NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	BASELINE VARIABLES PREDICTING TREATMENT RESPONSE AT 6 MONTHS IN ADULT RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB 5MG BID IN A NON-INTERVENTIONAL SETTING (TREAT-RA)
Protocol number	A3921342
Protocol version identifier	2.0
Date	14 January 2020
Active substance	L04AA29 tofacitinib
Medicinal product	Xeljanz
Research question and objectives	The primary objective of this non-interventional study is to identify baseline characteristics of patients that predict response at 6 months of treatment. The study also aims to describe the treatment patterns of RA patients prescribed tofacitinib in a real-world setting and assess the effect of treatment on patient quality of life and physical function. Finally the study will assess the use of healthcare resources and costs in patients with RA treated with tofacitinib in Greece.
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2. LIST OF ABBREVIATIONS

Table 1. List of Abbreviations

Abbreviation	Definition
ACR	American Colleague of Rheumatology
AE	Adverse Event
AEM	Adverse event monitoring
ALT	Alanine transaminase
AST	Aspartate transaminase
CCP	Cyclic citrullinated protein
DCT	Data Capture Tool
CDAI	Clinical Disease Activity Index
CIOMS	Council for International Organizations of Medical Sciences
DCTDCT	Data Collection Tool
CRP	C-reactive Protein
CSR	Clinical Study Report
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drugs
EDP	Exposure during pregnancy
EIU	Exposure in Utero
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQol five dimensions questionnaire
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GGT	Gamma-glutamyl transferase
GPP	Good Pharmacoepidemiology Practices
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	High-density lipoprotein,
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IL	Interleukin
INF	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

Abbreviation	Definition
JAK	Janus kinase
LDL	Low-density lipoprotein,
LFT	Liver function test
LSLV	Last subject, last visit
MCP	Metacarpophalangeal joint
MTX	Methotrexate
NI	Non-Interventional
NSAID	Nonsteroidal Anti-Inflammatory Drugs
PASS	Post-Authorization Safety Study
PCD	Primary Completion Date
PhRMA	Pharmaceutical Research and Manufacturers of America
PIP	Proximal interphalangeal joints
PML	Progressive multifocal leukoencephalopathy
PT	Prothrombin time
PY	Patient years
RA	Rheumatoid arthritis
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SDAI	Simplified Disease Activity Index
SmPC	Summary of Product Characteristics
SOA	Schedule of activities
SRA	Serum rheumatoid factor
TB	Tuberculosis
TNF	Tumor necrosis factor
TyK	Tyrosine kinase
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

3. RESPONSIBLE PARTIES

Table 2. Principal Investigator(s)

Name, degree(s)	Title	Affiliation	Address
PPD	Study Clinician	PPD	PPD
PPD	Study Manager	PPD	PPD

4. ABSTRACT

N/A.

5. AMENDMENTS AND UPDATES

Table 3. Amendments and Updates

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	14/01/2020	Title Page, 2	Updated Study Team.	Team Change.
		8.2.1	Clarified Inclusion criterion 3.	Clarifying treatment status at the enrolment.
		8.7.3.4.2	Updated formula for work productivity loss scoring.	Corrected typographical mistake.
		5	Updated Milestones.	Adapted to expected dates.
		Throughout	Updated template.	New Template issued.

6. MILESTONES

Table 4. Milestones

Milestone	Planned date
Completion of feasibility assessment	Oct 2019
Start of data collection	May 2020
End of data collection	May 2022
Final study report	April 2023

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint inflammation and destruction, leading to a progressive disability and adverse psychological effects with severe impact on patients' quality of life.[1] Apart from musculoskeletal complications directly related to their rheumatic disease, RA subjects are also at increased risk of suffering from co-morbidities such as cardiovascular and infectious diseases, osteoporosis, depression and cancer, contributing to the higher mortality rate observed in RA patients compared to the general population.[2]

The chronic nature of the disease deems necessary the long-term use of medication. Thus, RA represents significant health and socioeconomic burdens for the individual subject, healthcare systems and society, with indirect costs (productivity loss, absenteeism/disability, early retirement) accounting for up to ¾ of total costs for working patients.[3]

As there is currently no cure for RA, the target of treatment strategies is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, reduce the rate of joint damage, and, if possible, induce and maintain complete remission.[1] Although there are several effective treatments available nowadays, mainly biologic DMARDs, many patients fail to achieve or maintain the desired response and are treated sequentially with different drugs leading to increased costs, risk of toxicity and suboptimal effectiveness. Therefore, the ambition for personalized treatment has emerged and investigation to identify predictive tools of treatment response is a highly active area of research.[4]

Tofacitinib (CP-690,550) is an oral Janus kinase (JAK) inhibitor that targets inflammation by reducing pro-inflammatory cytokine signaling and production.[5]

The efficacy and safety evaluation of tofacitinib for the treatment of RA is based on a comprehensive clinical development program including six randomized, double blind, multicenter phase III studies in adult subjects with active rheumatoid arthritis (RA). In these trials tofacitinib consistently reduces signs and symptoms of RA, improves physical function and other subject-reported outcomes such as fatigue, pain and health-related aspects of quality of life in subjects with moderate to severe RA. Combined with its inhibition of the progression of structural damage, the development program has demonstrated tofacitinib as an effective targeted synthetic disease-modifying anti-rheumatic drug (DMARD) in treating RA.[6-11] Long-term extension and Phase 3b/4 post authorization safety studies are aimed to demonstrate sustained efficacy and a consistent safety profile as seen in the Phase 2 and 3 controlled clinical trials.

However, these trials may have limitations reflecting real world situations. It has been estimated that only 21-33% of patients documented in registries, reflecting more accurately routine care, would have met eligibility criteria of major trials as they often exclude patients with co-morbidities.[12] Also treatment of patients in daily clinical practice may vary from the strictly regulated schemes followed in clinical trials. Therefore, additional long-term data in registries and non-interventional studies of a European population would be helpful to further assess treatment outcomes in a real-world setting.

Furthermore, studies exploring the association between clinical and biochemical parameters with the efficacy of tofacitinib treatment are scarce. Prior, analyses based on P123 and LTE Tofacitinib data have shown: a) early achievement of clinical disease control seems to determine longer term treatment effect with Tofacitinib in MTX-naïve patients;
b) Tofacitinib treatment response at 6m may be higher for patients with higher disease activity at baseline based on CRP levels particularly for those with inadequate response to biologic DMARDs.[13,14] These results point out the need for more research and further investigation in order to help identify biomarkers that can predict response to tofacitinib treatment in patients with RA.

The impact of RA on work can be profound since permanent work disability (inability to continue working), is common among patients with RA.[15] In addition to the consequences for the patient, such as a decreased quality of life, work disability also leads to high costs. It is estimated that approximately one-third of the total cost for patients with RA is caused by production losses.[16] This implies that at-work productivity loss is an important concern, since work hours are not only lost incidentally through sick leave, but also more structurally and profoundly by at-work productivity loss. As so far data on the impact of Tofacitinib on work productivity are still limited, this study will assess the effect Tofacitinib on work productivity and non-work activities.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to identify clinical and/or biochemical factors that predict achievement of remission or LDA in patients with RA treated with tofacitinib.

The secondary objectives of the study are:

- To describe the treatment patterns of RA patients prescribed tofacitinib in a real-world setting;
- Assess the effect of treatment on patient quality of life and physical function;
- Estimate resource utilization and costs in patients with rheumatoid arthritis (RA) treated with tofacitinib in Greece.

Only a subset of non-serious AEs, collected in the study database, will be reported to Pfizer Safety. This subset will consist of the non-serious AEs that are actively sought due to Pfizer's intention to align with those areas identified as important missing information or a potential risk in the product risk management plan (RMP) of Tofacitinib.

8.1. Endpoints

8.1.1. Primary Endpoint:

a. Identify baseline characteristics that predict remission or LDA at month 6 of treatment, assessed by DAS28-4 (CRP) <2.6 and DAS28-4 (CRP) <3.2, respectively.

8.1.2. Key Secondary Endpoints:

a. Identify baseline characteristics that predict remission or LDA at month 12 of treatment, assessed by DAS28-4 (CRP) <2.6 and DAS28-4 (CRP) <3.2, respectively.

b. Change from Baseline in DAS 28-4 (ESR) and DAS 28-4 (CRP) at any time point.

c. Change from Baseline in HAQ-DI at any time point.

d. Rate of remission at any other time point, as assessed by: SDAI ≤3.3; CDAI ≤2.8; DAS 28-4 (ESR) <2.6 and DAS28-4 (CRP) <2.6.

e. Rate of LDA at any other time point, as assessed by: SDAI ≤11; CDAI ≤10; DAS 28-4 (ESR) <3.2 and DAS28-4 (CRP) <3.2.

f. Percentage HAQ-DI responders (decrease of at least 0.22) at any time point.

g. Change from Baseline in EuroQol EQ-5D Health State Profile at any time point.

h. Change from Baseline in FACIT-Fatigue scale at any time point.

i. Change from baseline in duration of morning stiffness at any time point.

j. Change from Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire at any time point.

k. Assess the use of healthcare resources and costs in patients with RA treated with tofacitinib in Greece.

l. Patients satisfaction with treatment at baseline and month 12.

m. Describe the treatment patterns of RA patients prescribed tofacitinib in a real-world setting.

9. RESEARCH METHODS

9.1. Study Design

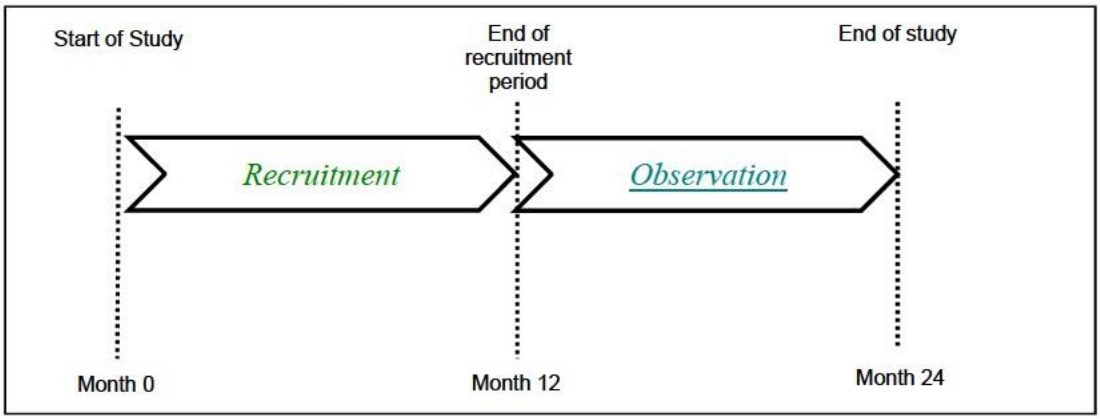
This is a 24-month, prospective, non-interventional, multi-center study with primary aim to identify clinical and/or biochemical factors that predict achievement of remission or LDA in patients with RA treated with tofacitinib in Greece. Eligible subjects will be followed from the date of first tofacitinib prescription until study end, death, or discontinuation, or loss to follow-up (whichever comes first) for the occurrence of the endpoints of interest.

In this study, the medicinal product(s) are prescribed in the usual manner in accordance with the terms of the marketing authorisation.

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

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

Figure 1. Study Design



9.2. Setting

The planned recruitment period is 12 months. With planned observation duration of 12 months per patient, the entire study would thus last for 24 months at maximum. The study is to start in May 2020 and will be ended in May 2022. Overall, about 200 patients in 19 centres are to be included in this non-interventional study. A patient will be followed up until the end of the planned study duration, regardless of any missing intermediate visits, as well as treatment changes during the course of follow-up.

9.2.1. Inclusion Criteria

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

Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study is a requirement for inclusion into this study.

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

Adult subjects with moderately to severely active rheumatoid arthritis who start treatment with tofacitinib in usual clinical practice conditions in compliance with the label.

1. Patients aged ≥18 years.
2. Confirmed Diagnosis of Rheumatoid Arthritis by rheumatologist.

3. Patients with moderate to severe RA diagnosed according to local practice who have already been started on treatment with tofacitinib, for at most seven working days.

4. Patients eligible for tofacitinib treatment according to current approved Summary of Product Characteristics (SmPC).

5. 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.

9.2.2. Exclusion Criteria

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

1. Exclusion Criteria according to the Xeljanz® SmPC.

2. Contraindications to Xeljanz® according to SmPC.

3. Hypersensitivity to the active substance (tofacitinib) or to any of the excipients.

4. Active tuberculosis (TB), serious infections, such as sepsis, or opportunistic infections.

5. Receipt of any investigational drug within 3 months before study inclusion as well as currently not participating in an interventional clinical trial.

6. Subjects who have received any previous treatment with tofacitinib or other JAK inhibitors.

7. Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

9.3. 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 (eDCT)	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs – dose	Exposure, Potential confounder, subgroup identifier	Case records and eDCT	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs - tolerability	Potential confounder, subgroup identifier	Case records and eDCT	Details will be provided in Statistical Analysis Plan
RA treatment with Tofacitinib and/or other DMARDs – route of administration	Potential confounder, subgroup identifier	Case records and eDCT	Details will be provided in Statistical Analysis Plan
Time of tofacitinib initiation	Exposure	Case records/eDCT	Details will be provided in Statistical Analysis Plan

Variable	Role	Data source(s)	Operational definition
Age	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Gender	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Height	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Weight	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Date of first diagnosis of RA	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Anti-citrullinated protein antibodies (ACPA)	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
RF	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Structural damage	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
RA Extra-articular manifestations	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Smoking history and current smoking status	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Alcohol intake	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Vaccination status	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Tuberculosis status	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Hepatitis status	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Co-morbidities	Baseline characteristic, potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Co-medication	Potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Prior medication for RA	Potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Concomitant medications for RA (steroids; NSAIDs, csDMARDs, bDMARDs)	Potential confounder, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Erythrocyte Sedimentation Rate (ESR)	Baseline characteristics and outcome variable	Case records/eDCT	Details will be provided in Statistical Analysis Plan
C-Reactive Protein (CRP)	Baseline characteristics and outcome variable	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Patient's global assessment of arthritis	Baseline and outcome variable	Case records/eDCT	Details will be provided in Statistical Analysis Plan

Variable	Role	Data source(s)	Operational definition
Physician's global assessment of arthritis	Baseline and outcome variable	Case records/eDCT	Details will be provided in Statistical Analysis Plan
EuroQol EQ-5D Health State Profile	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Health Assessment Questionnaire – Disability Index (HAQ-DI)	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Tender (28) joint count	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Swollen (28) joint count	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Functional Assessment of Chronic Illness Therapy (FACIT) Questionnaire	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Work Productivity and Activity Impairment (WPAI) Questionnaire	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Morning Stiffness	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Patient Assessment of Arthritis Pain	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Patients satisfaction with drug treatment	Baseline and Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Medical visits	Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Diagnostic tests	Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Hospitalizations	Outcome	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Educational level	Baseline, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan
Working status	Baseline and outcome, sub-group identifier	Case records/eDCT	Details will be provided in Statistical Analysis Plan

9.4. Data Sources

The data will be recorded using an electronic case report form (eDCT) for each patient included. The completed eDCTs 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 eDCTs 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 eDCTs must be signed by the treating physician or authorized personnel. All corrections of entries on the eDCTs 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 eDCTs must match the data in these records.

In some cases, the eDCT or part of the eDCT 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 eDCT and for which the eDCT 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. All questionnaires used in the study have been validated.

9.4.1. Study Procedures

Consecutive subjects attending will be included if they fulfil all selection criteria for the study and are started on treatment with tofacitinib for moderate to severely active rheumatoid arthritis.

All visits shall be scheduled according to clinical practice. Within this study 4 visits may be documented and one follow-up telephone communication at least 28 days after the last clinic visit for those patients with an ongoing treatment-related AE should be conducted. At each visit subjects will undergo procedures in compliance with the country label and as per standard of care. In order to collect comparable study data, visits occurring +/- 14 days of the scheduled visit date can be documented. If a patient misses one or more pre-planned study visits the patient can remain in the study.

After a training session the sites will get access to the eDCT where the data and findings of the patient are documented. Also 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 of the treatment, the initial tofacitinib dose and all changes and the reasons for changes are documented during the course of the evaluation. The concomitant medication is determined by the treating physician and is registered in the eDCT.

9.4.2. Study Period

The planned observation period of each patient is 12 months. In this time period up to 4 visits will be documented.

9.4.2.1. Baseline Visit

Following parameters will be documented at baseline visit:

- Informed Consent.
- Demographic data.
- Educational level.
- Working status.

- Medical History including RA.
- Duration since diagnosis.
- Comorbidities.
- Co-medication.
- Inclusion/Exclusion criteria according to protocol and SmPC.
- Vaccination status for pneumococcus, influenza, herpes zoster and hepatitis B.
- Tuberculosis status.
- Hepatitis status.
- Prior drug treatment of RA.
- Concomitant drug treatment.
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Serum rheumatoid factor (SRA).
- Cyclic Citrullinated Protein (CCP).
- Structural damage.
- Blood biochemistry & haematology.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- Patients Assessment of Arthritis Pain.
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- EuroQol EQ-5D Health State Profile.
- Work Productivity and Activity Impairment (WPAI) Questionnaire.

- FACIT (Functional Assessment of Chronic Illness Therapy) – Fatigue.
- Patients' overall satisfaction with treatment.

9.4.2.2. Scheduled Visits 2- 3/Month 3 – Month 6

Following parameters will be documented at each interim visit:

- Adverse event monitoring.
- Concomitant drug treatment.
- Co-medication.
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Blood biochemistry & haematology.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- Patient's Assessment of Arthritis Pain.
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- EuroQol EQ-5D Health State Profile.
- Work Productivity and Activity Impairment (WPAI) Questionnaire.
- FACIT (Functional Assessment of Chronic Illness Therapy) – Fatigue.
- Medical visits to Rheumatologist and other specialists.
- Diagnostic test performed.
- Hospitalizations.

9.4.2.3. Final (or Close Out) Visit 4/Month 12

Following parameters will be documented at final visit:

- Adverse event monitoring.
- Concomitant drug treatment.

- Co-medication.
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Blood biochemistry & haematology.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- Patient's Assessment of Arthritis Pain.
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- EuroQol EQ-5D Health State Profile.
- Work Productivity and Activity Impairment (WPAI) Questionnaire.
- FACIT (Functional Assessment of Chronic Illness Therapy) – Fatigue.
- Patients' overall satisfaction with treatment.
- Medical visits to Rheumatologist and other specialists.
- Diagnostic test performed.
- Hospitalizations.
- Working status.

9.4.2.4. Patient Withdrawal

Subjects experiencing AEs as listed in the Xeljanz SmPC [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 9.3).

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

Table 5. Schedule of Activities

Study Week	**Baseline** (Enrollment)	**Month 3**	**Month 6**	**Month 12**
Visit Number	1	2	3	4
Informed Consent	x			
Anamnesis/Medical History	x			
Demographic data	x			
Educational level	x			
Working status	x			x
Inclusion/exclusion criteria	x			
Vaccination status	x			
Treatment/Medication				
Prior RA drug treatment	x			
Concomitant RA drug treatment	x	x	x	x
Co-medication	x	x	x	x
Safety				
Inflammatory markers	x	x	x	x
Documentation of Comorbidities	x			
Documentation of AE		x	x	x
Efficacy				
Number of swollen and tender joints	x	x	x	x
Morning stiffness	x	x	x	x
Patients Global Assessment of Arthritis	x	x	x	x
Physicians Global Assessment of Arthritis	x	x	x	x
Patient Assessment of Arthritis Pain	x	x	x	x
Health Assessment Questionnaire – Disability Index (HAQ-DI)	x	x	x	x

Study Week	**Baseline** (Enrollment)	**Month 3**	**Month 6**	**Month 12**
Visit Number	1	2	3	4
EuroQol EQ-5D Health State Profile	x	x	x	x
Work Productivity and Activity Impairment (WPAI) Questionnaire	x	x	x	x
FACIT (Functional Assessment of Chronic Illness Therapy) – Fatigue	x	x	x	x
Overall satisfaction with treatment	x			x
Medical visits		x	x	x
Diagnostic tests		x	x	x
Hospitalizations		x	x	x

9.4.4. Assessments

9.4.5. Demographic Data

Demographic data will be documented at the Baseline Visit (Visit 1) including: date of birth, gender, weight, height, smoking status, alcohol intake.

9.4.6. Educational Level

Patient's educational level will be documented at the first visit (baseline visit).

9.4.7. Working Status

Patient's working status will be documented at the first (baseline visit) and the final visit (visit 4).

9.4.8. Medical History/Anamnesis

Patient's medical history will be documented at the first visit (baseline visit) including:

- RA diagnosis;
- Presence and level of RF and anti-citrullinated protein (ACPA) antibodies;
- Presence of erosions on x-rays;
- Presence of extra-articular manifestations (anemia, RA nodules, RA related vasculitis, amyloidosis or other).

9.4.9. Vaccination Status

At the Baseline Visit (Visit 1) current vaccination status of patients will be assessed for: pneumococcus, influenza, herpes zoster and hepatitis B.

9.4.10. Hepatitis and Tuberculosis Status

Hepatitis and tuberculosis status will be assessed at baseline visit (visit 1) according to the national guidelines.

9.4.11. Co-morbidities

At baseline visit (visit 1) the presence of co-morbidities will be documented. Co-morbidities of interest: cardiovascular disease, malignancies, infections, gastrointestinal disease (peptic ulcer and diverticulitis), osteoporosis, depression, hyperlipidaemia. For those co-morbidities present more information will be collected: year of diagnosis and treatment.

9.4.12. Prior and Concomitant Treatment

Relevant prior drug treatments will be recorded at the Baseline Visit (Visit 1). At each subsequent visit dose and route of administration of concomitant treatment will be documented.

9.4.13. Treatment of Rheumatoid Arthritis (RA-Treatment) with Tofacitinib and/or Other DMARDs

At each visit dose and route of administration (if applicable) of treatment with Tofacitinib and/or other DMARDs will be documented. 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.

9.4.14. Effectiveness Criteria

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

Table 6. 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]

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

9.4.15. Joint Counts

9.4.15.1. Tender/Painful Joint Count (TJC28)

At each visit (visits 1-4) twenty-eight (28) joints will be assessed to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial joints).

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.

9.4.15.2. Swollen Joint Count (SJC28)

At each visit (visits 1-4) the joint assessor will also assess these joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial joints).

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.

9.4.16. Patient Assessment of Arthritis Pain

At each visit (visits 1-4) 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.

9.4.17. Patient Global Assessment of Arthritis (PtGA)

At each visit (visits 1-4) subjects will answer the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The subject's response will be recorded using a 100 mm VAS with 0= very well and 100=very poorly.

9.4.18. Physician Global Assessment of Arthritis (PhyGA)

At each visit (visits 1-4) the Investigator will assess how the subject's overall arthritis appears at the time of the visit. This is an evaluation based on the subject's disease signs, functional capacity and physical examination, and should be independent of the Patient's Global Assessment of Arthritis. The Investigator's response will be recorded using a 100 mm VAS with 0=no disease activity and 100= worst disease activity.

9.4.19. Morning Stiffness

At each visit (visits 1-4) the duration of morning stiffness should be determined by asking the following questions: "Over the last 2 days, when did you wake in the morning?" "Over the last 2 days, when were you able to resume your normal activities without stiffness?"

9.4.20. Health Assessment Questionnaire – Disability Index (HAQ-DI)

The HAQ-DI[17] assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do". Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status. This questionnaire should be completed by the patient at each visit (visits 1-4) prior to any procedures being performed at the visit, if possible. The form should then be checked by the site staff for completeness.

9.4.21. EuroQol EQ-5D Health State Profile

The EuroQol EQ-5D Health State Profile[18] 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 has been established in a number of disease states, including rheumatoid arthritis. This questionnaire should be completed by the patient at each visit (visits 1-4) prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness.

9.4.22. Work Productivity and Activity Impairment (WPAI) Questionnaire

The Work Productivity & Activity Impairment Questionnaire (WPAI): Rheumatoid Arthritis is a 6-item questionnaire that is specific for rheumatoid arthritis and yields four types of scores: absenteeism, presenteeism (impairment at work/reduced job effectiveness), work productivity loss and activity impairment.[19] WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity.

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

The FACIT – Fatigue Scale is a subject completed questionnaire[20] consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better subject status (less fatigue). This questionnaire should be completed by the patient at each visit (visits 1-4) prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness.

9.4.24. C-reactive Protein (CRP)

The CRP shall be analysed by a local laboratory as per standard clinical practice and documented at each visit (visits 1-4). It will be used in the calculation of several efficacy parameters.

9.4.25. Erythrocyte Sedimentation Rate (ESR)

The ESR shall be analysed by a local laboratory and documented at each visit (visits 1-4). It will be used in the calculation of several efficacy parameters.

9.4.26. Overall Satisfaction with Treatment

Satisfaction with treatment will be assessed at baseline visit (visit 1) and at the final visit (visit 4) on a 5-point scale (where 0 = very dissatisfied and 4 = very satisfied) in response to the question "How satisfied are you with the drugs you received for your arthritis during the last year?"

9.4.27. Medical Visits

All Rheumatologist visits or medical visits to any other specialist made since the last visit related to the disease will be documented at visits 2-4.

9.4.28. Hospitalizations

RA-related and all-cause hospital admissions since the last visit will be documented at visits 2-4. Information collected will include number of days and reason for admission.

9.4.29. Diagnostic Tests

The number and type of diagnostic tests performed since the last visit will be documented at visits 2-4.

9.4.30. Safety Criteria

In contrast to the usual procedure for clinical trials in observational trials the treatment decision is independent of the protocol. Additionally selection criteria of patients at baseline are not as strict as for clinical trials. Thus, this study can provide new insights into the safety of Tofacitinib in routine care. All adverse events (AEs) that will occur during the observation period will be documented. Additionally, at the end of the observation both, the physician and the patient will be asked the general tolerability of the treatment with tofacitinib and reasons for premature discontinuation rates will be analysed.

9.5. Study Size

The primary objective of this study is to identify factors predictive of remission or LDA at month 6 of treatment. This will be investigated using a logistic regression model. For the purposes of the sample size, we will consider the LDA response rate.

Peduzzi et al suggest that such an analysis requires at least 10 events (ie, responders) per variable proposed in the model. The minimum number of subjects to include in the study can therefore be estimated using the following formula:

$N = 10\ k/p$

where p is the smallest of the proportions of responders or non-responders in the population and k the number of covariates.

Based on the results of previous studies, eg, A3921187 we would expect an LDA response rate of 50% at 6 months and assuming that the primary analysis will include ten covariates, it will be necessary to observe 100 events in approximately 200 patients (ie, 100 events/0.50).

It is expected that the amount of missing data and drop-outs will be minimal in this study, so no allowance has been made for this in the sample size calculation.

9.6. Data Management

9.6.1. Case Report Forms (DCTs)/Data Collection Tools (DCTs)

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

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

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

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

In some cases, the DCT may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the DCT, and for which the DCT will stand as the source document.

9.6.2. Record Retention

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

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

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

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

9.7. Data Analysis

This section gives an overview of the key methods and derivations required for the study. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. SAS (Version 9.1 or above) will be used for all analyses.

Unless specified otherwise, continuous variables will be summarised using descriptive statistics (n, mean, SD, median, min, max) and discrete variables will be summarised using counts and percentages.

9.7.1. 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.

9.7.2. 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.

Reasons given for premature discontinuation will also be summarized.

9.7.3. Efficacy Analysis

9.7.3.1. Primary Analysis

The primary analysis will investigate the potential role of several baseline clinical and biochemical parameters as independent predictive factors of remission or LDA at month 6 of treatment, assessed by DAS28-4 (CRP) <2.6 and DAS28-4 (CRP) <3.2, respectively and will be calculated as follows:

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

This will be investigated using logistic regression. The potential predictive factors that may be considered include:

- Age;
- Gender;
- Weight;
- Smoking history;
- Time (years) from RA diagnosis;
- Serology: RF, ACPA;
- Previous biologic DMARD use (number);
- Current concomitant treatment;
- Glucocorticoid dose;
- csDMARDs: number and dose;
- Acute phase reactants: ESR and CRP;
- DAS28-4 (CRP) score;
- HAQ-DI score;
- CDAI;
- Lipids (LDL);
- Hb levels.

The effect of each factor will firstly be tested with a univariate logistic regression model. All potential factors with a p-value resulting from univariate analysis less than 10% will then be included in a multivariate model, along with any factors considered important from a clinical point of view. Predictive factors and their interactions will be chosen using a backward (step-down) selection. Predictive factors chosen will be those which have a p-value less than 5%. In the case of a significant interaction, all individual components of the interaction will be "forced" in the model, whether they are statistically significant or not. It is anticipated that the primary model will include approximately ten covariates.

Full details, including methods for handling missing data, will be provided in the SAP. For the primary endpoints of remission or LDA, a non-responder imputation will be used for patients who have missing data at month 6.

9.7.3.2. Secondary Analysis

Investigate the potential role of several baseline clinical and biochemical parameters as independent predictive factors of remission or LDA at month 12 of treatment, assessed by DAS28-4 (CRP) <2.6 and DAS28-4 (CRP) <3.2, respectively.

9.7.3.2.1. DAS28-4 (ESR), DAS28-4 (CRP), HAQ-DI

DAS28-4 (ESR), DAS28-4 (CRP) and HAQ-DI will be calculated at each time point as follows:

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.

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 in mm.

HAQ-DI (Section 9.4.20) score will be calculated at baseline and at each time point. The HAQ-DI is calculated by:

- For each sub-category take the maximum score of all questions in that sub-category (score of 0-3).
- If aids were used for the sub-category a score of 0 or 1 is increased to 2 to more accurately represent underlying disability (scores of 3 are not modified).
- The average of the 8 categories is then calculated to obtain an overall HAQ-DI score of 0-3.

The summary statistics of the absolute value and the change from baseline at each visit will be reported.

9.7.3.3. Rate of Remission, LDA, HAQ-DI

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

- Remission is assessed by SDAI ≤3.3; CDAI ≤2.8; DAS 28-4 (ESR) <2.6 and DAS28-4 (CRP) <2.6.
- LDA is assessed by SDAI ≤11; CDAI ≤10; DAS 28-4 (ESR) <3.2 and DAS28-4 (CRP) <3.2.
- HAQ-DI response is defined as a decrease of at least 0.22.

Where the DAS 28 4 (ESR), DAS28 4 (CRP), SDAI and CDAI are calculated as:

- DAS28-4 (ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR in mm/hour) + 0.014*PtGA in mm.
- DAS28-4 (CRP) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.36*ln(CRP in mg/l +1) + 0.014*PtGA in mm +0.96.
- SDAI = TJC28 + SJC28 + PhyGA in cm + PtGA in cm + CRP in mg/dL.
- CDAI = TJC28 + SJC28 + PhyGA in cm + PtGA in cm.

9.7.3.4. Other PROs

The summary statistics of the absolute value and the change from baseline in EQ-5D (Section 9.7.3.4.1), FACIT-Fatigue Scale (Section 9.7.3.4.3), WPAI (Section 9.7.3.4.2) at each visit will be reported.

The change from baseline in EQ-5D (Section 9.7.3.4.1), FACIT-Fatigue Scale (Section 9.7.3.4.3), WPAI (Section 9.7.3.4.2) at each time point will be analyzed using mixed models for repeated measures (MMRM), with time-point as a fixed effect; the Baseline value will be entered in the model as a covariate, alongside the Baseline by time-point interaction.

9.7.3.4.1. EQ-5D

The EQ-5D 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 7:

Table 7. 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 (eg, 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 8.

Table 8. 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.

9.7.3.4.2. WPAI

The WPAI questionnaire provides consist of 6 questions, from which scores are derived for four domains; absenteeism, presenteeism, work production loss and activity impairment. These are calculated as percentage impairment.

- Absenteeism = (Q2/(Q2 + Q4))*100.
- Presenteeism = (Q5/10)*100.
- Work Production Loss = {((Q2/(Q2 + Q4)) + [(1 – (Q2/(Q2 + Q4)))*(Q5/10)]}*100.
- Activity Impairment = (Q6/10)*100.

9.7.3.4.3. FACIT

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.

9.7.4. Interim Analysis

An interim analysis will not be performed in this study.

9.8. Quality Control

Quality control

The study will be conducted according to the relevant Pfizer SOPs. During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol, GPP and GCPs where applicable are being followed. The monitors may review source documents to confirm that the data recorded on DCTs are accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Record retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, DCTs and hospital records), all original signed informed consent forms, copies of all DCTs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.9. 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.

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 (eg, CRP not measured or questionnaires not completed).

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed [unless a waiver of informed consent has been granted by an IRB/IEC]. The investigator will retain the original of each patient's signed consent document.

10.3. Patient Withdrawal

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

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

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), 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 FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

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

Table 9. Safety Requirements

Safety event	Recorded on the eDCT	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE.	All.	All.
Non-serious AE.	All.	Potential risk (RMP XELJANZ V5.0): - Malignancy; - Cardiovascular risk; - Gastrointestinal perforation; - Interstitial lung disease; - Progressive multifocal leukoencephalopathy; - Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents; - Increased risk of adverse events when tofacitinib is administered in combination with MTX; - Primary viral infection following live vaccination; - Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors; - Off-label use including children with JIA or IBD; - Higher incidence and severity of adverse events in the elderly. Missing information (RMP XELJANZ V5.0): - Effects on pregnancy and foetus; - Use in breastfeeding; - Effect on vaccination efficacy and use of live/attenuated vaccines; - Use in patients with mild, moderate, or severe hepatic impairment; - Use in patients with moderate or severe renal impairment; - Use in patients with evidence of hepatitis B or hepatitis C infection; - Use in patients with elevated transaminases; - Use in patients with malignancy.
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure.	All (regardless of whether associated with an AE), except occupational exposure.	All (regardless of whether associated with an AE).

