OBSERVATIONAL PLAN OF THE NON-INTERVENTIONAL STUDY (NIS) ESCALATE-RA

Study information

Title	ESCALATE-RA A NON-INTERVENTIONAL STUDY OF CRITICAL FACTORS FOR ESCALATING DRUG TREATMENT IN PATIENTS TREATED WITH TOFACITINIB FOR MODERATE TO SEVERE ACTIVE RHEUMATOID ARTHRITIS
Protocol number	A3921302
Protocol version identifier	Final 1.1
Date of last version of protocol	23-Aug-2017
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz®
Research question and objectives	The objective of this non-interventional study is to identify key factors that are driving treatment decisions by rheumatologists in the treatment of rheumatoid arthritis (RA) patients starting treatment with Tofacitinib in a real world setting. In addition to disease activity score (DAS) 28, the following factors may play an important role: difference between DAS28 at start of therapy and after 3-6 months, physician's global assessment of disease activity, patients' global assessment of disease activity, arthritis pain and patient

	satisfaction with drug treatment.
Author	PPD

Table 1 Study information

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	Anti-citrullinated protein antibodies
ACR	American Colleague of Rheumatology
AE	Adverse Event
AEM	Adverse event monitoring
AMS	Advanced Medical Services GmbH
BfArM	Bundestinstitut für Arzneitmittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
CAPEA	Course and Prognosis of Early Arthritis
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRA	Clinical Research Associate
csDMARD	Conventional Synthetic Disease Modifying Antirheumatic Drug
eCRF	Electronic Case Report Form
CRP	C-reactive Protein
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
EDC	Electronic Data Capture
EDP	Exposure during pregnancy

EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	a self-report questionnaire (a quality of life instrument) developed by the European Quality of Life (EuroQoL) Group
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EuroQoL	European Quality of Life [Group]
FACIT	Functional Assessment of Chronic Illness Therapy
FFbH	Functional Ability Questionnaire Hannover
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare Professional
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IR	Incidence Rate
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JAK	Janus-kinase
LDA	Low disease activity
MCP	Metacarpophalangeal joint
MTX	Methotrexate
NIS	Non-Interventional Study

PEI	Paul-Ehrlich Institut
PhyGA	Physician Global Assessment of Arthritis
PIP	Proximal interphalangeal joints
PtGA	Patient Global Assessment of Arthritis
PY	Patient years
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SDAI	Simplified Disease Activity Index
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SSL	Secure Sockets Layer
TJC	Tender Joint Count
TNF	Tumor necrosis factor
VAS	Visual Analogue Scale
Vfa	Verband der forschenden Pharma-Unternehmen [German Association of Research-Based Pharmaceutical Companies]

Table 2 List of Abbreviations

2. RESPONSIBLE PARTIES

Name, degree(s)	Title	Affiliation	Address
[redacted]	PPD [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Responsible Parties

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	23 – Aug-2017	Substantial	4, 7, 9	• Start of data collection in October • Add Insurance Type as confounder • Specify patient's satisfaction with drug treatment • Correct number of monitoring visits • Correct safety reporting to CRO AMS instead of Pfizer • Clarify that all events (both with Xeljanz® and DMARDs of other manufacturers) have to be reported	Update of timelines, change of confounders and correction/specification of safety reporting process

Table 4 Amendments and Updates

4. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	28-July-2017
Start of data collection	23-October-2017
End of data collection	23-October-2022
Final study report	23-October-2023

Table 5 Milestones

5. 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 musculoskeletal complications, RA patients suffer from increased frequencies and impacts of comorbidities such as cardiovascular and infectious diseases, osteoporosis or cancer, leading to higher mortality rates.[2,3,4] In addition, RA represents significant health and socioeconomic burdens for the individual patient and society, especially with regard to work disability and work productivity loss.[5,6]

With currently no curative therapy available, treatment strategies aim at controlling disease activity, alleviating signs and symptoms, maintaining physical function, improving quality of life, reducing the rate of joint damage, and, if possible, inducing complete remission.

Best treatment outcomes are achieved if RA is treated with disease modifying antirheumatic drugs (DMARDs) right from the beginning (‘hit hard and early’, ‘window of opportunity’).[7,8,9,10] Furthermore, treatment strategies that aim at a predefined target (‘treat-to-target’ concept) have been shown to be superior to former, traditional approaches (‘wait and see’).[11] Therefore, current European League Against Rheumatism (EULAR)-recommendations and the German S1 guideline derived from the EULAR-recommendations define treat-to-target as the basic therapeutic principle. The target to aim for is remission, especially in DMARD-naïve patients, or low disease activity, primarily in patients who failed previous therapies.[12] Although criteria for RA remission vary substantially in studies and clinical practice, the 28-joint Disease Activity Score (DAS28) is traditionally being widely

used where DAS28 < 2,6 defines remission and DAS28 ≤ 3,2 low disease activity.[13]According to EULAR recommendations, therapy has to be adjusted until the treatment target has been reached.

How is the treat to target approach applied in everyday care?

Despite insufficient response after 3 to 6 months therapy, treat-to-target recommendations of EULAR were only applied in 50% of the German course and prognosis of early arthritis cohort (CAPEA).[14] In an analysis of a cohort from the "Kerndokumentation", a national database of the German Collaborative Arthritis Centres, 45% of patients were not within DAS28 low disease activity range and therefore would have needed adaption of therapy according to current treatment guidelines. In contrast, rheumatologists' global assessment of disease activity differed, 80% perceived their patients to be in the low disease activity range and, hence, as being adequately treated.[15]

These observations suggest that in a real-world setting, criteria other than calculated DAS28 remission or low disease activity alone may guide treatment decisions. Among such criteria, satisfaction with drug treatment is of particular interest. On the one hand, a patient who is content with his current therapy is less likely to be willing to change a therapy solely to achieve a better DAS28 score. On the other hand, patient preference and satisfaction of a therapy strongly affects adherence to a prescribed medication, ultimately affecting treatment outcome and efficacy. A factor known to impact on patient satisfaction with a prescribed treatment is the route of administration. Here, several studies point to a preference for oral therapies, also among second-line DMARDs.[16,17]

Recently, Tofacitinib, an orally applied DMARD of the new class called Janus-Kinase-Inhibitors (JAK-Inhibitors) has been brought into the market in the European Union. Tofacitinib is indicated in combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD. Due to oral administration of Tofacitinib, the impact of patient's satisfaction with drug treatment on therapy decisions by rheumatologists may be especially pronounced.

EULAR recommendations have now endorsed individual patient related factors such as patient preferences and comorbidities as an overarching principle in the management of RA.

6. RESEARCH QUESTION AND OBJECTIVES

The objective of this non-interventional study is to identify key factors that are driving treatment decisions by rheumatologists in the treatment of RA patients starting treatment with Tofacitinib in a real world setting. In addition to DAS28 score, the following factors may play an important role: difference between DAS28 at start of therapy and after 3-6 months, physician's global assessment of disease activity, patient's global assessment of disease activity, arthritis pain and patient's satisfaction with drug treatment.

6.1. Endpoints

6.1.1. Primary Endpoint:

Impact of the following factors on the number of treatment escalations of Tofacitinib patients in 24 months

a. DAS28-4 with Erythrocyte Sedimentation Rate (ESR)

b. ΔDAS28-4 (ESR)

c. Physician Global Assessment of Arthritis

d. Patient's Assessment of Arthritis Pain

e. Patient's satisfaction with drug treatment

f. Patient's Global Assessment of Arthritis

Treatment escalation in this study is defined as a switch to another DMARD or combination of DMARDs when compared to the last visit.

6.1.2. Secondary Endpoints:

a) Time to first treatment escalation

b) Rate of Low Disease Activity (LDA) over time of patients on Tofacitinib (in combination therapy or monotherapy), as assessed by: Simplified Disease Activity Index (SDAI) ≤ 11; Clinical Disease Activity Index (CDAI) ≤10; DAS 28-4 (ESR) ≤3.2 and DAS28-4 with C-reactive Protein (CRP) ≤3.2.

c) Rate of remission over time of patients on Tofacitinib (in combination therapy or monotherapy), as assessed by: American College of Rheumatology (ACR)-EULAR Boolean remission criteria; SDAI ≤ 3.3; CDAI ≤2.8; DAS 28-4 (ESR) < 2.6 and DAS28-4 (CRP) < 2.6

d) Change from baseline over time of patients on Tofacitinib (in combination therapy or monotherapy) in DAS 28-4 (ESR) and DAS 28-4 (CRP)

e) Change from baseline of duration of morning stiffness over time of patients on Tofacitinib (in combination therapy or monotherapy)

f) Change from baseline in the Functional Ability Questionnaire Hannover (FFbH) over time of patients on Tofacitinib (in combination therapy or monotherapy)

g) Rate of patients with functional remission in FFbH (FFbH > 83%) over time of patients on Tofacitinib (in combination therapy or monotherapy)

h) Change from baseline in a self-report questionnaire (a quality of life instrument) developed by the European Quality of Life (EuroQoL) Group (EuroQoL EQ-5D) over time of patients on Tofacitinib (in combination therapy or monotherapy)

i) Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale over time of patients on Tofacitinib (in combination therapy or monotherapy)

j) Drug survival at month 12, 24 of patients on Tofacitinib (in combination therapy or monotherapy)

k) Patient's satisfaction with Tofacitinib treatment (in combination therapy or monotherapy) over time

7. RESEARCH METHODS

7.1. Study design

This is a 60-month, prospective, non-interventional, multi-centre study to evaluate the impact of the following factors on the number of treatment escalations of Tofacitinib patients in 24 months.

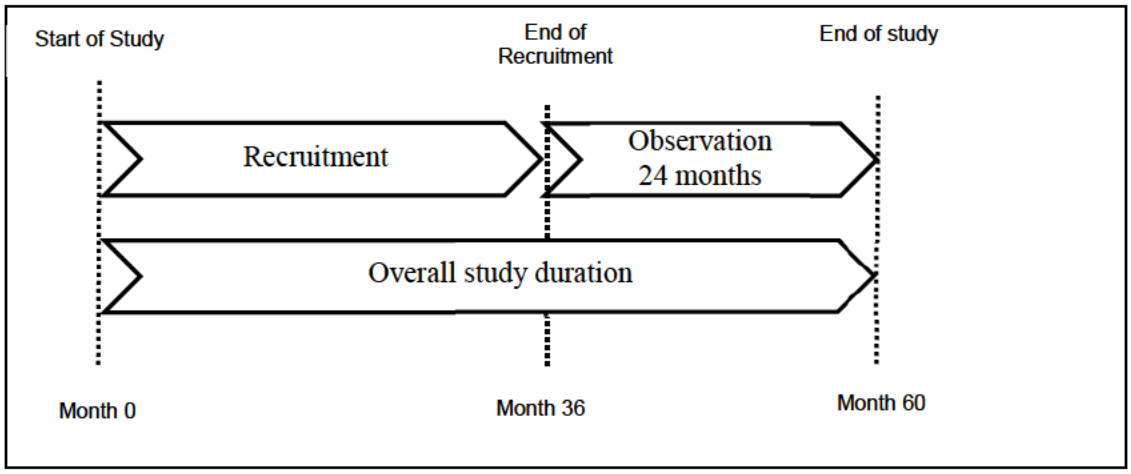
Eligible patients will be followed up from the date of first Tofacitinib prescription for 24 months. Patients who are switched from the initial Tofacitinib therapy to other therapies will also be followed up to 24 months. Patient documentation is expected quarterly as per standard clinical practice.

This study observes drug prescription and follow-up visits in daily medical care. Therapeutic strategies and frequency of patient follow-up are decided by the treating physician.

7.2. Setting

The planned recruitment period is 36 months. With planned observation duration of 24 months per patient, the entire study would thus last for 60 months. The study is to start in October 2017 and will end in October 2022. Overall, about 1500 patients in about 200 centres in Germany are to be included in this non-interventional study.

Figure 1. Timelines



7.2.1. Inclusion criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the healthcare professional's (HCP) 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. Confirmed Diagnosis of Rheumatoid Arthritis by rheumatologist
3. Patient is eligible for Tofacitinib treatment according to Summary of Product Characteristics (SmPC)
4. 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.

7.2.2. Exclusion criteria

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

1. Contraindications according to Xeljanz® SmPC
2. Receipt of any investigational drug within 3 months before study inclusion

3. Patients who have received any previous treatment with Tofacitinib or other JAK inhibitors

4. Patients who are investigational site staff members or patients who are Pfizer employees directly involved in the conduct of the study.

7.3. Variables

Variable	Role	Data source(s)	Operational definition
RA-treatment with Tofacitinib and/or other DMARDs - date of initiation	Exposure, Potential confounder, subgroup identifier	Case records and electronic Case Report Form (eCRF)	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs – dose	Exposure, Potential confounder, subgroup identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs - tolerability	Potential confounder, subgroup identifier	Case record/eCRF	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs – route of administration	Potential confounder, subgroup identifier	Case record/eCRF	Details will be provided in Statistical Analysis Plan
Age	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Gender	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Height	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Weight	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Insurance Type	Baseline characteristic, Potential confouncer, subgroup identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Date of first Diagnosis of RA	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan

Smoking history and current smoking status	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Comorbidities	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)	Baseline characteristics and outcome variable	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Rheumatoid Factor (RF), Anti-citrullinated protein antibodies (ACPA)	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Prognosis factors	Baseline characteristic, potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Prior drug treatment for RA	Potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Concomitant treatment of RA with Glucocorticoids	Potential confounder, sub-group identifier	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Patient's Global Assessment of Arthritis	Baseline and outcome variable	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Physician's Global Assessment of Arthritis	Baseline and outcome variable	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Patient's Assessment of Arthritis Pain	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Tender and swollen (28) joint count	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Duration of Morning Stiffness	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Functional Ability Questionnaire Hannover (FFbH)	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
EuroQoL EQ-5D-3L Health State Profile	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan
Patient's satisfaction with drug treatment	Baseline and Outcome	Case records/eCRF	Details will be provided in Statistical Analysis Plan

Table 6 Variables

7.4. Data sources

The data will be recorded using an electronic case report form (eCRF) for each patient included. The completed eCRFs 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 signed by the treating physician or authorized personnel.

All corrections of entries on the eCRFs must be explained (reason for change) and signed off (electronic signatures) if available signature was broken. Corrections of entries are automatically recorded by the system (incl. date of change, user changing data, 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.

In some cases, the eCRF or part of the eCRF can also serve as a source document. In these cases, a document must be available at the doctor's study site and at Pfizer and must clearly identify the data recorded in the eCRF and for which the eCRF is considered a source document.

The clinical parameters recorded, especially those used to assess efficacy, are usual, known and recognized variables within each respective indication.

7.5. Study procedure

Patients attending can be included by the HCP if they fulfil all selection criteria for the study and are started on treatment with Tofacitinib for moderate to severely active rheumatoid arthritis.

All visits shall be scheduled according to clinical practice. The treatment of a patient is independent from the patient enrolment into the study. Within this study 9 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 2 to 9 occurring +/- 14 days of the scheduled visit date will be used for data analysis.

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 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 regarding the treatment, the initial Tofacitinib dose and all changes and the reasons for changes are documented during the course of the evaluation. The concomitant treatment of rheumatoid arthritis with Glucocorticoids is determined by the treating physician and is registered in the documentation sheet.

7.5.1. Study Period

The planned observation period of each patient is 24 months. In this time period, up to 9 visits will be documented.

7.5.1.1. Baseline visit

The following parameters will be documented at baseline visit

- Informed Consent.
- Prognostic factors (from prior history)
- Documentation of initial diagnosis of RA
- Documentation of relevant comorbidities
- Demographic data
- Documentation of insurance type
- Physical Examination (weight, height)
- Smoking history and current smoking status
- Inclusion/ Exclusion criteria according to protocol
- Varicella vaccination status
- RA-Treatment with Tofacitinib and/or other DMARDs
- Prior drug treatment of RA
- Concomitant treatment of RA with Glucocorticoids
- Inflammatory Markers:
    - Erythrocyte sedimentation rate (ESR)

- C-reactive protein (CRP)

- Number of swollen and tender joints
- Duration of Morning stiffness
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis
- Patient's Assessment of Arthritis Pain
- Functional Ability Questionnaire Hannover (FFbH)
- EuroQoL EQ-5D-3L Health State Profile
- FACIT – Fatigue Scale
- Patient's overall satisfaction with prior drug treatment

7.5.1.2. Scheduled Visits 2- 8 /month 3 – month 21

Following parameters will be documented at each interim visit:

- RA treatment with Tofacitinib and/or other DMARDs
- Concomitant treatment of RA with Glucocorticoids
- Inflammatory Markers:
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Documentation of Adverse Events (AE)
- Number of swollen and tender joints
- Duration of Morning stiffness
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis

- Patient's Assessment of Arthritis Pain
- Functional Ability Questionnaire Hannover (FFbH)
- EuroQoL EQ-5D-3L Health State Profile
- FACIT – Fatigue Scale
- Patient's satisfaction with drug treatment

7.5.1.3. Final (or close out) Visit 9 / month 24

Following parameters will be documented at final visit:

- RA treatment with Tofacitinib and/or other DMARDs
- Concomitant treatment of RA with Glucocorticoids
- Inflammatory Markers:
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Documentation of AE
- Number of swollen and tender joints
- Duration of Morning stiffness
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis
- Patient's Assessment of Arthritis Pain
- Functional Ability Questionnaire Hannover (FFbH)
- EuroQoL EQ-5D-3L Health State Profile
- FACIT– Fatigue Scale
- Patient's satisfaction with drug treatment

7.5.1.4. Treatment Withdrawal

Patients experiencing adverse drug reactions as listed in the Xeljanz® SmPC or in the SmPCs of the other prescribed DMARDs with particular attention paid to Sections 4 (Contraindications), 5 (Special Warnings and 6 (Precautions)] should be monitored and if indicated, treatment should be withdrawn according to provision of the respective SmPC. If treatment with Tofacitinib or other DMARDs is withdrawn patients are followed up until the end of the observation period unless they withdraw from the study (see section 8.2).

7.5.2. Schedule of Activities

The schedule of activities table provides an overview of the visits that may be documented. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each documentation and assessment.

According to his clinical practice the HCP may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient. As this is a non-interventional study none of these visits are mandatory and every visit should be scheduled according to clinical practice.

Table 7. Schedule of Activities

Study Week	**Baseline** (Enrolment)	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**
Visit Number	1	2	3	4	5	6	7	8	9
Informed Consent	x								
Initial diagnosis of RA	x								
Prognostic factors	x								
Relevant comorbidities	x								
Demographic data	x								
Insurance type	x								
Smoking history and current smoking status	x								
Physical Examination (weight, height)	x								
Inclusion/Exclusion criteria	x								
Varicella vaccination status	x								
Prior drug treatment of RA	x								
RA-treatment with Tofacitinib and/or other DMARDs	x	x	x	x	x	x	x	x	x
Concomitant treatment of RA with Glucocorticoids	x	x	x	x	x	x	x	x	x

Inflammatory Markers	x	x	x	x	x	x	x	x	x
Documentation of AE	x	x	x	x	x	x	x	x	x
Number of swollen and tender joints	x	x	x	x	x	x	x	x	x
Duration of Morning stiffness	x	x	x	x	x	x	x	x	x
Patient's Global Assessment of Arthritis	x	x	x	x	x	x	x	x	x
Physician's Global Assessment of Arthritis	x	x	x	x	x	x	x	x	x
Patient's Assessment of Arthritis Pain	x	x	x	x	x	x	x	x	x
Functional Ability Questionnaire Hannover (FFbH)	x	x	x	x	x	x	x	x	x
EuroQoL EQ-5D-3L	x	x	x	x	x	x	x	x	x
FACIT – Fatigue Scale	x	x	x	x	x	x	x	x	x
Patient's satisfaction with drug treatment	x	x	x	x	x	x	x	x	x

7.6. Assessments

7.6.1. Physical Examination

At the Baseline Visit (Visit 1) height and weight will be documented.

7.6.2. Prognostic Factors

Prognostic factors will be determined at the Baseline Visit (Visit 1) based on prior medical history. The EULAR recommendation for the management of rheumatoid arthritits with synthetic and biological disease-modifying antirheumatic drugs [12] defines the following poor prognostic factors:

- Moderate (after conventional synthetic DMARD [csDMARD] therapy) to high disease activity according to composite measures
- High acute phase reactant levels
- High swollen joint counts
- Presence of RF especially at high levels
- Presence of ACPA, especially at high levels
- Combinations of the above
- Presence of early erosions
- Failure of two or more csDMARDs

7.6.3. Insurance Type

Insurance type will be documented at the first visit (baseline visit). Patients can either have statutory health insurance or private insurance.

7.6.4. Varicella vaccination status

At the Baseline Visit (Visit 1) current varicella vaccination status of patients will be assessed.

7.6.5. Treatment of Rheumatoid Arthritis (RA-Treatment) with Tofacitinib and/or other DMARDs

At each visit (visits 1-9) dose and route of administration (if applicable) of treatment with Tofacitinib and/or other DMARDs will be documented. If an escalation (as defined in section 6.1.1) occurred since the last visit, in addition stop date of previous DMARD(s), start date of new DMARD(s) and reason for switch (lack of efficacy or intolerability) will be documented.

7.6.6. Concomitant treatment for rheumatoid arthritis with glucocorticoids

At each visit (visits 1-9) dose and route of administration of concomitant treatment with glucocorticoids will be documented.

7.6.7. Effectiveness criteria

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

Table 8. Disease Activity Indicators

Indicator	Definition/Calculation
DAS28-4 (CRP)	0.56*√(TJC28) + 0.28*√(SJC28) + 0.36*ln(CRP in mg/l +1) + 0.014*PtGA in mm+ 0.96
DAS28-4 (ESR)	0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm
Simplified Disease Activity Index (SDAI)	(TJC28) + (SJC28) + [PhyGA in cm] + [PtGA in cm] + [CRP in mg/dL]
Clinical Disease Activity Index (CDAI)	(TJC28) + (SJC28) + [PhyGA in cm] + [PtGA in cm]
ACR/EULAR Boolean-based definition of remission	A patient must satisfy all of the following: tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1 mg/dL, subject's global assessment of arthritis ≤ 1 on a 0-10 scale

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 Arthritis; PhyGA = Physician's Global Assessment of Arthritis

7.6.8. Joint Counts

7.6.8.1. Tender/Painful Joint Count (TJC28)

Twenty-eight (28) joints will be assessed to determine the number of joints that are considered tender or painful. The 28 joints to be assessed are the shoulders, elbows, wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees. Artificial joints will not be assessed.

The response to pressure/motion on each joint will be assessed.

7.6.8.2. Swollen Joint Count (SJC28)

The 28 swollen joint count includes the following joints: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. Artificial joints will not be assessed.

The swelling of each joint will be assessed.

7.6.9. Patient Assessment of Arthritis Pain

Patients will assess the severity of their arthritis pain using a 100 mm visual analog scale (VAS) by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponds to the magnitude of their pain. "How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today."

7.6.10. Patient Global Assessment of Arthritis (PtGA)

Patients will answer the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The patient's response will be recorded using a 100 mm VAS with anchors on 0 = very well and 100 = very poorly.

7.6.11. Physician Global Assessment of Arthritis (PhyGA)

The HCP will assess how the patient's overall arthritis appears at the time of the visit. This is an evaluation based on the patient's disease signs, functional capacity and physical examination, and should be independent of the Patient's Global Assessment of Arthritis. The HCP's response will be recorded using a 100 mm VAS with 0 mm = no disease activity and 100 mm = worst disease activity. "Physician's Global Assessment of Rheumatoid Arthritis. Place a vertical mark on the line below to indicate the Disease Activity."

7.6.12. Duration of Morning Stiffness

The duration of morning stiffness will be determined by asking the following questions:
"When you wake up in the morning, do you currently suffer from morning stiffness?"
"How long does the morning stiffness last from the time you wake up?"

7.6.13. Functional Ability Questionnaire Hannover (FFbH)

The FFbH for RA is a German Short questionnaire for the assessment of patientive functional capacity in the context of basic everyday activities (range: 0-100% functional capacity)[18]. Functional remission in FFbH is defined as functional capacity > 83 %.

7.6.14. EuroQoL EQ-5D-3L Health State Profile

The EuroQoL EQ-5D-3L Health State Profile[19] is 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. 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.

7.6.15. Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale

The FACIT – Fatigue Scale is a patient completed questionnaire[20]consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue). This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness.

7.6.16. Patient's satisfaction with drug treatment

Satisfaction with treatment will be assessed on a 5-point Likert scale (where 0 = extremely dissatisfied, 1= dissatisfied, 2 = neither satisfied nor dissatisfied, 3 = satisfied

and 4 = extremely satisfied) in response to the question "How satisfied are you with the drugs that you have received for your arthritis since your last visit?"

7.6.17. C-reactive Protein (CRP)

The CRP shall be analysed by a local laboratory according to usual practice. It will be used in the calculation of several efficacy parameters.

7.6.18. Erythrocyte Sedimentation Rate (ESR)

The ESR shall be analysed by a local laboratory according to usual practice. It will be used in the calculation of several efficacy parameters.

7.6.19. Safety

All adverse events (AEs) that will occur during the observation period will be documented. At the final visit or if a patient is switched from Tofacitinib to another DMARD, the HCP will be asked to assess the general tolerability of the treatment with Tofacitinib and the reasons for discontinuation (intolerability or lack of efficacy) will be analysed.. Patient's satisfaction with drug treatment will be assessed as described in section 7.6.16.

7.7. Study size

The analysis of the primary endpoint is a time to event analysis, where the event is treatment escalation. It is possible for multiple events to occur for each patient within the follow-up period. The primary analysis aims to investigate which of the factors listed actually affect the rate at which a patient's treatment is changed. In order to determine an appropriate sample size for this study recurrent event data was simulated, using the methods described by Jahn-Eimermacher *et al*. (2015), and analysed using cox proportional-hazards models.[21]

The distribution of each of the factors was obtained from the ORAL STANDARD study:

Achieve DAS28 < 3.2	-	Binomial(n, 0.2)
Achieve ΔDAS28 > 1.8	-	Binomial(n, 0.6)
ΔPatient Global Assessment	-	Normal(-29.31, 38.579^2)
ΔPhysician Global Assessment	-	Normal(-27.01, 30.966^2)
ΔPain score	-	Normal(-34.99, 24.672^2)

The baseline hazard rate was assumed to be 3.16 events per patient over the follow-up period.

The impact of each the factors on the hazard rate, (entered as the regression coefficient), is used to simulate the event times for each patient given their values for the simulated factors. The regression coefficients were assumed to be (-0.288, -2.303, -0.01, -0.01, -0.01). Simulations were carried out for sample sizes ranging from 100 to 4,500.
Figure 2 shows the power to detect an effect of each factor against sample size for the 5 different factors.

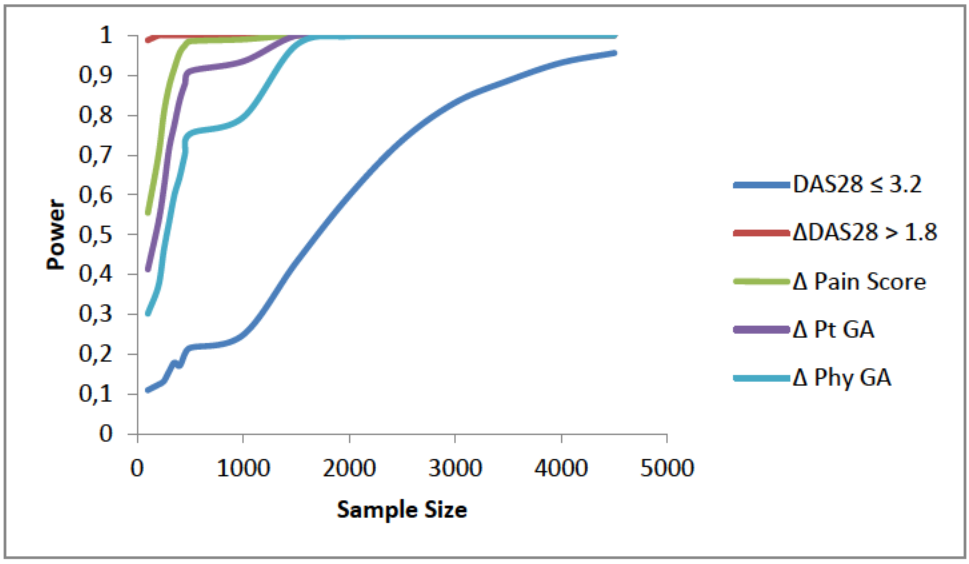


Figure 2: Plot of Power against Sample Size for simulations of recurrent event data analysed using cox-proportional hazards model including all 5 factors of interest.

Given the initial assumptions the power to detect an impact of 4 of the 5 factors, within the full cox proportional hazards model was greater than 80% with a sample size of 1000 patients. The power to detect an effect of the remaining factor, achieving DAS28 < 3.2, was around 50% for 1500 patients and 60% for 2000 patients. The power is very high for ΔDAS28 > 1.8, mainly due to the high proportion of patients assumed to achieve the criteria and the high impact achieving the criteria is assumed to have on the rate of treatment escalation (significantly reducing it).
Sensitivity analyses were carried out around the assumptions made for the simulations. Full details of the sensitivity analyses will be included in the SAP.

Based on the results of the initial simulation and of sensitivity analyses, it is deemed that 1500 patients should provide a reasonable sample size on which to draw conclusions of the effect of the achieving change from baseline in DAS28 > 1.8 and the patient/physician VAS scores on the rate of treatment escalation. Based on sensitivity analysis, if achieving DAS28 ≤ 3.2 does in fact have a bigger effect on the event rate than initially assumed there should be sufficient power to detect this effect.

7.8. Data management

Patients' personal data will be collected, stored and processed exclusively in pseudonymised form in accordance with the national data protection laws. All data will remain in pseudonymised 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. Pfizer 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 data capture (EDC) system Clincase (Quadratek Data Solutions Ltd.). Clincase fulfills all requirements of 21 Code of Federal Regulations (CFR) Part 11 and the central server situated in Germany is backed up once a day. Access to the system takes place via a secure website (Secure Sockets Layer (SSL) encryption). Access is only given to registered users who log in with a unique user name and password. Depending on their function in the study, individual users are assigned defined access rights. Access rights to the EDC system are monitored by authorised Advanced Medical Services GmbH (AMS) employees.

Documentation by physicians will take place using paper questionnaires or eCRF masks. Patient questionnaires will be handed out in paper form and entered in the EDC system by AMS. Automatic checking 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 the physician's electronic signature.

Please refer also to previous sections 7.2, 7.3 Variables, and 0 Data sources

7.9. 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. SAS (Version 9.1, 9.2, 9.3 or 9.4) will be used for all analyses.

7.9.1. Analysis Populations

The Full Analysis Set is defined as patients who receive at least one dose of Tofacitinib and have at least one set of post-baseline measurements. 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.

7.9.2. Efficacy Analysis

7.9.2.1. Primary analysis

The primary analysis will investigate the impact of various factors on the rate of treatment escalation. Cox proportional-hazards modelling will be used, with status of each patient (whether they experienced a treatment escalation or not) and the times of such treatment escalations being used for the baseline model.

The factors that will be investigated and thus included in the model will be:

- whether or not a patient achieves LDA, as defined by DAS28-4 (ESR) ≤3.2.
- whether or not a patient achieves change from baseline in DAS28-4 (ESR) > 1.8
- Patient's Global Assessment of Arthritis
- Physician Global Assessment of Arthritis
- Patient's Assessment of Arthritis Pain
- Patient's satisfaction with drug treatment

If patients withdraw or are lost to follow-up they will be censored at the time of the last available visit.

7.9.2.2. Secondary Analysis

7.9.2.2.1. Time to Event Analysis

Time to event endpoints will be investigated using Kaplan-Meier methodology and, where appropriate, Cox-Proportional Hazards modelling will be used to look at differences in event rate between sub-groups. . The time to event will be summarised in terms of medians and confidence intervals. Kaplan-Meier plots of the time to event over the study duration will be presented.

7.9.2.2.2. Rate of DAS28 Low Disease Activity (LDA) and Remission

The rate of DAS28 LDA or remission will be presented as frequency and proportion of the patients achieving the relevant criteria at each time point. See Section 7.9.2.2.4 for all definitions of LDA and Remission that will be used in the analysis.

7.9.2.2.3. Change from Baseline

The summary statistics of the absolute value and the change from baseline at each visit will be reported. Change from baseline will be presented for DAS28-4 (ESR) and DAS28-4 (CRP) as well as the scores resulting from the PRO questionnaires; FFbH, EQ-5D-3L, FACIT-Fatigue and Patients satisfaction with treatment.

7.9.2.2.4. Definitions and Derivations

- Remission is assessed by: ACR-EULAR Boolean remission criteria; SDAI ≤ 3.3; CDAI ≤2.8; DAS 28-4 (ESR) < 2.6 and DAS28-4 (CRP) < 2.6
- Functional remission is defined as FFbH score > 83%
- LDA is assessed by: SDAI ≤ 11; CDAI ≤10; DAS 28-4 (ESR) ≤3.2 and DAS28-4 (CRP) ≤3.2.

Where

DAS28-4 (CRP) = 0.56*$\sqrt{}$(TJC28) + 0.28*$\sqrt{}$(SJC28) + 0.36*ln(CRP in mg/l +1) + 0.014*PtGA in mm + 0.96

DAS28-4 (ESR) = 0.56*$\sqrt{}$(TJC28) + 0.28*$\sqrt{}$(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm.

SDAI = TJC28 + SJC28 + PhyGA in cm + PtGA in cm + CRP in mg/dL

CDAI = TJC28 + SJC28 + PhyGA in cm + PtGA in cm

Where TJC is the Tender Joint Count, SJC is the Swollen Joint Count, CRP is the C-reactive protein in mg/L, ESR is the Erythrocyte Sedimentation Rate in mm/first hour and PtGA is the Patient's Global Assessment of Health and PhyGA is the Physicians Global Assessment.

7.9.2.2.5. Functional Ability Questionnaire-FFbH

The FFbH consists of 18 questions with 3 possible responses (Yes; Yes, but with effort; No or only with outside help).

The total score is the sum of the scores of all 18 questions, where for each question:

- Yes = 2 points
- Yes, but with effort = 1 point

- No or only with outside help = 0 points

The Functional capacity [%] is then

(Total score*100)/(2*number of valid responses)

7.9.2.2.6. EQ-5D-3L

The EQ-5D-3L is a standardised 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 three responses and the patient is asked to select the response that best describes them. The responses are scored 1-3 as shown in Table 9.

Table 9: EQ-5D scores

Dimension	Response	Score
Mobility	I have no problems in walking about	1
	I have some problems in walking about	2
	I am confined to bed	3
Self-care	I have no problems with self-care	1
	I have some problems washing or dressing myself	2
	I am unable to wash or dress myself	3
Usual activities (e.g. work, study, housework, family or leisure activities)	I have no problems with performing my usual activities	1
	I have some problems with performing my usual activities	2
	I am unable to perform my usual activities	3
Pain/discomfort	I have no pain or discomfort	1
	I have moderate pain or discomfort	2
	I have extreme pain or discomfort	3
Anxiety/depression	I am not anxious or depressed	1
	I am moderately anxious or depressed	2
	I am extremely anxious or depressed	3

The score for each dimension is weighted in accordance with Table 10.

Table 10: EQ-5D weightings

EQ-5D Dimension	Score = 1	Score = 2	Score = 3
Mobility	0	0.069	0.314
Self-Care	0	0.104	0.214
Usual Activities	0	0.036	0.094
Pain/Discomfort	0	0.123	0.386
Anxiety/Depression	0	0.071	0.236

The following algorithm is then applied to calculate the EQ-5D Total Score:

1. If **all** five EQ-5D dimensions have a score of 1 then the EQ-5D Total Score is 1.
2. If **any** of the five EQ-5D dimensions have a score of 3, then the EQ-5D Total Score is:

$$1 - 0.081 - \left(\sum_{1}^{5} weighted\ dimension\ score\right) - 0.269$$

3. If **none** of the five EQ-5D dimensions has a score of 3, then the EQ-5D Total Score is:

$$1 - 0.081 - \left(\sum_{1}^{5} weighted\ dimension\ score\right)$$

Missing weighted dimension scores are replaced by the mean of the non-missing weighted dimension scores. If a weighted score is missing and replaced in this way by a mean weighted score of zero, step 3 of the algorithm is applied.

7.9.2.2.7. FACIT-Fatigue Scale

The FACIT-Fatigue Scale is derived by taking the sum of the scores for the 13 questions in the instrument, resulting in a score between 0 and 52.

7.9.1. Safety Analysis

Adverse events will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information collected during the course of the study will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data collected at Screening will be included in the study database.

Adverse events will be reported according to the 3-tier approach as describe in section 9.1.

Reasons given for premature discontinuation will also be summarized.

7.10. Interim Analysis

It is planned that there will be at least one interim analysis. The details of the timing and criteria for any interim analyses will be outlined in the SAP.

7.11. Quality control

The Sponsor delegates the conduct of this NIS to the Contract Research Organization AMS.

Study Coordination has been assigned to a Project Manager and monitoring is conducted by clinical research associates (CRAs) of the company AMS.

Upon enrolment of the first patient at the site, the CRA contacts the site to discuss details of the study and to clarify any questions.

A total of 140 monitoring visits will be conducted. During each visit the CRA will check whether:

- the patients have been informed and consented to their participation in the NIS,
- all data have been entered into the eCRF and
- all data can be verified in accordance with original patient files.

A data manager from AMS will perform quality analyses of the data recorded in the eCRF in order to reveal any inconsistent or missing responses and a plausibility check will be run on the database to reveal any deviant values.

Coherency tests will be conducted according to predefined criteria. If any inconsistencies are discovered in the eCRFs, the relevant data will be checked.

Before the start of the study, the physician grants the CRA access to all medical records of the patients taking part in the NIS and supports the CRA in the performance of their tasks. The physicians also consent to the CRAs conducting site visits, if necessary repeatedly, for the purpose of monitoring the data collected and agree to ensure sufficient time for these visits.

Additionally remote monitoring calls will be performed quarterly to discuss and solve inconsistencies or missing data in the eCRF with a site.

The accompanying quality assurance measures are based on the Guidelines for Proper Conduct in Epidemiological Research (GEP), on the Draft Joint Recommendations of the German Federal Institute for Drugs and Medical Devices (Bundesamt für Arzneimittel und Medizinprodukte, BfArM), on the recommendations of the Paul Ehrlich Institute (PEI) on the planning, conducting and analysing non-interventional studies, as well as on the German Association of Research-Based Pharmaceutical Companies (vfa [Verband der forschenenden Pharma-Unternehmen]) – Recommendations for the Improvement of

Quality and Transparency of Non-Interventional StudiesLimitations of the research methods.

7.12. Limitations of the research methods

Randomised controlled trials are important and powerful tools in assessing efficacy and safety but have their limitations in terms of generalisability. In order to assess health economics, 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-randomised studies in general are the risk of selection/ascertainment bias and some 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 (e.g. CRP not measured or FFbH questionnaire not completed). . Following up patients after treatment escalation, rather than discontinuing patients from the study when they switch from Tofacitinib, should result in a higher proportion of the patients remaining in the study until the planned completion date. Where data are missing, information from the patient at other visits may be used in the primary analysis model to assess predictors of treatment decisions. 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.

7.13. Other aspects

Not applicable.

8. PROTECTION OF PATIENTS

8.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the independent ethics committee (IEC) and Pfizer before use.

The HCP must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The HCP, or a person designated by the HCP, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The HCP will retain the original of each patient's signed consent form.

8.2. 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 HCP or sponsor for safety, behavioural, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The HCP should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events. The further treatment of a patient is independent from his/her withdrawal.

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.

8.3. Independent Ethics Committee (IEC)

An IEC will review and approve the protocol before any patients are enrolled.

8.4. Ethical Conduct of the Study

The study will be conducted with scientific purpose, value and rigor in accordance with legal and regulatory requirements, such as §67 (6) of the German Drug Law (AMG) and the recommendations for the conduct of non-interventional studies ("Anwendungsbeobachtungen") of the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institut Furthermore, it will follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices

(GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and/or equivalent.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1. 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 the CRO AMS. 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, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Table 11 Requirements for recording safety events

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to the CRO AMS 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 HCP 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 right column of the table above must be reported to the CRO AMS within 24 hours of awareness of the event by the HCP **regardless of whether the event is**

determined by the HCP to be related to a drug under study. In particular, if the SAE is fatal or life-threatening, notification to the CRO AMS 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 HCP does not become immediately aware of the occurrence of a safety event, the HCP 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 the CRO AMS within 24 hours of awareness, the HCP is obligated to pursue and to provide any additional information to the CRO AMS in accordance with this 24-hour timeframe. In addition, an HCP may be requested by the CRO AMS 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 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 the CRO AMS.

9.1.1. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of *Tofacitinib (*Xeljanz®*)* or the time of the patient's informed consent if s/he is already exposed to *Tofacitinib (*Xeljanz®*)*, 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 the CRO AMS 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 HCP 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 (*Xeljanz®*)*, the SAE also must be reported to the CRO AMS.

9.1.2. Causality assessment

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

An HCP's *Tofacitinib (*Xeljanz®*)or other DMARDs* causality assessment is the determination of whether there exists a reasonable possibility that *Tofacitinib (*Xeljanz®*) or other DMARDs* caused or contributed to an AE. If the HCP's final determination of causality is "unknown" and s/he cannot determine whether *Tofacitinib (*Xeljanz®*) or other DMARD* caused the event, the safety event must be reported within 24 hours.

If the HCP cannot determine the etiology of the event but s/he determines that *Tofacitinib (*Xeljanz®*) or other DMARD* did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

9.1.3. Definitions of safety events

9.1.3.1. Adverse events (AE)

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 HCP 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.

9.1.3.2. 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 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)

9.1.4. Scenarios necessitating reporting to the CRO AMS 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 (*Xeljanz®*) or other DMARDs*, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to *Tofacitinib (*Xeljanz®*)or other DMARDs* (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 (*Xeljanz®*) or other DMARDs* 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 (*Xeljanz®*) or another DMARD*, this information must be submitted to the CRO AMS, 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 (*Xeljanz®*) or another DMARD* 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 the CRO AMS 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 HCP 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 HCP must submit the following medication errors to the CRO AMS, 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.

<u>Overdose, Misuse, Extravasation</u>

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

<u>Lack of Efficacy</u>

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

<u>Occupational Exposure</u>

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

9.2. Single reference safety document

The Summary of product characteristic for Xeljanz® 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 the CRO AMS by the HCP during the course of this study.

The Product Label should continue to be used by the HCP for prescribing purposes and guidance.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Communication of study results

It is planned that there will be at least one interim analysis. Results of interim analyses as described in the SAP are planned to be presented on national and international congresses. Final study results are additionally planned to be published peer-reviewed journals.

10.2. 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 HCP is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, the CRO AMS should be informed immediately.

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

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12. LIST OF TABLES

13. LIST OF FIGURES

ANNEX 1 LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2 ADDITIONAL INFORMATION

Not applicable