NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	NON-INTERVENTIONAL STUDY TO REVIEW THE CHANGES OF DEPRESSION AFTER FIRST-YEAR OF TOFACITINIB TREATMENT IN RHEUMATOID ARTHRITIS (XELJANZ®)
Protocol number	A3921330
Protocol version identifier	Version 2.0
Date	18 June 2021
EU Post Authorization Study (PAS) register number	EUPAS40263
Active substance	L04AA29 tofacitinib
Medicinal product	Xeljanz®
Product reference	EU/1/17/1178/003 SUKL code 0222098
Procedure number	N/A
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	The primary objective of this study is to describe and evaluate the changes of depression level within 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression. The secondary objectives of this study are to

	describe and evaluate the level and changes of pain, anxiety, and insomnia in patients with rheumatoid arthritis (RA) and at least minimal level of depression. Additionally, it will describe the safety and effectiveness of tofacitinib for the treatment of RA.
Country of study	Czech Republic
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Marketing Authorization Holder(s)

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2. LIST OF ABBREVIATIONS

Table 1. List of Abbreviations

Abbreviation	Definition
ACR	American Colleague of Rheumatology
AE	Adverse Event
AEM	Adverse event monitoring
ALT	Alanine transaminase
AST	Aspartate transaminase
bDMARD	Biologic Disease Modifying Anti Rheumatic Drug
csDMARD	Conventional Synthetic Disease Modifying Anti Rheumatic Drug
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
CRP	C-reactive Protein
CUDOS	Clinically Useful Depression Outcome Scale
CUXOS	Clinically Useful Anxiety Outcome Scale
CYP	Cytochrome P450
DAS	Disease Activity Score
DCT	Data Collection Tools
DMARD	Disease Modifying Antirheumatic Drug
eCRF	electronic Case Report Form
EDP	Exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-3L	EuroQol five dimensions three level
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GPP	Good Pharmacoepidemiology Practices
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
JSEQ	Jenkins Sleep Evaluation Questionnaire
LDA	Low Disease Activity
LFT	Liver function test
LSLV	Last subject, last visit

Abbreviation	Definition
MAH	Marketing Authorization Holder
MAPK	Mitogen-activated protein kinase
MTX	Methotrexate
NI	Non-interventional
NIS	Non-Interventional Study
NSAID	Nonsteroidal Anti-Inflammatory Drugs
PASS	Post-authorization safety study
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PT	Prothrombin time
PtGA	Patient's Global Assessment of Health
PY	Patient years
RA	Rheumatoid arthritis
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAPK	Stress-activated protein kinases
SJC	Swollen joint count
SmPC	Summary of Product Characteristics
STAT	Signal Transducer and Activator of Transcription proteins
SUKL	State Institute for Drug Control
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumor necrosis factor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
ULN	Upper limit of normal
USA	United States of America
VAS	Visual Analogue Scale

3. RESPONSIBLE PARTIES

Table 2. Responsible Parties Accountable for the Design and Implementation of the Protocol

Name, degree(s)	Title	Affiliation	Address
Martin Kabina, PharmD.	Medical Manager	NI Study Lead	Pfizer spol. s. r. o. Radlická 1c Praha 5
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Table 3. Country Coordinating Investigator and Principal investigator of the protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

In Annex 1 as a standalone document.

5. AMENDMENTS AND UPDATES

Table 4. Amendments and Updates

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 substantial	18 June 2021	6 Milestones	Milestones were updated.	The milestones were adjusted to reflect the current recruitment rate.
		7 Rational and background	Updated details of previous studies to align with current knowledge.	Updated information.
		8.1.2 Secondary endpoint	Added safety endpoints.	To align with PASS requirements.
		9.2 Setting	Changed the definition of loss to follow-up. Enrollment months increased from 24 to 48 Clarified CUDOS score Updated study visit attendance and added further criteria for clarity	The definition was previously wrong and was now corrected.
		9.2.2 Exclusion criteria	Deleted criteria.	Patients will be prescribed study drug according to standard of care; therefore, some exclusion criteria were not required.
		9.3 Variables	Safety variables added.	The study meets criteria for being considered a PASS.
		9.3 Variables 9.4.1 Study procedures 9.4.1.2 Schedule of activities	Assessment of satisfaction with treatment will not be collected. Removed variable ‘current RA treatment with tofacitinib’ and eCRF where it was no longer applicable	Will not be relevant to the final data analysis.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.3 Variables 9.4.1 Study procedures 9.4.1.2 Schedule of activities	Physician global assessment will not be collected.	Will not be relevant to the final data analysis.
		9.4 Data source	Added details about data flow in CRF.	For clarification.
		9.4.3 Assessments – Efficacy	Updated patient assessments. Clarification that CRP and ESR are not required per protocol and that disease activity indicator (DAS 28) is evaluated as standard of care assessment.	For clarification.
		9.4.4.1 Safety Criteria	Section was updated to contain more clarity.	For clarification.
		9.6 Data Management	Process of Patient reported outcome (PRO) completion and processing updated.	For clarification.
		9.7.2 Efficacy analysis	Deleted details about EQ-5D-3L PRO.	These details will be documented in the SAP and are not required in the protocol.
		9.7.4 Interim analysis	Details regarding Statistical Analysis Plan were added.	Clarification where methodology of statistical analysis can be found.
		9.8 Quality control	Data review and data cleaning processes were added.	Details on how data will be reviewed and cleaned were missing and were added.
		10.5 Ethical conduct of the study	Not applicable requirements were deleted and only local and study specific requirements were kept.	This section was adapted to the study type and the location. Only applicable requirements were kept in this paragraph.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		11.1 Safety requirements (Table 9)	Added the list of AEs which have to be reported to the sponsor.	These changes were made to align with the processes of the sponsor.
		Section 12	Updated submission timeline to SUKL from 150 days to 12 months.	To align with internal timelines.
		Throughout the protocol	Change the time window for the 12 months visit from ±30 days to ±45 days for V3. Minor editorial updates throughout	This change was decided to allow more flexibility.

6. MILESTONES

Table 5. Milestones

Milestone	Planned date
Start of data collection	01 June 2019
End of data collection	22 Jan 2024
Registration in the EU PAS register	30 April 2021
Final study report	21 December 2024

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint inflammation and destruction, progressive disability and adverse psychological effects.[1] Apart from the risk of suffering from musculoskeletal complications directly related to their rheumatic disease, RA patients are also at risk of suffering from other diseases called co-morbidities. Such risk seems to be higher in RA than in the general population in particular with regard to some particular diseases (eg, cardiovascular and infectious diseases, osteoporosis, and some cancers).[2]

Such increased risk in comparison to the general population can be explained by both the treatment of RA (eg, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs)) and also by the systemic inflammation observed in RA.

RA represents significant health and socioeconomic burdens for the individual patient and society. There is currently no cure for RA. The purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, reduce the rate of joint damage, and, if possible, induce complete remission.

Tofacitinib is an oral Janus kinase (JAK) inhibitor that targets inflammation by reducing pro-inflammatory cytokine signaling and production.[3] Tofacitinib acts inside the cell by preferentially inhibiting signaling by cytokine receptors associated with JAK1 or JAK3.[4] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL) -2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN) γ.[5,6] At higher exposures, inhibition of erythropoietin, prolactin, and other hormones can occur via inhibition of JAK2 signaling.

The efficacy and safety evaluation of tofacitinib for the treatment of RA is based on a comprehensive clinical development program including six randomized, double-blind, multi-center Phase III studies in adult subjects with active in rheumatoid arthritis (RA). In these trials tofacitinib consistently reduces signs and symptoms of RA, improves physical function and other patient-reported outcomes such as fatigue, pain, and health-related aspects of quality of life in patients with moderate to severe RA. Combined with its inhibition of the progression of structural damage, the clinical development program has demonstrated tofacitinib as an effective targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) in treating RA.[7-12] Long-term extension studies demonstrated sustained efficacy and a consistent safety profile as seen in the Phase 2 and 3 controlled clinical trials.[13,14]

The post hoc analysis of SF-36 Mental Component Summary score in tofacitinib Phase 3 and 3b/4 clinical trials showed a significantly greater improvement in "probable major depressive disorder" and in "probable generalized anxiety disorder" in RA patients treated with tofacitinib versus placebo or adalimumab.[15]

The safety database currently includes data from more than 7000 RA clinical trial subjects with over 22875 patient-years (PYs) of exposure and more than 9.5 years of observation.[16,17] However, these trials may have limitations reflecting real world situations. It has been estimated that only 21-33% of patients documented in registries, reflecting more accurately routine care, would have met eligibility criteria of major trials as they often exclude patients with co-morbidities.[18] It is furthermore well known that RA is a systemic inflammatory disease, and that it is associated with increased cardiovascular risks and respiratory problems.[19] Compared with controls, people with RA have increased rates of lung disease, are twice as likely to suffer from diabetes mellitus, eight-times as often from hypertension and almost four-times as often from osteoporosis.[20] Also treatment of patients in daily clinical practice may vary from strict regulations in clinical trials.

By targeting intracellular JAK tofacitinib represents a new class of oral DMARDs. All other available therapy options given after failure of methotrexate (MTX) and other csDMARDs are administered parenterally. It has been shown that up to 22% of patients have difficulties injecting to themselves [21] and that around 40% of patients discontinuing bDMARD treatment, reported the need for self-injection as one reason for discontinuation.[22] Additionally data from different surveys confirmed a patient preference for an oral application.[23,24] However data on influence of the route of administration on drug survival, patient satisfaction and quality of live are still limited.

The prevalence of psychological and psychiatric comorbidities (depression, anxiety, sleep disturbances) is increased in patients with rheumatoid arthritis (RA) similarly to other progressive rheumatologic diseases. These conditions substantially influence the patient´s quality of life and therefore merit further investigation and better understanding. Several studies have investigated the prevalence of psychological comorbidities in RA patients, but the literature data revealing the influence of the novel biologic therapy on the occurrence or severity of these comorbidities are inadequate.[25]

Patients with chronic pain often suffer from pain-related anxiety, overall affecting physical, social and emotional functioning of the patients.[26,27] The retrospective study from Taiwan with 3657 RA patients and 14628 controls with 10 year follow-up showed 2.06 higher risk of developing the depressive disorders in RA patients compared to the general population ($p < 0.001$).[28] These results are supported by study comparing two commonly used anxiety and depression scales in 169 RA patients.[29] Interestingly, there might be also increased prevalence of bipolar disorder in RA patients.[30]

The high influence of psychological factors on quality of life in RA and psoriatic arthritis patients was revealed in study with 282 patients. The prevalence of moderate to severe levels of depressive symptoms was found in 25.1% RA patients.[31]

These psychological conditions can be attributable to the psychological stressors and physical impairment in medically ill patients. Recently, data were published suggesting that the activation of the immune system that results in the higher activity of cytokines such as TNF-α, IFN-α, IL-1 and IL-6 can be involved in pathogenesis of psychological comorbidities. A possible common thread linking inflammation in RA to cytokine responses that are strongly implicated in the pathogenesis and progression of clinical depression probably involves activation of stress-activated protein kinases/mitogen-activated protein kinases (SAPK/MAPK) and Janus kinases/signal transducer and activator of transcription proteins (JAK/STAT) pathways by pro-inflammatory cytokines.[32] Animal model was used to investigate the role of Janus kinase in major depressive disorder. The data show that stress reduces neurogenesis, which is restored by application of Jak-3 inhibitors. Inhibition of neurogenesis correlated with an anxious-depressive behavior that was also normalized upon application of Jak-3 inhibitor.[33]

Overall, the occurrence of depression, pain, anxiety, and sleep disturbances can be connected to RA. As expected, these comorbidities lead to the prescription of the analgesics (opioid, non-opioid, adjuvants), anxiolytics, antidepressants and/or hypnotics. Whether the use of JAK inhibitor in the treatment of the primary disease is associated with change in the prevalence or severity of these comorbidities is not well known. This prospective, observational, non-interventional study aims to assess the changes in the level of depression in RA patients. This study will enroll patients with at least a minimal level of depression (by CUDOS scale) which is a sub-population of RA patients which has not been sufficiently described in the previous trials and the information is thus limited.

This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to describe and evaluate the changes of depression level within 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression. The primary goal is to find out if treatment by tofacitinib reduces the depression by at least 10% during 12 months, based on the Clinically Useful Depression Outcome Scale (CUDOS) score.

The secondary objectives of this study are to describe and evaluate the level and changes of pain, anxiety, and insomnia in patients with RA and at least minimal level of depression. Additionally, it will describe the safety and effectiveness of tofacitinib for the treatment of RA.

8.1. Endpoints

8.1.1. Primary Endpoint

The primary endpoint of the study is:

- Relative change between visit 3 and baseline of Clinically Useful Depression Outcome Scale (CUDOS) score.

8.1.2. Secondary Endpoints

The secondary endpoints of this study are:

- Baseline value and relative change between visit 2 and baseline of CUDOS score.
- Baseline value and relative change between visit 2 and baseline and between visit 3 and baseline of Clinically Useful Anxiety Outcome Scale (CUXOS), Jenkins Sleep Evaluation Questionnaire (JSEQ) and Visual Analog Scale (VAS) score for evaluation of anxiety, insomnia, and arthritis assessment.
- Baseline counts of concomitant medication (antidepressants, analgesics, anxiolytics, and hypnotics) together with doses for each and the change in number of used medications and in their dosage between visit 3 and baseline.
- Baseline value and absolute change between visit 2 and baseline and between visit 3 and baseline of DAS28-4 (Erythrocyte sedimentation rate (ESR)), DAS28-4 (C-reactive protein (CRP)).
- Remission as assessed by: DAS28-4 (ESR) <2.6 or DAS28-4 (CRP) <2.6.
- LDA as assessed by: DAS28-4 (ESR) <3.2 or DAS28-4 (CRP) <3.2.

- Change from Baseline in EuroQol Three Dimension – 3L (EQ-5D-3L) Health State Profile.

- Incidence of any adverse event (AE) reported by the patient or investigator

9. RESEARCH METHODS

9.1. Study Design

This is a 12-month, single arm, prospective cohort, non-interventional, multi-center study according to Czech legal definitions (Law 378/2007 Sb.).

Data for the study will be obtained from clinical practice records and patients printed questionnaires and transcribed to an anonymous electronic case report form (eCRF).

The primary aim of the study is to review the changes of depression after first year of tofacitinib (XELJANZ®) treatment in rheumatoid arthritis patients. For the description and evaluation of depression in RA patients the prospective data from a 12-month follow-up will be used. The depression assessment will be performed by using the CUDOS questionnaire[34] in form of a printed patient questionnaire presented to patients on each study visit.

For the description and evaluation of arthritis, anxiety, and insomnia in RA patients with at least minimal depression (as per CUDOS questionnaire) the prospective data from a 12-month follow-up will be used. The patient assessment of arthritis, anxiety and insomnia will be performed by using the 100mm VAS scale, CUXOS[35] and JSEQ[36] questionnaire, respectively, in form of a printed patient questionnaire presented to patients on each study visit.

The study follows one cohort of patients who were newly prescribed tofacitinib at baseline and who scored at least 11 points on CUDOS scale (equivalent of minimal depression).

There are 3 visits planned for each patient:

- Visit 1 (start of tofacitinib treatment).

- Visit 2 (6 months after start of tofacitinib treatment).

- Visit 3 (12 months after start of tofacitinib treatment).

Observation period: Eligible patients will be followed from the date of first tofacitinib prescription until study end, death, or loss to follow-up (whichever comes first) for the occurrence of the endpoints of interest.

In this study, tofacitinib is prescribed in the usual manner in accordance with the terms of the marketing authorization.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by this protocol but falls within current practice and the prescription of the medicine should be clearly separated from the decision to include the patient in the study.

No additional diagnostic or monitoring procedures will be applied to the patients and follow-up visits are captured as part of normal medical practice. Investigators will be actively asking patients about the occurrence of any AEs. Epidemiological methods will be used for the analysis of collected data.

All patients are required to sign a written consent form with their participation in this study. All assessments except CUDOS, CUXOS and JSEQ described in this protocol are performed only when directed by the treating physician as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the Czech Republic where this non-interventional study is being conducted.

9.2. Setting

This non-interventional study follows the population of 154 patients with moderate to severe rheumatoid arthritis, which were currently prescribed tofacitinib treatment for the first time and who scored at least 11 points on CUDOS scale (equivalent of minimal depression).

Patients will be followed for the period of 12 months and are likely to have a total of 3 visits per patient as per common medical care.

The data will be collected by physicians allowed (according to indication restriction of reimbursement) to prescribe tofacitinib and, in the same time are specialized in the treatment of rheumatoid arthritis – rheumatologists. The total number of 10 to 20 out-patient physicians will be involved.

Requirements for the physician´s eligibility are as followed: out-patient setting of the clinical practice, satisfactory experience in the care of patients with rheumatological diseases, and sufficient number of patients with diagnosis of rheumatoid arthritis.

It is expected (based on the clinic experience) that the patients will be enrolled within 48 months from the start of the study – the enrollment of new subjects will be closed as soon as there are 154 patients enrolled. If there are not 154 patients enrolled within 48 months, the enrollment period can be prolonged as required. The aim of the study is to provide additional information on the population of RA patients with depression. Only patients with at least minimal level of depression score ≥11 (as per CUDOS questionnaire score ranging 0 to 72) may be included, as per the inclusion criteria. This setting will ensure the ability of this study to assess changes of depression and changes of arthritis, anxiety, and insomnia outcomes in correlation to depression level of enrolled patients.

Subjects may be discontinued for the following reasons:

- The switch to a different treatment (for any reason – eg, new contraindication as per Summary of Product Characteristics (SmPC), tofacitinib interaction with other medicine, adverse reactions).
- Non-compliance with the study schedule – the patient not coming for the planned study visit (which by the non-interventional setting of the study has to be planned for the same date as the visit planned within normal clinical practice). The period for study visit attendance is ±30 days for V2 and ±45 days for V3.

Study flow:

- Patient signed informed consent.
- Evaluation of inclusion/exclusion criteria.
- Patient enrollment.
- Visit 1 (Baseline visit) (start of tofacitinib treatment).
  - eCRF completion.
  - Completion of printed patient questionnaires.
- Visit 2 (6 months ±30 days after start of tofacitinib treatment):
  - AE detection, processing, and reporting, if applicable.
  - eCRF completion.
  - Completion of printed patient questionnaires.
- Visit 3 (12 months ±45 days after start of tofacitinib treatment):
  - AE detection, processing, and reporting, if applicable.
  - eCRF completion.
  - Completion of printed patient questionnaires.

