after adjusting for the demographic characteristics. Of the propensity score methods, we will be utilizing the matching, weighted, covariate-adjusted, and stratified methods. The propensity score will be estimated and used to balance the covariates between the groups. After the quality evaluation to assess whether the covariates are well balanced, treatment satisfaction and quality of life score with propensity score adjustment will be compared. Along with the various propensity score methods, multivariate linear regression will also be used to compare the results between the groups.

7.8. Quality control

It is performed in accordance with the Study Plan and the Good Outcomes Research Practices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and may be monitored regularly by Pfizer or its agents during the study to confirm this. Here, monitoring includes its own in-house monitoring.

7.9. Limitations of the research methods

This non-interventional, multicenter, and multi-dimensional observation study has the following limitations.

First, there can be causality problems. A cross-sectional study has practicality or convenience given its snapshot characteristic. However, it is difficult to use this as evidence for establishing causality. This can be explained as the case of two variables being related when measured from the same perspective, but it being difficult to determine that there is causality between the two.

Second, there is a limitation in controlling disturbance variables. Disturbance variables are those measured variables that can affect the relationships between variables of interest; however, they do not affect the major variables. There is the limitation of unmeasured disturbance variables, which cannot be considered during the adjustment.

Third, there can be a recall bias. Even when the investigator uses the same patient questionnaires as those that have been confirmed for their validity, patients are unable to report the answers accurately in relation to the past history. This can increase or decrease the effects of a particular variable, and therefore, as a result, affect the study outcomes.

7.10. Other aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.

The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

8.2. Patient consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

8.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.4. Institutional review board (IRB)/Independent ethics committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with

the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.5. Ethical Conduct of the Study

This study is conducted in accordance with the general principles set out in the Regulations and Regulatory Requirements, the Good Outcomes Research Practices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the Declaration of Helsinki (World Medical Association 1996, 2008 and 2013).

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The following table summarizes the requirements for recording safety events on the data collection tools and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious adverse events (AEs) (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety event	**Recorded on the data collection tool**	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator regardless of whether the event is determined by the investigator to be related to a drug under study. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection tools. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of tofacitinib citrate and adalimumab or the time of the patient's informed consent if s/he is already exposed to tofacitinib citrate and adalimumab, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to tofacitinib citrate and adalimumab, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to tofacitinib citrate and adalimumab, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that tofacitinib citrate and adalimumab caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether tofacitinib citrate and adalimumab caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that tofacitinib citrate and adalimumab did not cause the event, this should be clearly documented on the data collection tool and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;

- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;

- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These

cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) tofacitinib citrate and adalimumab, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to tofacitinib citrate and adalimumab (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to tofacitinib citrate and adalimumab prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with tofacitinib citrate and adalimumab, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to tofacitinib citrate and adalimumab in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a

live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- An identifiable reporter;

- A suspect product;

- The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.1. Single reference safety document

The CCI [redacted] SAFETY REPORTING LANGUAGE: OTHER PRIMARY DATA COLLECTION STUDY (A type) will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study results will be submitted to domestic or international academic journal.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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12. LIST OF TABLES

13. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable