STATISTICAL ANALYSIS PLAN (SAP)

Non-Interventional Study Protocol
A3921302

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

Statistical Analysis Plan
(SAP)

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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	Anti-citrullinated protein antibodies
ACR	American Colleague of Rheumatology
AE	Adverse Event
ALL	All Patient Set
bDMARD	Biological Disease Modifying Antirheumatic Drug
CAPEA	Course and Prognosis of Early Arthritis
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
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
EMA	European Medicines Agency
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
FAS	Full Analysis Set
FFbH	Functional Ability Questionnaire Hannover
HCP	Healthcare Professional
JAK	Januskinase
LDA	Low disease activity
MTX	Methotrexate
NIS	Non-Interventional Study
PF	Prognostic Factor
PhyGA	Physician Global Assessment of Arthritis
PPAS	Per Protocol Analysis Set
PtGA	Patient Global Assessment of Arthritis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SDAI	Simplified Disease Activity Index
SFAS	Secondary Full Analysis Set
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics

TJC	Tender Joint Count
TNFi	Tumor necrosis factor inhibitor
tsDMARD	Disease Modifying Antirheumatic Drug
VAS	Visual Analogue Scale

2 AMENDMENTS FROM PREVIOUS VERSION(S)

The Protocol A3921302_ObservationalPlan_Finalv1.1_23Aug2017.docx states that:

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.

As the visits will be scheduled according to clinical practice there are likely to be many visits outside of the windows defined in the protocol. To ensure the primary analysis incorporates all visits at which a patient might experience a treatment escalation all visits will be included. A further per-protocol analysis will be conducted using the analysis windows set out in Section 12.1.1.

Populations used during interim analyses were updated.

Additional details regarding the definition of the primary endpoint were added, because the definition provided in the protocol was not specific enough. Escalations were classified into 3 different types: Step-up, step-down or termination. The analysis of the primary endpoint will be conducted overall and per escalation type. A table with all possible treatment type changes has been added together with the corresponding type of escalation.

The assignment of escalations occurring in-between scheduled visits has been mostly aligned with that for the secondary endpoints for consistency across analyses and for greater precision of the assignment. In addition, imputation rules for missing values of covariates to be included in the analyses of the primary endpoint, have been added.

3 INTRODUCTION

Note: in this document any text taken directly from the Non-Interventional (NI) study protocol is ***italicised***.

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

oftofacitinib, 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.

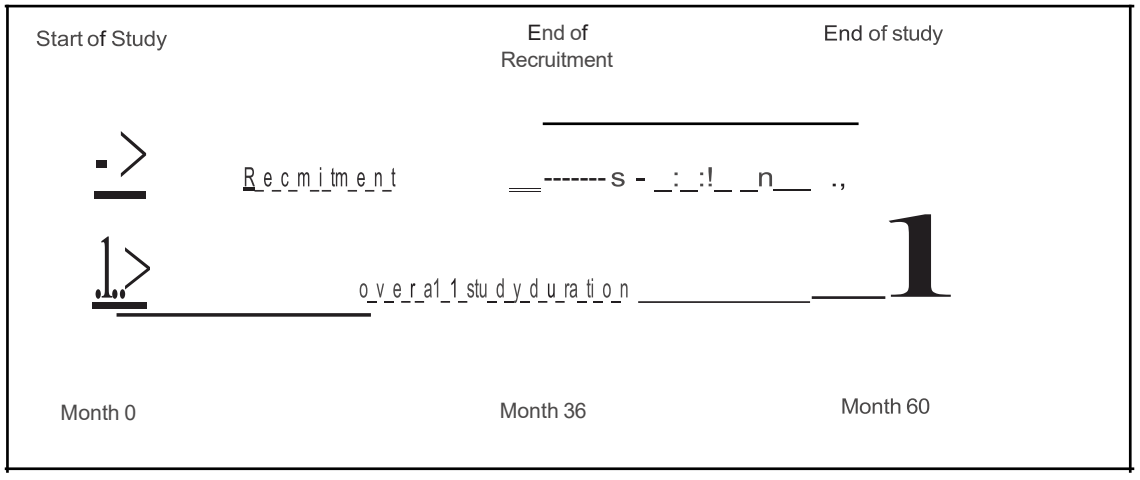
3.1 STUDY DESIGN

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.

Figure 1. Study Design



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 started in October 2017 and, due to an extension of the recruitment period of9 months, the study will end in July 2023. Overall, about 1500 patients in about 200 centres in Germany are to be included in this non-interventional study.

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 1. Schedule of Activities

Study Week	Baseline (Enrolmen()	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
Info1med Consent	x								
Initial dia211osis of RA	x								
Proimostic factors	x								
Relevant comorbidities	x								
Demographic data	x								
Insurance type	x								
Smoking history and cwTent smoking status	x								
Phvsical 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
InflammatoIY 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 ofMoming 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
EuroOoL E0-5D-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 diug treatment	x	x	x	x	x	x	x	x	x

3.2 STUDY POPULATION

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. The protocol states that data from Visits 2 to 9 occurring +/- 14 days of the scheduled visit date will be used for the analysis, however this definition will be amended within the SAP (see Sections 12.1.1 and 6 for further detail).

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.

3.2.1 TREATMENT/COHORT LABELS

For the primary analysis, the number and timing of treatment escalations of tofacitinib patients in 24 months will be presented (see Section 7.1.1). The treatment labels for other analyses are presented below:

3.2.1.1 TREATMENT LABEL FOR SECONDARY ANALYSIS

tofacitinib (in Monotherapy or in Combination with MTX)

3.2.1.2 TREATMENT LABEL FOR SECONDARY ANALYSIS – SUBGROUP SEQUENCE OF THERAPY

tofacitinib in Monotherapy
tofacitinib in Monotherapy ➔ Combination with MTX
tofacitinib in Combination with MTX
tofacitinib in Combination with MTX ➔– tofacitinib Monotherapy

3.3 STUDY 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, 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's overall satisfaction with treatment.

4 INTERIM AND FINAL ANALYSES

4.1 INTERIM ANALYSIS

A first interim analysis was carried out after 50% of the planned number of patients (i.e. 750 patients) had reached their M12 visit. The M12 interim analysis only considered the secondary endpoints.
Two analysis populations were used:

1) M12 Population: all those patients that have completed the M12 visit
2) Baseline Population: all those that have completed at least the baseline visit.

A second interim analysis was carried out after 50% of patients had reached their M24 visit. The M24 interim analysis considered the secondary endpoints in addition to summary tables of the primary endpoint (no statistical modelling was undertaken within the interim analysis). Two analysis populations were used:

1) M24 Population Set: all those patients that have completed the M24 visit
2) M12 Population Set: all those patients that have completed the M12 visit
3) Baseline Population Set: all those that have completed at least the baseline visit.

A third Interim Analysis was conducted with a database export of 31st January 2022 following the methods of the second Interim Analysis described above.

The outputs required for the interim analyses were a subset of the final outputs and methods were the same as for the final analysis. Therefore, a separate analysis plan was not required. Details of the output requirements were provided in the list of tables.

4.2 FINAL ANALYSIS

The final analysis will include all enrolled patients and will be carried out after all patients have reached their final visit (at month 24). The final datasets will be extracted from the database and locked before final analysis. Any exclusions from the analysis will be agreed and documented prior to database lock. The final analysis will be based on the populations described under 6 Analysis Sets/ populations, the populations M12 and M24 used for the interim analyses will not be used for the final analysis.

4.3 POOLED ANALYSIS

The data from this protocol is also planned to be included in a pooled analysis with other European non-interventional studies. Details will be included in a separate analysis plan. The pooled analysis is not part of the final analysis.

5 HYPOTHESES AND DECISION RULES

Data will be summarised descriptively. Tables will include appropriate confidence intervals (CIs) so as to provide information on the precision of the estimates. For the primary endpoint a predictive model will be used to assess the impact of a number of factors on the number and timing of treatment escalations.

6 ANALYSIS SETS/ POPULATIONS

6.1 ALL PATIENT SET

The All Patient Set (ALL) includes all patients enrolled in the study and will include all data collected at both scheduled and unscheduled visits. The ALL will primarily be used for disposition analyses and listings.

6.2 FULL ANALYSIS SET

The Full Analysis Set (FAS) will include all patients who receive at least one dose of tofacitinib and have at least one post-baseline visit. The primary analysis will use the FAS. The FAS will include all data collected during the study, both scheduled and unscheduled visits.

The protocol states that patients will be enrolled if they fulfil all selection criteria for the study and are started on treatment with tofacitinib for moderate to severely active rheumatoid arthritis.

6.3 SECONDARY FULL ANALYSIS SET

Patients with data collected while taking tofacitinib will be assigned to the Secondary Full Analysis Set (SFAS) at a given time point, which will be used for all secondary endpoint analyses. A patient is considered on tofacitinib at a given timepoint if the patient has not terminated or paused tofacitinib at the time of the visit or event. Termination or pauses are documented in eCRF instrument “Rheumatologische Medikation” for therapy class tsDMARD/bDMARD, where variable *Change* (BDCM.CHANGECD) is set to “Therapy stop” = termination or set to “Therapy paused” = pause.

6.4 SAFETY ANALYSIS SET

The Safety Analysis Set (SAS) will consist of all patients who receive at least one dose of tofacitinib. All reporting of safety data will utilize the SAS.

6.5 PER PROTOCOL ANALYSIS SET

Patients with data collected at scheduled visits, which fall within the defined visit windows (see section 12.1.1) will be assigned to the Per-Protocol Analysis Set (PPAS).

6.6 SUBGROUPS

The following subgroups will be considered for the analysis of the secondary endpoints if sufficient numbers of patients are available.
:

1) Sequence of therapy, where subgroups (with treatment labels as defined in 2.2.1.2) are:

    a) Patients who were on tofacitinib as a Monotherapy throughout the study.
    b) Patients who were on tofacitinib as a Monotherapy and switched to tofacitinib in combination with MTX.
    c) Patients who were on tofacitinib in Combination with MTX throughout the study.
    d) Patients who started on tofacitinib in Combination with MTX and switched to tofacitinib as a Monotherapy.

Note: Only a patient's first switch will be used to classify them into a subgroup.

If above classification is too granular, the following subgroups will be used for sequence of therapy:

a) Patients who were on tofacitinib as a Monotherapy throughout at least 60% of their observational time
b) Patients who were on tofacitinib as a Combination with MTX throughout at least 60% of their observational time

2) Medication history of RA treatment where the subgroups are:

    a) Those on 2nd line treatments prior to starting study.
    b) Those on 3rd line treatments prior to starting study.

    The eCRF will be referred to for a list of drug names for each category.

3) Patient's Switch Status, where the subgroups are:

    a. Patients with a treatment step- up as defined in section 7.1.1: switch up
    b. Patients that remain on tofacitinib treatment or patients with a treatment step-down: no switch up

4) Number of Treatment Escalations (as defined in section 7.1.1):

    a) Patients with no treatment escalations.

b) Patients with 1 treatment escalation.
c) Patients with 2 treatment escalations.
d) Patients with 3 or more treatment escalations.

7 ENDPOINTS AND COVARIATES

7.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

7.1.1 PRIMARY ENDPOINTS

Number and timing of treatment escalations of tofacitinib patients in 24 months, where Treatment Escalation in this study is defined as a switch to another DMARD or combination of DMARDs when compared to the last visit.

The following types of escalations will be distinguished:

1. Treatment **Termination**, which is the termination of a DMARD (or multiple when on combination therapy) without starting a new DMARD therapy. Premature study terminations (without documented treatment termination) will not be considered treatment terminations.

2. Treatment **Step-up** which is an increase from the current treatment regime towards e.g. a combination of DMARDs

3. Treatment **Step-down**, which is a de-escalation from the current treatment regime, e.g. from combination therapy to monotherapy

Patients start their therapy at baseline with tofacitinib either in Monotherapy or in Combination therapy with MTX. Subsequent therapy changes are documented on eCRF instrument “Rheumatologische Medikation“ by:

- adding additional DMARDs on top of the current therapy

- stopping the current DMARD in monotherapy and adding a new DMARD

- stopping one of multiple DMARDs when on combination therapy

- stopping one of multiple DMARDs when on combination therapy and adding a new DMARD

- stopping all DMARDs and not starting a new therapy. The escalation types depend on the combination of DMARD classes (tsDMARD vs bDMARD vs TNFi vs csDMARD). The eCRF does not explicitly distinguish between tsDMARD vs bDMARD vs TNFi, but combines all rheumatic medications belonging to the above classes under

tsDMARD/bDMARD. For the definition of treatment escalations, the following assignment of rheumatic medication to DMARD classes will be done:

tsDMARDS:
- baricitinib
- upadacitinib
- filgotinib

TNFi:
- etanercept
- adalimumab
- certolizumab
- golimumab
- infliximab

bDMARDs (excluding TNFi):
- abatacept
- rituximab
- anakinra
- tocilizumab
- sarilumab

For details of treatment escalations, e.g., which DMARD class addition or reduction leads to a particular escalation type, see table 12.2 in section 12.1.2.