9.2.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study.

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

1. Patients aged ≥18 years.
2. Moderate to severe activity of rheumatoid arthritis (DAS28 ≥3.2).
3. Patient for whom the physician decision has been made to initiate a treatment with tofacitinib.
4. Patient with at least minimal level of depression (CUDOS questionnaire ≥11 points).
5. Capable of understanding and signing a written informed consent form.
6. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study is a requirement for inclusion into this study.

9.2.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patients unwilling/unable to fill in printed patient questionnaires.

9.3. Variables

Table 6. Study Variables

Variable	Role	Data Source(s)	Operational Definition
RA treatment with tofacitinib – date of initiation	Exposure, Potential confounder, subgroup identifier	Case records	Details will be provided in Statistical Analysis Plan
RA treatment with tofacitinib – dose	Exposure, Potential confounder, subgroup identifier	Case records	Details will be provided in Statistical Analysis Plan
RA treatment with tofacitinib - tolerability	Potential confounder, subgroup identifier	Case records	Details will be provided in Statistical Analysis Plan
Age	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Gender	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Height	Baseline characteristic,	Case records	Details will be provided

Variable	Role	Data Source(s)	Operational Definition
	potential confounder, sub-group identifier		in Statistical Analysis Plan
Weight	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Smoking history and current smoking status	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Alcohol intake	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Date of first diagnosis of RA	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Co-morbidities	Baseline characteristic, potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Prior pharmacotherapy for RA	Potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Co-medication relevant to RA and mental health	Potential confounder, sub-group identifier	Case records	Details will be provided in Statistical Analysis Plan
Patient Assessment of Depression (CUDOS)	Baseline and Outcome	Printed questionnaire	Details will be provided in Statistical Analysis Plan
Patient Assessment of Arthritis	Baseline and Outcome	Printed questionnaire	Details will be provided in Statistical Analysis Plan
Patient Assessment of Anxiety (CUXOS)	Baseline and Outcome	Printed questionnaire	Details will be provided in Statistical Analysis Plan
Patient Assessment of Insomnia (JSEQ)	Baseline and Outcome	Printed questionnaire	Details will be provided in Statistical Analysis Plan
Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP)	Baseline and Outcome	Case records	Details will be provided in Statistical Analysis Plan
DAS28-4 (CRP) or DAS28-4 (ESR)	Baseline and Outcome	Case records	Details will be provided in Statistical Analysis Plan
EuroQol EQ-5D-3L Health State Profile	Baseline and Outcome	Printed questionnaire	Details will be provided in Statistical Analysis Plan
Occurrence of adverse events	Outcome	Case records and eCRF	Details will be provided in Statistical Analysis Plan

9.4. Data Sources

This is a multisite study and includes private outpatient clinics and hospitals. The data will be recorded using an electronic case report form (eCRF) and printed patient questionnaires for each patient included. The completed original eCRFs and printed questionnaires are the sole property of Pfizer and must not be provided to third parties in any format without the written approval of Pfizer, with the exception of authorized representatives of Pfizer or the appropriate competent authorities.

The treating physician is ultimately responsible for the collection and reporting of all clinical data, safety and laboratory data entered on the eCRFs and other forms for data collection (source documents) and must guarantee that they are accurate, authentic/original, traceable, complete, consistent, legible, timely (contemporaneous), permanent, and available as required. The eCRFs must be sent by the treating physician or authorized personnel. Once sent through the web interface (browser), the data is backed-up on the encrypted and secured server. Once sent, the data cannot be modified. Incomplete forms can be also saved by the physician and the session can be completed upon the next login.

The treating physician is ultimately responsible for the distribution and re-collection of printed questionnaires from enrolled patients and must guarantee that they are correctly identified and available as required (once completed by a patient).

All corrections of entries on the eCRFs must be explained (reason for change) and properly described. Corrections of entries are recorded by the physician via email to the responsible Contract Research Organization (CRO) (incl. date of correction, old and new value, reason for change).

In most cases, the source documents are patient records in the hospital or at the doctor's office. In these cases, the data collected on the eCRFs must match the data in these records.

The clinical parameters recorded, especially those used to assess efficacy, are usual known, and recognized variables within each respective indication. All questionnaires used in the study (CUDOS, CUXOS, JSEQ) have been validated.

9.4.1. Study Procedures

Consecutive patients attending will be included if they fulfil all selection criteria for the study and are started on treatment with tofacitinib for moderate to severely active rheumatoid arthritis and (as per CUDOS evaluation criteria) have at least minimal level of depression.

All visits shall be scheduled according to clinical practice. Within this study 3 visits may be documented. At each visit patients will undergo procedures in compliance with the country label and as per standard of care. In order to collect comparable study data, visits occurring ±30 days for V2 and ±45 days for V3 of the scheduled visit date can be documented.

After a training session the sites will get access to the eCRF, where the data and findings of the patient are documented. Additionally, a folder with printed patient questionnaires will be provided. The collection of all data is prospective.

Dose and duration of treatment should be based on clinical and individual needs and are determined by the treating physician. To provide accurate information of the treatment, the initial tofacitinib dose and all changes and the reasons for changes are documented during the course of the evaluation. The concomitant medication is determined by the treating physician and is registered in the documentation sheet.

9.4.1.1. Study Period

The planned observation period of each patient is 12 months. In this time period up to 3 visits will be documented.

9.4.1.1.1. Baseline Visit

Following parameters will be documented at baseline visit:

- Informed Consent.
- Inclusion/Exclusion criteria according to protocol and SmPC.
- Duration since diagnosis.
- Demography.
- Prior drug treatment of RA.
- Treatment of RA with tofacitinib.
- Concomitant drug treatment relevant to RA or mental health.
- Comorbidities.
- CUDOS questionnaire.
- CUXOS questionnaire.
- JSEQ questionnaire.
- Patients Assessment of Arthritis.
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).
- DAS28-4 (CRP) and/or DAS28-4 (ESR).
- EuroQol EQ-5D-3L Health State Profile.