7.1.2 SECONDARY ENDPOINTS

This study has a number of secondary efficacy endpoints:

7.1.2.1 TIME TO FIRST TREATMENT ESCALATION

For patients who experience a treatment step-up (as defined in section 7.1.1), the Treatment Escalation Status and Time to First Treatment Escalation will be recorded as follows:

- Status = 1
- Time = Date of first treatment escalation – Date of initiation on tofacitinib

For patients who don't experience a treatment escalation, the Treatment Escalation Status and time to first treatment escalation will be recorded as follows:

- Status = 0

- Time = Date of final visit – Date of initiation on tofacitinib

If a patient is lost to follow-up or withdraws from the study, they will be censored at the date of their last visit.

The analysis for time to first treatment escalation type step-up may be extended to escalation type step-down.

7.1.2.2 RATE OF LDA

The Rate of Low Disease Activity (LDA) will be calculated over time for patients taking tofacitinib using 4 different definitions:

a) SDAI ≤ 11;

b) CDAI ≤10;

c) DAS 28-4 (ESR) ≤3.2 and

d) DAS 28-4 (CRP) ≤3.2.

These are defined in detail below.

7.1.2.2.1 SDAI LDA

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) SDAI LDA is derived as:

SDAI_LDA = 1 if SDAI ≤ 11
SDAI_LDA = 0, otherwise.

The proportion of patients in SDAI LDA at Month X is then calculated as:

No. of patients with SDAI LDA at Month X / Total Number of patients with non-missing SDAI LDA at Month X.

7.1.2.2.2 CDAI LDA

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) CDAI LDA is derived as:

CDAI_LDA = 1 if CDAI ≤10
CDAI_LDA = 0, otherwise.

The proportion of patients in CDAI LDA at Month X is then calculated as:

No. of patients with CDAI LDA at Month X / Total Number of patients with non-missing CDAI LDA at Month X.

7.1.2.2.3 DAS28-4 (ESR) LDA

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) DAS 28-4 (ESR) LDA is derived as:

DAS 28-4 (ESR) LDA = 1 if DAS 28-4 (ESR) ≤ 3.2.
DAS 28-4 (ESR) LDA = 0, otherwise.

DAS28-4 (ESR) is calculated as in Section 7.1.2.4.1

The proportion of patients in DAS 28-4 (ESR) LDA at Month X is then calculated as:

No. of patients with DAS 28-4 (ESR) LDA at Month X / Total Number of patients with non-missing DAS 28-4 (ESR) LDA at Month X.

7.1.2.2.4 DAS28-4 (CRP) LDA

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) DAS 28-4 (CRP) LDA is derived as:

DAS 28-4 (CRP)_LDA = 1 if DAS28-4 (CRP) ≤ 3.2.
DAS 28-4 (CRP)_LDA = 0, otherwise.

DAS28-4 (CRP) is calculated as in Section 7.1.2.4.1

The proportion of patients in DAS 28-4 (CRP) LDA at Month X is then calculated as:

No. of patients with DAS 28-4 (CRP) LDA at Month X / Total Number of patients with non-missing DAS 28-4 (CRP) LDA at Month X.

7.1.2.3 RATE OF REMISSION

The Rate of Remission will be calculated over time for patients taking tofacitinib, using 5 definitions:

a) American College of Rheumatology (ACR) – European League Against Rheumatism (EULAR) Boolean remission criteria;

b) Simplified Disease Activity Index (SDAI) ≤ 3.3;

c) Clinical Disease Activity Index (CDAI) ≤2.8;

d) DAS 28-4 (ESR) < 2.6 and

e) DAS28-4 (CRP) < 2.6

These are defined in more detail below.

7.1.2.3.1 ACR-EULAR BOOLEAN REMISSION CRITERIA

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) ACR Remission is derived as:

ACR_Remission = 1, if: SJC28 ≤1, TJC28 ≤1, CRP ≤1 mg/dL, and PtGA <= 2cm

ACR_Remission = 0, Otherwise.

The proportion of patients in ACR Remission at Month X is then calculated as:

No. of patients with ACR Remission at Month X / Total Number of patients with non-missing ACR Remission at Month X.

7.1.2.3.2 SDAI REMISSION

At each time point (M3, M6, M9, M12, M15, M18, M21, M24) SDAI is calculated as:

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

SDAI_Remission = 1, if SDAI ≤ 3.3
SDAI_Remission = 0, otherwise.

The proportion of patients in SDAI Remission at Month X is then calculated as:

No. of patients with SDAI Remission at Month X / Total Number of patients with non-missing SDAI Remission at Month X.

7.1.2.3.3 CDAI REMISSION

At each time point (M3, M6, M9, M12, M115, M18, M21, M24) CDAI Remission is derived as:

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

CDAI_Remission = 1, if CDAI ≤ 2.8
CDAI_Remission = 0, otherwise.

The proportion of patients in CDAI Remission at Month X is then calculated as:

No. of patients with CDAI Remission at Month X / Total Number of patients with non-missing CDAI Remission at Month X.

7.1.2.3.4 DAS28-4 (ESR) REMISSION

At each time point (M3, M6, M9, M12, M115, M18, M21, M24) DAS 28-4 (ESR) Remission is derived as:

DAS 28-4 (ESR)_Remission = 1, if DAS28-4 (ESR) < 2.6
DAS 28-4 (ESR)_Remission = 0, otherwise.

The proportion of patients in DAS 28-4 (ESR) Remission at Month X is then calculated as:

No. of patients with DAS 28-4 (ESR) Remission at Month X / Total Number of patients with non-missing DAS 28-4 (ESR) Remission at Month X.

7.1.2.3.5 DAS28-4 (CRP) REMISSION

At each time point (M3, M6, M9, M12, M115, M18, M21, M24) DAS 28-4 (CRP) Remission is derived as:

DAS 28-4 (CRP)_Remission = 1, if DAS28-4 (CRP) < 2.6
DAS 28-4 (CRP)_Remission = 0, otherwise.

The proportion of patients in DAS 28-4 (CRP) Remission at Month X is then calculated as:

No. of patients with DAS 28-4 (CRP) Remission at Month X / Total Number of patients with non-missing DAS 28-4 (CRP) Remission at Month X.

7.1.2.4 CHANGE FROM BASELINE IN DAS28-4 (ESR) AND DAS28-4 (CRP)

7.1.2.4.1 DAS28-4

DAS28-4 (ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm.

DAS28-4 (CRP) is similarly calculated by:

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

Where TJC28 is the Tender Joint Count, SJC28 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 in mm. PtGA will be used in this calculation.

The change from baseline in DAS28-4 (ESR) will be calculated at each time point as:

DAS28-4 (ESR) at time point – DAS28-4 (ESR) at baseline.

Similarly change from baseline in DAS28-4 (CRP) will be calculated at each time point as:

DAS28-4 (CRP) at time point – DAS28-4 (CRP) at baseline.

Change from Baseline in DAS 28-4 at all time points (M3, M6, M9, M12, M15, M18, M21, M24) will be presented.

7.1.2.5 CHANGE FROM BASELINE IN DURATION OF MORNING STIFFNESS

The duration of stiffness in the morning will be provided in the eCRF.
The change from baseline in duration of morning stiffness will be calculated as.

Morning Stiffness at time point – Morning Stiffness at baseline.

7.1.2.6 CHANGE FROM BASELINE IN FFBH

The FFbH questionnaire 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)

The change from baseline will then be calculated at each time point as:

Functional capacity at timepoint – Functional capacity at baseline

Change from Baseline in FFbH functional capacity at all time points (M3, M6, M9, M12, M115, M18, M21, M24) will be presented.

7.1.2.7 RATE OF FUNCTIONAL REMISSION (FFBH)

At each time point FFbH remission is derived as:

FFbH_Remission = 1, if FFbH > 83%

FFbH_Remission = 0, Otherwise

The proportion of patients with FFbH Functional Remission at Month X is then calculated as:

No. of patients with FFbH_Remission at Month X / Total Number of patients with non-missing FFbH Remission at Month X.

7.1.2.8 CHANGE FROM BASELINE IN EQ-5D

The EQ-5D is a self-reported questionnaire developed by the European Quality of Life (EuroQoL) Group. It is a standardised instrument used to measure quality of life. Change from baseline in EQ-5D will be collected over time and analysed for patients taking tofacitinib. 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 2.

Table 2: 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 3**.

Table 3: EQ-5D Weightings

Weights from Germany are used:

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:

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

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

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

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.

The change from baseline in EQ-5D will be calculated for each time point as:

EQ-5D at timepoint X – EQ-5D at baseline

7.1.2.9 CHANGE FROM BASELINE IN FACIT-FATIGUE

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

The change from baseline in FACIT-Fatigue score will be calculated for each time point as:

FACIT-Fatigue score at time point X – FACIT-Fatigue score at baseline

7.1.2.10 DRUG SURVIVAL STATUS OF TOFACITINIB

For patients who terminate tofacitinib, the drug survival status will be recorded as follows:

Those who terminate tofacitinib:

- Status = 1
- Time = Termination date tofacitinib – Date of initiation on tofacitinib

Tofacitinib is terminated when indicated on instrument "Rheumatologische Medikation" for therapy class tsDMARD/bDMARD variable *Change* (BDCM.CHANGECD) is set to "Therapy stop". Tofacitinib pauses, where variable *Change* is set to "Therapy paused", are not considered terminations.

Patients who do not terminate tofacitinib:

- Status = 0
- Time = Date of final visit – Date of initiation on tofacitinib

If patient is lost to follow-up or withdraws from the study they will be censored at the date of their last visit.

7.1.2.11 PATIENT'S SATISFACTION WITH DRUG TREATMENT

Patient's overall satisfaction with treatment is assessed via a 5-point likert question (extremely dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied and extremely satisfied).

At each visit, Visit X, overall satisfaction will be presented only for those who remained on tofacitinib at the last visit, Visit X-1. This will be split by those who stop taking tofacitinib at Visit X and those that remain on tofacitinib at Visit X.

7.2 SAFETY ENDPOINTS

Incidence and severity of all adverse events including serious adverse events (SAEs).

The reporting of safety data will be in accordance with Pfizer Data Standards.

7.3 COVARIATES, FACTORS AND POTENTIAL CONFOUNDERS

7.3.1 FACTORS OF INTEREST FOR PRIMARY ANALYSIS

The following covariates will be included in the primary analysis:

a. DAS 28-4 (ESR) LDA (see sections 6.1.2.4.1 and 6.1.2.2.3 for derivations) [Note: this is a binary endpoint].

b. Indicator variable for whether patient has achieved change from baseline of DAS28-4 (ESR) > 1.8 (see section 6.1.2.4.1 for derivations of DAS28-4 (ESR)) [Note: this is a binary endpoint].

   Change from baseline will be calculated as:

   ΔDAS28-4 (ESR) = DAS28-4 (ESR) at time point – DAS28-4 (ESR) at baseline

   If a patient has achieved ΔDAS28-4 (ESR) > 1.8 the indicator will be 1,

   If ΔDAS28-4 (ESR) > 1.8 is not achieved, the indicator will be 0.

c. Physician Global Assessment of Arthritis – measured on a visual analogue scale (0-100mm).

d. Patient's Global Assessment of Arthritis – measured on a visual analogue scale (0-100mm).

e. Patient's Assessment of Arthritis Pain – measured on a visual analogue scale (0-100mm).

f. Patient's overall satisfaction with treatment:

For each patient the response to the question 'How satisfied are you with the drugs that you have received for your arthritis since your last visit?' will be assigned as below:

0 = extremely dissatisfied,

1= dissatisfied,

2 = neither satisfied nor dissatisfied,

3 = satisfied

4 = extremely satisfied

7.3.2 FACTORS OF INTEREST FOR SENSITIVITY OF THE PRIMARY ANALYSIS

The following covariates will be included in a sensitivity analysis of the primary endpoint:

a. DAS28-4 with Erythrocyte Sedimentation Rate (ESR) (section 7.1.2.4.1). [Note: this is a continuous endpoint].

b. ΔDAS28-4 (ESR), [Note: this is a continuous endpoint].

c. Physician Global Assessment of Arthritis

d. Patient's Global Assessment of Arthritis

e. Patient's Assessment of Arthritis Pain

f. Patient's overall satisfaction with treatment

g. Incidence of comorbidities

- 1 if patient has at least one comorbidity
- 0 if no comorbidities are recorded

7.3.3 POTENTIAL CONFOUNDERS TO BE INCLUDED IN THE PRIMARY ANALYSIS

A number of potential confounders will also be included in the primary analysis and all sensitivity analyses:

- Age at baseline
- Gender
- Duration of disease at baseline
- Indicator of tofacitinib dose
    - 1 if recommended dose of 5mg per day (i.e. TofInterval = BID),
    - 0 if reduced dose of 2.5mg per day (i.e. TofInterval = Daily).
- Poor prognostic factors (PF) indicator (1 if at least one Poor PF is present, 0 otherwise)

- Indicator of dose of MTX or combination partner (1 if increase in dose since last visit, 0 otherwise)
- Indicator of dose of Glucocorticoids (1 if increase in dose since last visit, 0 otherwise)
- Whether patient on 2nd or 3rd line treatment (see below)

    A patient is defined as on 2nd line treatment if they were prescribed only csDMARDs prior to enrolling in the study.

    A patient is defined as on 3rd line treatment if they were prescribed bDMARDs prior to enrolling in the study.

    For a list of the medications considered to be csDMARDs and bDMARDs please see the eCRF.

- Indicator of tolerability issues (1 if treatment termination due to tolerability issues, 0 otherwise).
- Indicator of efficacy issues (1 if treatment termination due to efficacy issues, 0 otherwise).
- Incidence of the following comorbidities documented at the baseline visit (a term will be fitted for each comorbidity with the value 1 if the comorbidity is recorded for a patient or 0 otherwise):
    - Ischemic cardiovascular disease
    - Malignancies
    - Infections
    - Gastro disease
    - Osteoporosis
    - Depression

Any other variables observed to be potential confounders will also be investigated.

8 HANDLING OF MISSING VALUES

8.1 TIME TO EVENT (PRIMARY ANALYSIS, TIME TO FIRST TREATMENT ESCALATION AND DRUG SURVIVAL)

Time to event should be determined for the events without any date imputation.

If a patient experiences the event of interest the status will be 1, and the time will be the time at which the event occurred (or visit at which it was recorded).

If a patient doesn't experience the event of interest the status will be 0, and the time will be the last time that the patient was known to be in the study (last visit). If this is not the end of the study then the time will be censored at this time point.

The primary endpoint is a time-to-event endpoint, although it takes into account the possibility of multiple events occurring for each patient. For each patient the data for analysis should consist of the times at which they experienced the event of interest and the values of the covariates at each time point. Any missing data within the covariates to be included in the models for primary analysis will be replaced by the nearest available value to the event. If more than one value qualifies, the later value will be used .

8.2 BINARY ENDPOINTS

Missing data will not be imputed unless stated otherwise.

8.3 CONTINUOUS ENDPOINTS

Missing data will not be imputed unless stated otherwise.

8.4 PATIENT REPORTED OUTCOMES (PROS)

The questionnaires that will be used in the study (EQ-5D-5L, FACIT-Fatigue and FFbH) are accompanied by rules for replacing missing values. If these rules result in the patient having a missing score at a visit, then the missing values will be assumed to be missing at random.

9 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1 STATISTICAL METHODS

Descriptive statistics will be presented to describe patient characteristics. Generally, categorical covariates will be described by frequency distribution while continuous covariates expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate. Graphical displays may also be used.

9.1.1 ANALYSIS FOR RECURRENT EVENT DATA

In order to account for the possibility that there are multiple events occurring for each patient cox-proportional hazards modeling will be used with adjustment for recurrent events. This involves fitting either the Andersen and Gill or Prentice, Williams and Peterson gap-time models to the data.

For each patient, the data will be split into time periods, then data for each time window should include the patient's status, the time of event (if the event occurred) and the value of each of the factors of interest:

So, for patient A, who had events at M6 and M18, their data could look like this:

Patient	Start	Stop	Treatment Escalation Status	Factor A	Factor B	Factor C
A	0	M6	1	3.9	0.6	-10
A	M6	M12	0	3.0	1.5	-20
A	M12	M8	1	2.8	1.7	-10
A	M18	M24	0	2.2	2.3	-10

The cox proportional hazards model (using PROC PHREG) is then used, including the factors of interest (Section 7.3.1) to determine which, if any of them, have an impact on the rate at which treatment changes occur.

Any potential confounders should be included in the model also (Section 7.3.3).

The estimated event rate will be presented, along with 95% confidence interval and p-value, for each of the covariates of interest. Note: These will not be presented for the variables considered to be confounders.

The number and proportion of people experiencing an event at each time point will be presented.

Supportive tables will also be presented which summarises each of the covariates in the model at each visit.

The analysis will be performed for each type of escalation as defined in section 7.1.1 and overall.

9.1.2 ANALYSIS FOR TIME TO EVENT DATA

The time to first event will be summarised in terms of mean, standard deviation, median, minimum and maximum. The table of the estimated hazard rate will be presented, along with a Kaplan-Meier plot of the hazard function.

9.1.3 ANALYSIS OF CONTINUOUS DATA

The absolute values and change from baseline in each endpoint will be summarised for each time point using N, mean, standard deviation, median, minimum and maximum.

9.1.4 ANALYSIS FOR BINARY DATA

Binary data will be presented using counts and percentages. To calculate the percentage, the denominator will be the number of subjects with a non-missing value. These will be presented for each time point.

9.1.5 ANALYSIS OF CATEGORICAL DATA

Categorical data will be summarized in terms of number and percentage of patients within each category at each visit. Shift tables of changes from baseline will also be presented.

9.1.6 COMPARISON BETWEEN TREATMENTS

As there is only one cohort, those who are initiated on tofacitinib, there will be no formal comparison between treatment groups, although endpoints may be summarised by treatment subgroups (Section 6.6). All descriptive statistics will be presented overall and for all secondary analyses this will only be done using the data recorded when patients were taking tofacitinib.

9.2 STATISTICAL ANALYSES

The statistical software SAS 9.3 (or higher) will be used to conduct the statistical analysis.

The results will be presented in tables and plots programmed within SAS.

Both the interim and final analyses will be performed using the methods described in this SAP. The outputs to be produced for the interim analysis will be flagged in the list of tables.

9.2.1 BACKGROUND AND DEMOGRAPHIC CHARACTERISTICS AND STUDY DISPOSITION

The Demographic and baseline variables will be summarised:
Continuous: Mean, standard deviation, median, minimum and maximum
Categorical: Frequency and Percentage of population.

This will include age, sex, height, weight, smoking history, smoking status, severity of disease, duration of disease, anti-citrullinated protein antibodies (ACPA) / RF, vaccination status, presence of Poor Prognostic Factors, comorbidities, co-medication and concomitant medication and will be based on the Full Analysis Set.

The number and percentage of patients at each time point will be provided along with reasons for withdrawal from the study. For patients who have discontinued tofacitinib treatment but remain in the study, information on the treatments prescribed following study treatment (tofacitinib) will be provided.

The baseline visit for each patient will be their Baseline (Enrollment) visit (Visit 1).

9.2.2 PRIMARY ANALYSES

Each of the factors that will be included in the models for the primary analysis will be summarized by time point.

The Primary endpoint will be analysed as recurrent event data (as described in Section 9.1.1). The factors of interest as well as potential confounders (as described in Section 7.3.1 and section 6.3.3 respectively) will be included so as to determine whether they have an impact on the rate of treatment change. The population used for this analysis will be the FAS, including all visits (scheduled and unscheduled). The analysis will be repeated using the PPAS with visit windows as outlined in Section 12.1.1).

Escalations occurring in-between two planned visits will be assigned to visits using the visit windows provided in section 12.1.1. If two or more escalations fall into the same window, all escalations will be counted. Escalations, which are assigned to the baseline visit, will be counted under the Month 3 Visit, unless the escalation occurred before first tofacitinib treatment. Escalations, which fall outside the visit windows, will be assigned to the visit nearest to the Target Day. If two visits are equal distance from the escalation date in absolute value, the later visit should be used.

Sensitivity analyses, using both the FAS and PPAS, will be carried out with the covariates mentioned in section 7.3 along with the confounders mentioned above. An exploration of covariates will be carried out to assess any colinearity.

A further sensitivity analysis will be carried out using the FAS and PPAS population where treatment switches will be assigned to the visit prior to the date at which it occurred.

9.2.3 SECONDARY ANALYSES

All secondary endpoints will be analysed using the SFAS.

Other subgroup analyses maybe carried out, these will be defined prior to database lock.

NOTE: Although a subject will be included in the analysis set regardless of their sequence of treatment, only data collected while a subject was on tofacitinib will be included in the secondary analyses. Methods used are described in Section 9.1.2 - 9.1.4.

9.2.3.1 TIME TO FIRST TREATMENT ESCALATION

Time to first treatment escalation will be analysed as in Section 9.1.2 using the SFAS. Missing or incomplete dates will not be imputed (as per Section 8.1).

9.2.3.2 RATE OF LDA

Each definition of LDA (Section 7.1.2.2) will be presented as in Section 9.1.4, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2).

9.2.3.3 RATE OF REMISSION

Each definition of Remission (Section 7.1.2.3) will be presented as in Section 9.1.4, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2).

9.2.3.4 CHANGE FROM BASELINE IN DAS28-4 (ESR) AND DAS28-4 (CRP)

Change from baseline in DAS28-4 (ESR) and DAS28-4 (CRP) will be presented and analysed as in Section 9.1.3, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2)

9.2.3.5 CHANGE FROM BASELINE IN DURATION OF MORNING STIFFNESS

Duration of morning stiffness will be presented as in Section 9.1.3, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2)

9.2.3.6 CHANGE FROM BASELINE IN FFBH

Change from baseline in FFbH score will be presented and analysed as in Section 9.1.3, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2)

9.2.3.7 RATE OF FUNCTIONAL REMISSION

Rate of Functional Remission (Section 7.1.2.7) will be presented as in Section 9.1.4, using the SFAS, only including data when patients were taking tofacitinib. Missing data will not be imputed (as per Section 8.2).

9.2.3.8 CHANGE FROM BASELINE IN EQ-5D

Change from baseline in EQ-5D score (Section 7.1.2.8) will be presented and analysed as in Section 9.1.3, using the SFAS, only including data when patients were taking tofacitinib.

9.2.3.9 CHANGE FROM BASELINE IN FACIT-FATIGUE

Change from baseline in FACIT-FATIGUE score (Section 7.1.2.9) will be presented and analysed as in Section 9.1.3, using the SFAS, only including data when patients were taking tofacitinib.

9.2.3.10 DRUG SURVIVAL STATUS OF TOFACITINIB

Time to cease taking tofacitinib (drug survival) will be analysed as per Section 9.1.2, using the SFAS. Missing data will not be imputed (as per Section 8.1).

9.2.3.11 PATIENT'S SATISFACTION WITH DRUG TREATMENT

The Patient satisfaction is measured through a 5-point likert question asked at each visit and will be presented as in Section 9.1.5, using the FAS. At each visit, Visit X, only those who remained on tofacitinib at the previous visit, Visit X-1, will be presented. At each visit the satisfaction will be summarised split by those who remain on tofacitinib at Visit X and those who stop taking tofacitinib at Visit X.

9.2.4 SAFETY ANALYSES

- *Adverse events will be summarized according to Pfizer standards.*

Two sets of 'All Causality' and 'Treatment Emergent' adverse events will be summarised:

The first set will contain adverse event data for subjects while they were taking tofacitinib either as a monotherapy or in combination with MTX (patients will be included in this group if they have taken MTX at any point in the study in combination tofacitinib regardless of duration). This AE table will summarise AEs under one treatment heading

for tofacitinib (which includes monotherapy and combination therapy with MTX).. A drug lag of 28 days will be used to assign treatment emergence to tofacitinib. The second set will contain treatment emergent adverse events, which are related to tofacitinib and reported in a separate table.

Adverse events which occurred under another DMARD, following cessation of Tofacitinib, will only be listed and presented in a separate listing. AEs, which starts on the first day of a new treatment, e.g. Enbrel will be assigned to tofacitinib if the AE is within 28 days of tofacitinib. For non-Tofacitinib therapies a drug lag of 0 days will be applied. The AE will hence, also appear in the listing for other DMARDs as the AE started after the initiation of Enbrel. Therefore, any event which occurs during a 28 day lag of discontinuing tofacitinib will appear under tofacitinib in the tables and listings, and under the new treatment in the DMARD listing.

An all AE listing will show all AEs, individual rheumatologic therapies that are linked to the AE and whether the AE is tofacitinib treatment emergent.

Treatment labels for reporting adverse events:

Primary Adverse event table to assess AEs during tofacitinib treatment:

tofacitinib

9.2.5 SUBGROUP ANALYSIS

In addition to the analyses described above secondary endpoints will be analysed split by the subgroups described in section 6.6, as appropriate.

If additional subgroup analyses are needed, the details will be included as an amendment to this SAP prior to database release.

9.2.6 SUMMARY OF ANALYSES

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Number of Treatment Escalations	FAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR) ≤ 3.2, ΔDAS28-4(ESR) > 1.8, PtGA, PhyGA,	Imputation

					Pain, Satisfaction Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic factors (PF) Indicator, Indicator of dose of MTX or combination partner, Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment, Indicator of tolerability issues, Indicator of efficacy issues, comorbidities: Ischemic cardiovascular disease, Malignancies, Infections, Gastro disease, Osteoporosis, Depression (Note: will be assessed as individual covariates or as a composite, with 1 if a patient has any comorbidity or 0 otherwise, as appropriate).	
Number of Treatment Escalations	PPAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR) ≤ 3.2, ΔDAS28-4(ESR) > 1.8, PtGA, PhyGA, Pain, Satisfaction Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic	No Imputation

					factors (PF) Indicator, Indicator of dose of MTX or combination partner, Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment, Indicator of tolerability issues, Indicator of efficacy issues, comorbidities: Ischemic cardiovascular disease, Malignancies, Infections, Gastro disease, Osteoporosis, Depression (Note: will be assessed as individual covariates or as a composite, with 1 if a patient has any comorbidity or 0 otherwise, as appropriate).	
Number of Treatment Escalations (Sensitivity Analysis)	FAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR), ΔDAS28 4(ESR), PtGA, PhyGA, Pain, Satisfaction, Comorbidities (1 if patient has any comorbidity, 0 otherwise). Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic factors (PF) Indicator, Indicator of dose of MTX or combination partner,	No Imputation

					Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment, Indicator of tolerability issues, Indicator of efficacy issues, If the overall comorbidity covariate is significant the individual comorbidity covariates (Ischemic cardiovascular disease, Malignancies, Infections, Gastro disease, Osteoporosis, Depression) may be included as confounders instead as appropriate.	
Number of Treatment Escalations (Sensitivity Analysis)	PPAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR), ΔDAS28-4(ESR), PtGA, PhyGA, Pain, Satisfaction, Comorbidities (1 if patient has any comorbidity, 0 otherwise). Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic factors (PF) Indicator, Indicator of dose of MTX or combination partner, Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment,	No Imputation

					Indicator of tolerability issues, Indicator of efficacy issues. If the overall comorbidity covariate is significant the individual comorbidity covariates (Ischemic cardiovascular disease, Malignancies, Infections, Gastro disease, Osteoporosis, Depression) may be included as confounders instead as appropriate.	
Number of Treatment Escalations (where treatment switch is assigned to prior visit – further sensitivity)	FAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR) ≤ 3.2, ΔDAS28-4(ESR) > 1.8, PtGA, PhyGA, Pain, Satisfaction Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic factors (PF) Indicator, Indicator of dose of MTX or combination partner, Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment, Indicator of tolerability issues, Indicator of efficacy issues, comorbidities: Ischemic cardiovascular disease, Malignancies,	Imputation

					Infections, Gastro disease, Osteoporosis, Depression (Note: will be assessed as individual covariates or as a composite, with 1 id a patient has any comorbidity or 0 otherwise, as appropriate).	
Number of Treatment Escalations (where treatment switch is assigned to prior visit – further sensitivity)	PPAS			Cox-Proportional hazards with recurrent events (Section 9.1.1)	Covariates: DAS28-4(ESR) ≤ 3.2, ΔDAS28-4(ESR) > 1.8, PtGA, PhyGA, Pain, Satisfaction Confounders: Age, Gender, Duration of disease, Indicator of tofacitinib dose, Poor prognostic factors (PF) Indicator, Indicator of dose of MTX or combination partner, Indicator of dose of Glucocorticoids, Whether patient on 2nd or 3rd line treatment, Indicator of tolerability issues, Indicator of efficacy issues, comorbidities: Ischemic cardiovascular disease, Malignancies, Infections, Gastro disease, Osteoporosis, Depression (Note: will be assessed as individual covariates or as a composite, with 1 id a patient has any	No Imputation

					comorbidity or 0 otherwise, as appropriate).	
Time to First Treatment Escalation	FAS			Kaplan-Meier Plots and Table (Section 9.1.2)		No imputation
Rate of LDA	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.4)		No imputation
Rate of Remission	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.4)		No imputation
Change from baseline DAS28-4	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.3)		No imputation
Change from baseline in Morning Stiffness	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.3)		No imputation
Change from baseline in FFbH	FAS, including only data collected with		Therapy Sequence, RA	Summary Tables (Section 9.1.3)		No imputation

	patient remained on tofacitinib		Medication History, Switch Status, Number of Treatment Switches (Section 6.6)			
Rate of functional remission in FFbH	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.4)		No imputation
Change from baseline in EQ-5D score	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.3)		No imputation
Change from baseline in FACIT score.	FAS, including only data collected with patient remained on tofacitinib		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches (Section 6.6)	Summary Tables (Section 9.1.3)		No imputation
Drug Survival	FAS			Kaplan-Meier Plots and Table (Section 9.1.2)		No imputation
Patient's Satisfaction with Drug Treatment	FAS,		Therapy Sequence, RA Medication History, Switch Status, Number of Treatment Switches	Summary Tables (Section 9.1.5)		No imputation

			(Section 6.6)			

10 LIST OF TABLES AND TABLE SHELLS

To be presented in a separate document.

11 REFERENCES

1 Strand V, Singh JA. Improved health-related quality of life with effective disease modifying antirheumatic drugs: evidence from randomized controlled trials. The American journal of managed care. 2007;13 Suppl 9:S237-51. Epub 2007/01/12.

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

3 Brown K. Rheumatoid Lung Disease. Proc Am Thorac Soc 2007;4:443–448

4 Gerhold K, Richter A, Schneider M, Bergerhausen H-J 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 Rheumatology (Oxford) 2015;54(10):1858–1866

5 Boonen A, Severens JL. The burden of illness of rheumatoid arthritis. Clin Rheumatol. 2011;30 Suppl 1:S3–8

6 Zhang W, Anis AH. The economic burden of rheumatoid arthritis: beyond health care costs. Clin Rheumatol. 2011;30 Suppl 1:S25–32. CT24-GSOP-RF03 NI Study Protocol Template; Version 3.0, Effective Date 10-Oct-2014 Pfizer Confidential Page 47 of 50 Tofacitinib citrate A3921302 OBSERVATIONAL PLAN NON-INTERVENTIONAL STUDY Final, 27 June 2017

7 Emery P. Evidence supporting the benefit of early intervention in rheumatoid arthritis. J Rheumatol Suppl. 2002 Nov;66:3-8.

8 Pincus T. Rheumatoid arthritis: a medical emergency? Scand J Rheumatol Suppl. 1994;100:21-30.

9 Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43:906–14.

10 van Nies JA, Krabben A, Schoones JW, et al. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis 2014 May;73(5):861-70.

11 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a singleblind randomized controlled trial. Lancet 2004;364:263–9.

12 Smolen, J. S., R. Landewe, J. Bijlsma, G. Burmester, K. Chatzidionysiou, M. Dougados, J. Nam, *et al.* "Eular Recommendations for the Management of Rheumatoid Arthritis with Synthetic and

Biological Disease-Modifying Antirheumatic Drugs: 2016 Update." [In eng]. *Ann Rheum Dis* 76, no. 6 (Jun 2017): 960-77

13 Felson DT, Smolen JS, Wells G, et al. American college of rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

14 Albrecht et al. 2016 Klinische Remission bei rheumatoider Arthritis – Daten aus der Früharthritiskohortenstudie CAPEA Z. Rheumatol 75:90-96).

15 Albrecht et al. 2017, Versorgung der rheumatoiden Arthritis 2014 – Aktuelle Daten aus der Kerndokumentation, Z. Rheumatol 76:50-57

16 Louder MA,Singh A, Saverno K, Cappelleri JC, Aten AJ et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9(2):84-93

17 Krüger K, Alten R, Schiffner-Rohe J, Behmer OS, Schiffhorst G, J. Rellecke J, Nolting H. D. Patient preference in the choice of disease modifying anti-rheumatic drugs. Poster presented at the EULAR Annual European Congress of Rheumatology, Rome, Italy, June 10-13, 2015

18 A3921302_ObservationalPlan_Finalv1.1_23Aug2017.docx

12 APPENDICES

12.1 APPENDIX 1: DATA DERIVATION DETAILS

12.1.1 A1.1 DEFINITION AND USE OF VISIT WINDOWS IN REPORTING

Visit windows will be used for efficacy variables, and for any safety displays that display by month. The visit windows for the analysis defined in the table differ from that outlined in the protocol. The analysis visit windows will be M1, M3±14 days, all subsequent visits MX ± 28 days.

Table 11.1: Visit windows

Visit Label	Target Day	Definition [Day window]
Enrolment	1	1
Month 3	91	77 to 105
Month 6	182	154 to 210
Month 9	273	245 to 301
Month 12	365	337 to 393
Month15	456	428 to 484
Month18	547	519 to 575
Month 21	638	610 to 666
Month 24	730	702 to 758

For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls within 40 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

For the other values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

If baseline is missing there will be no imputation and although the subject's data will be included in summary data it will not be included in any change from baseline analyses.

If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equal distance from the Target Day in absolute value, the later visit should be used.

For the primary endpoint analysis, escalations occurring in-between two planned visits will be assigned to visits using the visit windows described above. If two or more escalations

fall into the same window, all escalations will be counted. Escalations, which are assigned to the baseline visit, will be counted under the Month 3 Visit, unless the escalation occurred before first tofacitinib treatment. Escalations, which fall outside the visit windows, will be assigned to the visit nearest to the Target Day. If two visits are equal distance from the escalation date in absolute value, the later visit should be used.

(Safety analysis may follow Pfizer standard)

12.1.2 DEFINITION OF TREATMENT ESCALATIONS

Table 11.2 provides an overview of all possible treatment switch combinations relevant for the analysis of the primary endpoint and defines the type of escalations, e.g., whether the treatment switch relates to a step-up, step-down or termination.

Table 12.2: Definition of treatment escalations

Therapy*>	Mono Tofa	Mono tsDMARD	Mono csDMARD	MonoTNFi	Mono bDMARD	Combo+ csDMARD	Combo tsDMARD +csDMARD	ComboTNFi +csDMARD	Combo bDMARD+ csDMARD	Therapy Stop
MonoTofa	-	Step-up	Step-down	Step-up	Step-up	Step-up	Step-up	Step-up	Step-up	Treatment termination
Mono tsDMARD	Step-up	Step-up if different tsDMARD	Step-down	Step-up	Step-up	Step-up	Step-up	Step-up	Step-up	Treatment termination
Mono csDMARD	Step-up	Step-up	Step-up if different csDMARD	Step-up	Step-up	Step-up	Step-up	Step-up	Step-up	Treatment termination
MonoTNFi	Step-up	Step-up	Step-down	Step-up if different TNFi	Step-up	Step-up	Step-up	Step-up	Step-up	Treatment termination
Mono bDMARD	Step-up	Step-up	Step-down	Step-up	Step-up if different bDMARD	Step-up	Step-up	Step-up	Step-up	Treatment termination
Combo+ csDMARD	Step-down	Step-up	Step-down	Step-up	Step-up	Step-up if different csDMARD	Step-up	Step-up	Step-up	Treatment termination
Combo tsDMARD +csDMARD	Step-up	Step-up if different tsDMARD; Step-down otherwise	Step-down	Step-up	Step-up	Step-up	Step-up if different tsDMARD or csDMARD	Step-up	Step-up	Treatment termination
Combo TNFi + csDMARD	Step-up	Step-up	Step-down	Step-down, if same TNFi, Step-up if different TNFi	Step-up	Step-up	Step-up	Step-up if different csDMARD/TNFi	Step-up if different bDMARD or csDMARD	Treatment termination
Combo bDMARD+ csDMARD	Step up	Step up	Step down	Step up	Step down if same bDMARD; Step-up otherwise	Step up	Step up	Step up	Step up if different bDMARD or csDMARD	Treatment termination

*) **Definitions:**

Mono= Monotherapy

Combo= Combination

Tofa= tofacitinib

TNFi= Tumor Necrosis Factor Inhibitor

Mono Tofa= Monotherapy tofacitinib

Mono tsDMARD= Monotherapy any tsDMARD other than Tofa

Mono csDMARD= Monotherapy any csDMARD

Mono TNFi= Monotherapy any TNFi

Mono bDMARD= Monotherapy any bDMARD other than TNFi

Combo Tofa= Combination therapy tofacitinib with any csDMARD

Combo csDMARD= Combination therapy tofacitinib + any csDMARD

Combo tsDMARD + csDMARD= Combination therapy tsDMARD other than tofacitinib + any csDMARD

Combo TNFi + csDMARD= Combination therapy any TNFi+ any csDMARD

Combo bDMARD + csDMARD= Combination therapy bDMARD other than TNFi+ anycsDMARD

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