9.4.1.1.2. Scheduled Visit 2 – Visit 3/Month 6 – Month 12

Following parameters will be documented at each visit:

- Treatment of RA with tofacitinib.
- Concomitant drug treatment relevant to RA or mental health.
- CUDOS questionnaire.
- CUXOS questionnaire.
- JSEQ questionnaire.
- Patients Assessment of Arthritis.
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).
- DAS28-4 (CRP) and/or DAS28-4 (ESR).
- EuroQol EQ-5D-3L Health State Profile.
- Adverse event monitoring.

9.4.1.2. Schedule of Activities

The Schedule of Activities table provides an overview of the visits that may be documented.

According to his/her clinical practice the investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities (see the table below); in order to conduct evaluations or assessments required to protect the well-being of the patient. As this is a non-interventional study the study visits should be scheduled according to clinical practice.

Table 7. Schedule of Activities

Study Week	**Baseline (Enrollment)**	**Month 6**	**Month 12**
Visit Number	**1**	**2**	**3**
Protocol required assessments			
Inclusion/exclusion criteria	x		
Informed Consent	x		
Safety			
Documentation of AE (		x	→
Standard of care assessment			
RA Duration	x		
Demographic data	x		
Documentation of Comorbidities	x		
Treatment/Medication			
Prior RA treatment	x		
RA treatment with tofacitinib	x	x	x
Concomitant drug treatment relevant to RA and mental health	x	x	x
Assessment of Disease activity based on CRP and/or ESR	x	x	x
DAS28-4 (CRP) and/or DAS28-4 (ESR)	x	x	x
Protocol-Required Efficacy Assessments			
Efficacy			
Patient Assessment of Depression (CUDOS)	x	x	x
Patient Assessment of Anxiety (CUXOS)	x	x	x
Patient Assessment of Insomnia (JSEQ)	x	x	x
Patient Assessment of Arthritis	x	x	x
EuroQol EQ-5D-3L Health State Profile	x	x	x

9.4.2. Assessments – Treatment/Medication

9.4.2.1. Prior Treatment of Rheumatoid Arthritis (RA Treatment)

Prior RA treatment (name of medicinal product or active substance) will be recorded at the Baseline Visit (Visit 1). In case of prior biologic RA treatment, the reason for change will be recorded.

9.4.2.2. RA Treatment with Tofacitinib

At each visit dose of treatment with tofacitinib will be documented. In case of tofacitinib discontinuation the reason will be recorded in eCRF.

9.4.2.3. Concomitant Treatment

Relevant concomitant RA medication (Methotrexate YES/NO and its dosing + other current RA medication) will be recorded at the Baseline Visit (Visit 1). At each subsequent visit such concomitant treatment will be documented.

Other relevant concomitant drug treatment (active substance and dosing of antidepressants, anxiolytics, hypnotics, and analgesics) will be recorded at the Baseline Visit (Visit 1). At each subsequent visit such concomitant treatment will be documented.

9.4.3. Assessments – Efficacy

9.4.3.1. Patient Assessment of Depression

The CUDOS questionnaire assesses the level of depression in the past week. It consists of 18 statements. For each statement of the questionnaire the patient indicates how well it describes his feelings during past week: 0 – not at all true, 1 – rarely true, 2- sometimes true, 3 – often true, 4-almost always true. The score ranges from 0 to 72, the higher the score, the more severe the depression. Further details will be included in the SAP. The form should then be checked by the site staff for completeness.

9.4.3.2. Patient Assessment of Anxiety

The CUXOS questionnaire assesses the level of anxiety in the past week. It consists of 20 statements. For each statement of the questionnaire the patient indicates how well it describes his feelings during past week: 0 – not at all true, 1 – rarely true, 2- sometimes true, 3 – often true, 4-almost always true. The score ranges from 0 to 80, the higher the score, the higher the anxiety level. Further details will be included in the SAP. The form should then be checked by the site staff for completeness.

9.4.3.3. Patient Assessment of Insomnia

The JSEQ questionnaire (Jenkins Sleep Evaluation Questionnaire) assesses the level of insomnia, sleep disturbance in the past month. It consists of 4 questions related to 1) trouble falling asleep, 2) trouble staying asleep, 3) waking up several times per night, and 4) waking up feeling tired and worn out after a usual amount of sleep. The response alternatives are not at all (0), 1-3 days (1), 4–7 days (2), 8–14 days (3), 15–21 days (4), and 22–30 days (5). The score ranges from 0 to 20, the higher the score, the lower the sleep quality. Further details will be included in the SAP. The form should then be checked by the site staff for completeness.

9.4.3.4. Patient Assessment of Arthritis

Patients will assess how much arthritis impacting their life using a 100 mm visual analogue scale (VAS) by placing a mark on the scale between 0 (not affecting) and 100 (maximal impact), which corresponds to the level arthritis affects their life. Further details will be included in the SAP. The form should then be checked by the site staff for completeness.

9.4.3.5. C-reactive Protein (CRP) and/or Erythrocyte Sedimentation Rate (ESR)

CRP and ESR measurements are not required by the protocol and will be recorded in the eCRF if they were assessed as standard of care.

9.4.3.6. DAS28

The DAS28 is evaluated as standard of care and will be recorded in the eCRF if available.

The effectiveness of the treatment with tofacitinib will be documented using, one of the following tools for the evaluation of the course of the disease:

Table 8. Disease Activity Indicators

Indicator	Definition
DAS28-4 (CRP)	$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.36 \times \ln$ (CRP in mg/l +1) + 0.014 × PtGA in mm + 0.96
DAS28-4 (ESR)	$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times$ In (ESR in mm/ hour) + 0.014 × PtGA in mm

TJC = tender joint count; SJC = swollen joint count; CRP = C-reactive protein in mg/L; ESR = erythrocyte sedimentation rate in mm/first hour, PtGA = Patient's global assessment of health.

9.4.3.7. EuroQol EQ-5D-3L Health State Profile

The EuroQol EQ-5D-3L Health State Profiles a copyrighted, patient completed instrument designed to assess impact on health-related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. Further details will be included in the SAP. The validity and reliability of the EuroQol EQ-5D-3L has been established in a number of disease states, including rheumatoid arthritis. The form should then be checked by site staff for completeness.

9.4.4. Assessments – Safety

9.4.4.1. Safety Criteria

In contrast to the usual procedure for clinical trials in observational studies the treatment decision is independent of the protocol. Additionally, selection criteria of patients at baseline are not as strict as for clinical trials. Thus, this study can provide new insights into the safety of tofacitinib in routine care. At each visit after initiation of tofacitinib, the patient will be asked for the occurrence of adverse events. All adverse events (AEs) will be documented in the eCRF and if applicable reported to the sponsor's safety unit, as indicated in Table 9.

9.5. Study Size

The goal of the study is to describe the change of the CUDOS score after 12 months of treatment – to assess the change in depression after the treatment. Since the hypothesis lies in the relative decrease, t-test is used to test the null hypothesis that the ratio between the score after and before the therapy equals to 1 against the alternative that there is percentage difference in score after and before the treatment. The sample size is computed to detect the reduction of score by 10%, which is expected by current research articles.

The sample size is calculated for paired t-test of logarithm of CUDOS score with 5% alpha level, power 90% and two-sided alternative. For the calculation, it is assumed that the score is reduced by 10% after the therapy. Standard deviation is based on assumption that mean baseline score is 27.9 with standard deviation 9.9[1] and decreases by 10% to mean value score 25.1 keeping the same standard deviation 9.9 after the therapy. Correlation between the second and first measurement is expected to be 0.5, which is based on expert opinion.

To have the sufficient 90% power at least 123 patients need to be analyzed. When include a 20% drop-out rate, 154 patients need to be recruited in total.

9.6. Data Management

Patients' personal data will be collected, stored, and processed exclusively in anonymized form in accordance with the national data protection laws. All data will remain in anonymized form. The data will not be used for any other purposes other than for the research which is described in the patient information and the declaration of consent. During the conduct of the study, Value Outcomes undertakes responsibility to guarantee data protection and will adhere to all applicable laws and regulations on data protection.

All study data will be recorded by the study sites in the electronic case report form system. Access to the system takes place via a secure website. Access is only given to registered users who log in with a unique username and password. Access rights to the eCRF system are monitored by authorized employees of Value Outcomes.

Patients complete paper patient reported outcomes (PROs) at visit, the results are manually entered in the eCRF by site personnel. A copy of the anonymous patient questionnaires will be provided in paper form to Value Outcomes for verification (eCRF versus source paper form). Automatic checks of the data for plausibility and completeness using programmed so-called edit checks will take place already during electronic data entry by the study site. Other discrepancies will be clarified additionally with the study site using manual queries.

Due to the non-interventional nature of the study, the extent of data cleansing is limited and missing and/or implausible values are to be anticipated at the end of the study. In the Statistical Analysis Plan, handling of these values will be described in detail.

Confirmation of the data collected is required by final submission of the eCRF by the physician.

9.6.1. Electronic Case Report Forms (eCRFs)

As used in this protocol, the term eCRF should be understood to refer to an electronic data record.

An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the eCRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the eCRFs must match those charts. In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

This section gives an overview of the key methods and derivations required for the study.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. STATA (StataCorp LP, USA Version 13.1 or above) will be used for all analyses.

Unless specified otherwise, continuous variables will be summarized using descriptive statistics (n, mean, SD, median, min, max) and discrete variables will be summarized using counts and percentages. To access drop-out, study flow-chart (patient disposition) between visits will be preset.

All adverse events will be presented as absolute numbers, frequency, and line-listings.

9.7.1. Analysis Populations

The Full Analysis Set is defined as patients who receive at least one dose of tofacitinib and have the data for evaluation of primary hypothesis, which means CUDOS score reported both at baseline and visit 3. This population will be used for all efficacy analysis. Details of any methods employed to deal with missing data will be outlined in the SAP.

The Safety Analysis Set is defined as all patients who receive at least one dose of tofacitinib. This population will be used for all safety analysis.

9.7.2. Efficacy Analysis

9.7.2.1. Primary Analysis

The ratio of CUDOS at visit 3 and baseline CUDOS score will be described as continuous variable, together with geometric mean. The primary hypothesis about relative decrease in CUDOS score will be tested by ratio t-test with hypothesis that the ratio of CUDOS at visit 3 and baseline CUDOS equals 1 against two-sided alternative with alpha level 0.05.

Furthermore, the primary endpoint will also be assessed in the original metric of measure using a paired t-test, details will be specified in the SAP.

9.7.2.2. Secondary Analysis

The baseline CUDOS score and the ratio of CUDOS at visit 2 and baseline CUDOS will be described as continuous variables. For the ratio geometric mean will be presented too. When the primary hypothesis test reaches significance and primary hypothesis is rejected, the same test will be performed for ratio of CUDOS at visit 2 and baseline to examine if the effect of the treatment was already present after 6 months to describe the effect in more detail. Because of the fixed sequence of testing, no adjustment of alpha value is needed.

9.7.2.2.1. Anxiety, Insomnia and Arthritis

Anxiety, insomnia, and arthritis assessment will be accessed via particular questionnaire scores (CUXOS, JSEQ, VAS scale). Each score will be summarized at baseline, as ratio of value at visit 3 and baseline value and as ratio of value at visit 2 and baseline value. For ratios geometric means will be presented too. The efficacy in secondary endpoints will be accessed via hierarchical testing separately, eg, the ratio of value at visit 3 and baseline will be tested by ratio t-test and only if this test reaches significance, the same test of ratio of value at visit 2 and baseline will be performed with the same alpha level.

9.7.2.2.2. Antidepressants, Analgesics, Anxiolytics and Hypnotics

The number and percentage of patients who dropped/started concomitant treatment between baseline, visit 2 and visit 3 will be reported, as well as the summary of changes in dosing in concomitant treatment between baseline and visit 2 and between baseline and visit 3 if relevant data will be available. These descriptive statistics will be presented for each group of treatment (antidepressants, analgesics, anxiolytics, and hypnotics) separately.

9.7.2.2.3. DAS28-4 (ESR), DAS28-4 (CRP)

For DAS28-4 (ESR), DAS28-4 (CRP) physicians will be asked to provide a final value (depends on which scale do they use in their common clinical practice). The summary statistics of the baseline value and the absolute change from baseline at each visit will be reported.

9.7.2.2.4. Rate of Remission, LDA

The rate of Remission and LDA will be presented as frequency and proportion of the patients achieving the relevant criteria at each time point.

Where:

- Remission is defined as DAS28-4 (ESR) <2.6 or DAS28-4 (CRP) <2.6.
- LDA is defined as DAS28-4 (ESR) <3.2 or DAS28-4 (CRP) <3.2.

9.7.2.2.5. EQ-5D-3L

The EQ-5D-3L is a standardized instrument used to measure quality of life. It is based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 responses and the patient is asked to select the response that best describes them.

9.7.3. Safety Analysis

Adverse events will be reviewed and summarized on ongoing basis during the study to evaluate the safety of patients. Safety data will be presented in tabular and/or graphical format showing absolute numbers, frequency and summarized descriptively.

9.7.4. Interim Analysis

An interim analysis will not be performed in this study. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

The Sponsor delegates the conduct of this non-interventional study (NIS) to the Contract Research Organization named Value Outcomes. Study Coordination has been assigned to Project Manager and central as well as remote monitoring is conducted by Data Manager.

Completeness and quality of data recorded in the eCRF will be regularly monitored by Data Manager. The schedule is detailed in the Monitoring plan. If in doubt a query will be raised to the investigator via Email. Data Manager creates an Error report based on the email (including date of correction, old and new value, reason for change). The dataset is backed-up in regular periods so that an audit trail is available.

If there is missing, unused, or inconsistent data, Data Manager will query the site to complete missing data. The formal-logic control of data will be done at the beginning of statistical analysis for detection of missing numbers, unused or inconsistent data via automated quality checks and by manual reviews, as well. Missing data handling is specified in the Statistical Analysis Plan.

9.9. Limitations of the Research Methods

Randomized controlled trials are important and powerful tools in assessing efficacy and safety but have their limitations in terms of generalizability. In order to assess clinical effectiveness and safety of tofacitinib in a usual care setting, parameters need to be determined by performing observational studies.

Inherent limitations of non-interventional, observational, non-controlled, non-randomized studies in general are the risk of selection/ascertainment bias and lack of a parallel control group, which complicate the interpretation of the causality between treatment and outcomes. Furthermore, as with any "as observed" analysis, there is a potential risk of bias due to missing outcome data; the risk increases with increasing number of missing outcome data.

As data captured will be limited to information available from the physician participating in the study under a usual care setting, there is a greater possibility that there will be individual items of missing data (eg, CRP not measured). If the different factors being considered in the primary statistical model to look at impact of treatment change are highly correlated it may not be clear which of the factors is in fact driving the rate of treatment escalation. Other sensitivity analyses may be explored to assess the impact of any confounding. Further details will be included in the SAP.

Patients selected for study inclusion represent a population who are initiated on tofacitinib as part of a usual care setting. The sample of patients will be obtained from physicians who are willing to participate in the study and there is a possibility that certain types of patients will be selected to be prescribed tofacitinib (selection bias) and join the study and this could potentially have an impact on findings of the primary analysis (if the 'type' is expected to impact the rate of treatment escalation). Therefore, study findings may not be generalizable to all RA patients.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. 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.

10.2. 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.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

10.3. 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 possible. The investigator should 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.

If the patient voluntarily withdraws from the study or he/she is discontinued at the discretion of the investigator, the investigator shall inform the CRO within next 10 working days.

10.4. 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, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Requirements

The table below summarizes the requirements for recording safety events on the eCRF 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 AEs (as applicable); and (3), scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of Safety Events".

Table 9. Safety Requirements

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	- Effect on Vaccination Efficacy and the use of Live/Attenuated Vaccines, which are Derived from Disease-Causing Pathogens such as Bacteria or Viruses that have been Weakened under Laboratory conditions - Viral infection after receiving a type of vaccine containing weakened virus (primary viral infection following live vaccination) - Cancer (malignancy) - Heart (cardiovascular) risk - A hole or tear through the stomach, large bowel, or small intestine (gastrointestinal perforation) - A group of lung diseases that affects the tissue and space around the air sacs of the lungs, which can lead to inflammation and scarring (interstitial lung disease) - Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents - Increased risk of adverse events when tofacitinib is administered in combination with methotrexate in RA or PsA patients - Risk of increased exposure to tofacitinib with certain medications such as ketoconazole or fluconazole (increased exposure to tofacitinib when coadministered with CYP3A4 and CYP2C19 inhibitors)

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
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). Note: Any associated AE is reported together with the exposure scenario.

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

Safety events listed in the table above must be reported to Pfizer Safety 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 tofacitinib.** In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety 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 safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer Safety within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer Safety in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event 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 Safety or its designated representative.

11.1.1. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of tofacitinib or the time of the patient's informed consent if she/he is being treated with tofacitinib at study start, 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 (eg, patient changes his/her mind about participation), 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, the SAE also must be reported to Pfizer Safety.

11.1.2. 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, 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 tofacitinib causality assessment is the determination of whether there exists a reasonable possibility that tofacitinib caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether tofacitinib 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 did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

11.1.3. Definition of Safety Events

11.1.3.1. 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 adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event).
- 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 adverse event 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 adverse event 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.

11.1.3.2. Serious Adverse Events

A serious adverse event 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 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 (eg, 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 (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, 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 (eg, for work-up of persistent pre-treatment lab abnormality).
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

11.1.4. 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 (eg, environmental) tofacitinib or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to tofacitinib (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, 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 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 exposures 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 this information must be submitted to Pfizer Safety, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure tofacitinib in a pregnant woman (eg, a patient 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labelling or prescription on the part of the healthcare provider or the patient/consumer).
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer Safety, 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 (eg, 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 Safety 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 Safety 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 Safety by the investigator, irrespective of the presence of an associated AE/SAE.

11.2. Single Reference Safety Document

The Xeljanz SmPC 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.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final report of this study will be submitted to SUKL within 12 months after the end of data collection.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the 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.

13. REFERENCES

1. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2007 Dec;13 Suppl 9:S237-251.

2. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2011 Aug;25(4):469–83.

3. Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, et al. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol. 2008 Jan;26(1):127–32.

4. Meyer DM, Jesson MI, Li X, Elrick MM, Funckes-Shippy CL, Warner JD, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm Lond Engl. 2010 Aug 11;7:41.

5. Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol Baltim Md 1950. 2007 Mar 1;178(5):2623–9.

6. O'Sullivan LA, Liongue C, Lewis RS, Stephenson SEM, Ward AC. Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease. Mol Immunol. 2007 Apr;44(10):2497–506.

7. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs - Fleischmann - 2012 - Arthritis & Rheumatism - Wiley Online Library [Internet]. [cited 2021 Mar 30]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/art.33383

8. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):495–507.

9. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012 Apr;64(4):970–81.

10. Kremer J, Li Z-G, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013 Aug 20;159(4):253–61.

11. Burmester GR, Benda B, Gruben D, Bradley J, Mebus C. Tofacitinib for rheumatoid arthritis - Authors' reply. Lancet Lond Engl. 2013 May 25;381(9880):1812–3.

12. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):508–19.

13. Kremer JM, Bingham CO, Cappelli LC, Greenberg JD, Madsen AM, Geier J, et al. 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 Rheumatol. 2021;3(3):173–84.

14. Wollenhaupt J, Lee E-B, Curtis JR, Silverfield J, Terry K, Soma K, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019 Apr 5;21(1):89.

15. Citera G. Tofacitinib in Patients with Rheumatoid Arthritis and Indicative of Depression And/or Anxiety: A Post Hoc Analysis of Phase 3 and Phase 3b/4 Clinical Trials [Internet]. ACR Meeting Abstracts. [cited 2021 Apr 1]. Available from: https://acrabstracts.org/abstract/tofacitinib-in-patients-with-rheumatoid-arthritis-and-indicative-of-depression-and-or-anxiety-a-post-hoc-analysis-of-phase-3-and-phase-3b-4-clinical-trials/

16. Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension Studies over 9 Years - ACR Meeting Abstracts [Internet]. [cited 2021 Mar 30]. Available from: https://acrabstracts.org/abstract/tofacitinib-an-oral-janus-kinase-inhibitor-in-the-treatment-of-rheumatoid-arthritis-safety-and-efficacy-in-open-label-long-term-extension-studies-over-9-years/

17. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020 Oct;6(3).

18. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Nov;54(11):3399–407.

19. Brown KK. Rheumatoid Lung Disease. Proc Am Thorac Soc. 2007 Aug 15;4(5):443–8.

20. Gerhold K, Richter A, Schneider M, Bergerhausen H-J, Demary W, Liebhaber A, et al. Health-related quality of life in patients with long-standing rheumatoid arthritis in the era of biologics: data from the German biologics register RABBIT. Rheumatol Oxf Engl. 2015 Oct;54(10):1858–66.

21. McInnes IB, Combe B, Burmester G. Understanding the patient perspective - results of the Rheumatoid Arthritis: Insights, Strategies & Expectations (RAISE) patient needs survey. Clin Exp Rheumatol. 2013 Jun;31(3):350–7.

22. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence. 2015 Jan 20;9:121–31.

23. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016 Apr;9(2):84–93.

24. Krüger K, Alten R, Schiffner-Rohe J, Behmer O, Schiffhorst G, Rellecke J, et al. THU0350 Patient Preferences in the Choice of Disease Modifying Anti-Rheumatic Drugs. Vol. 74, Annals of the Rheumatic Diseases. 2015. 322 p.

25. Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, et al. Infliximab, a TNF-α antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int. 2012 Feb;32(2):323–30.

26. Strahl C, Kleinknecht RA, Dinnel DL. The role of pain anxiety, coping, and pain self-efficacy in rheumatoid arthritis patient functioning. Behav Res Ther. 2000 Sep;38(9):863–73.

27. Young LD. Psychological factors in rheumatoid arthritis. J Consult Clin Psychol. 1992;60(4):619–27.

28. Wang S-L, Chang C-H, Hu L-Y, Tsai S-J, Yang AC, You Z-H. Risk of developing depressive disorders following rheumatoid arthritis: a nationwide population-based study. PloS One. 2014;9(9):e107791.

29. Covic T, Cumming SR, Pallant JF, Manolios N, Emery P, Conaghan PG, et al. Depression and anxiety in patients with rheumatoid arthritis: prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the hospital, Anxiety and Depression Scale (HADS). BMC Psychiatry. 2012 Dec;12(1):6.

30. Hsu C-C, Chen S-C, Liu C-J, Lu T, Shen C-C, Hu Y-W, et al. Rheumatoid Arthritis and the Risk of Bipolar Disorder: A Nationwide Population-Based Study. Kumar A, editor. PLoS ONE. 2014 Sep 17;9(9):e107512.

31. Kotsis K, Voulgari PV, Tsifetaki N, Machado MO, Carvalho AF, Creed F, et al. Anxiety and depressive symptoms and illness perceptions in psoriatic arthritis and associations with physical health-related quality of life. Arthritis Care Res. 2012 Oct;64(10):1593–601.

32. Malemud CJ, Miller AH. Pro-inflammatory cytokine-induced SAPK/MAPK and JAK/STAT in rheumatoid arthritis and the new anti-depression drugs. Expert Opin Ther Targets. 2008 Feb;12(2):171–83.

33. Gulbins A, Grassmé H, Hoehn R, Kohnen M, Edwards MJ, Kornhuber J, et al. Role of Janus-Kinases in Major Depressive Disorder. Neurosignals. 2016;24(1):71–80.

34. Zimmerman M, Chelminski I, McGlinchey JB, Posternak MA. A clinically useful depression outcome scale. Compr Psychiatry. 2008 Apr;49(2):131–40.

35. Zimmerman M, Chelminski I, Young D, Dalrymple K. A clinically useful anxiety outcome scale. J Clin Psychiatry. 2010 May;71(5):534–42.

36. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol. 1988;41(4):313–21.

14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	18 June 2021	Abstract: A3921330 Non-interventional study to review the changes of depression after first-year of tofacitinib (XELJANZ®) treatment in rheumatoid arthritis patients
2	ANNEX 2	08 June 2021	A3921330 ENCePP checklist

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

In Annex 1 as a standalone document.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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