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

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

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

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of tofacitinib in the study or the time of the patient's informed consent if s/he is already exposed to tofacitinib, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

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

Causality assessment

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

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

If the investigator cannot determine the etiology of the event but s/he determines that tofacitinib did not cause the event, this should be clearly documented on the electronic case report form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

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

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

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

- Drug overdose;
- Drug withdrawal;

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

Abnormal test findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

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

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 PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

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

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

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);

- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

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

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

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

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

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

As a general rule, prospective and retrospective 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 this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to tofacitinib in a pregnant woman (eg, 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 (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

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

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

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

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

Exposure during breastfeeding

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

Medication error

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

Medication errors include:

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

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

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

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

Lack of Efficacy

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

Occupational Exposure

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

11.1. Single Reference Safety Document

The Summary of Product Characteristics 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 Pfizer Safety by the investigator during the course of this study.

The Single reference safety document (SRSD) should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Final study results are planned to be published in peer-reviewed journals and presented in national congresses.

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors. Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Plans For Disseminating and Communicating Study Results, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

COMMUNICATION OF ISSUES

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

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

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14. LIST OF TABLES

15. LIST OF FIGURES

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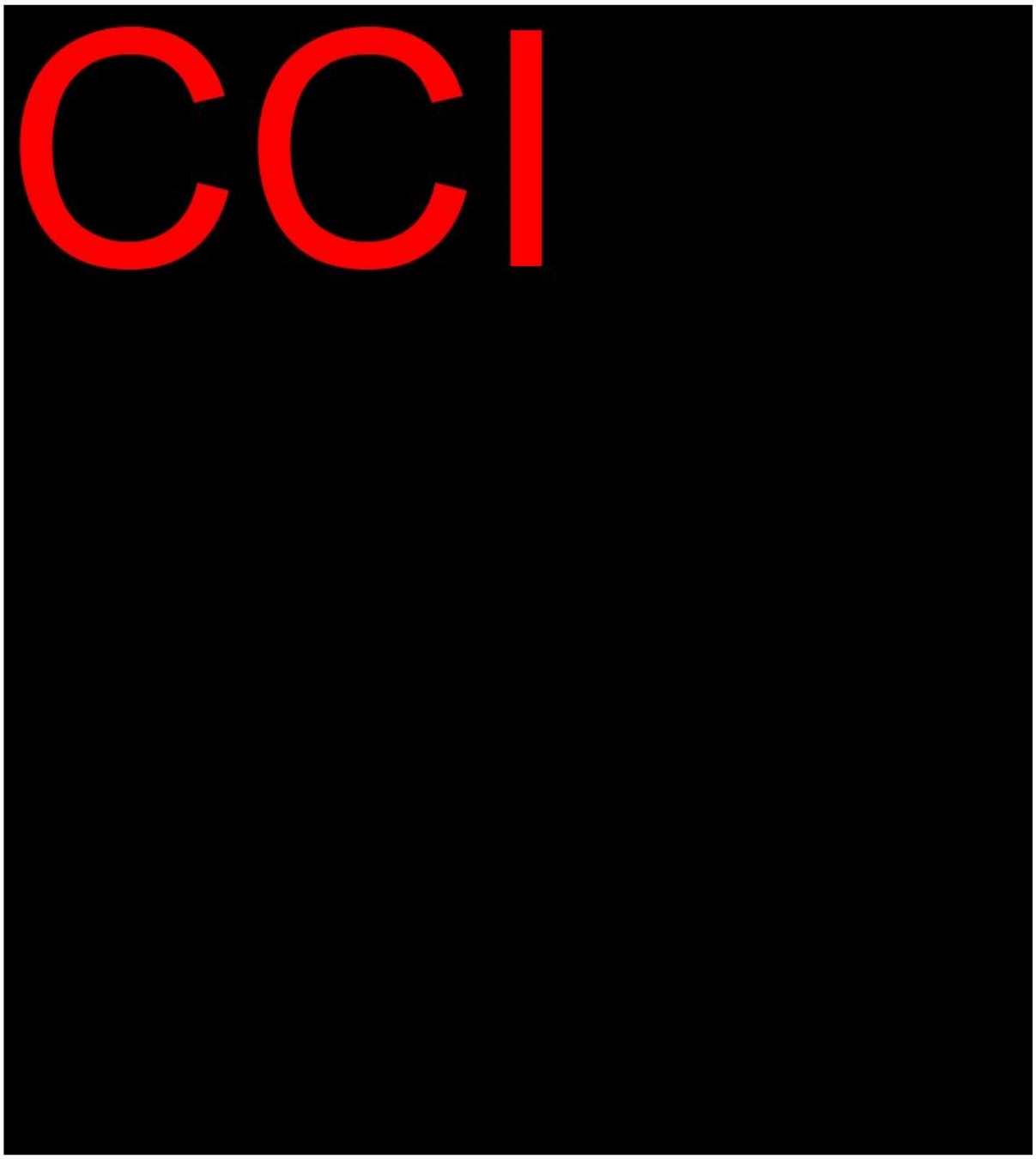

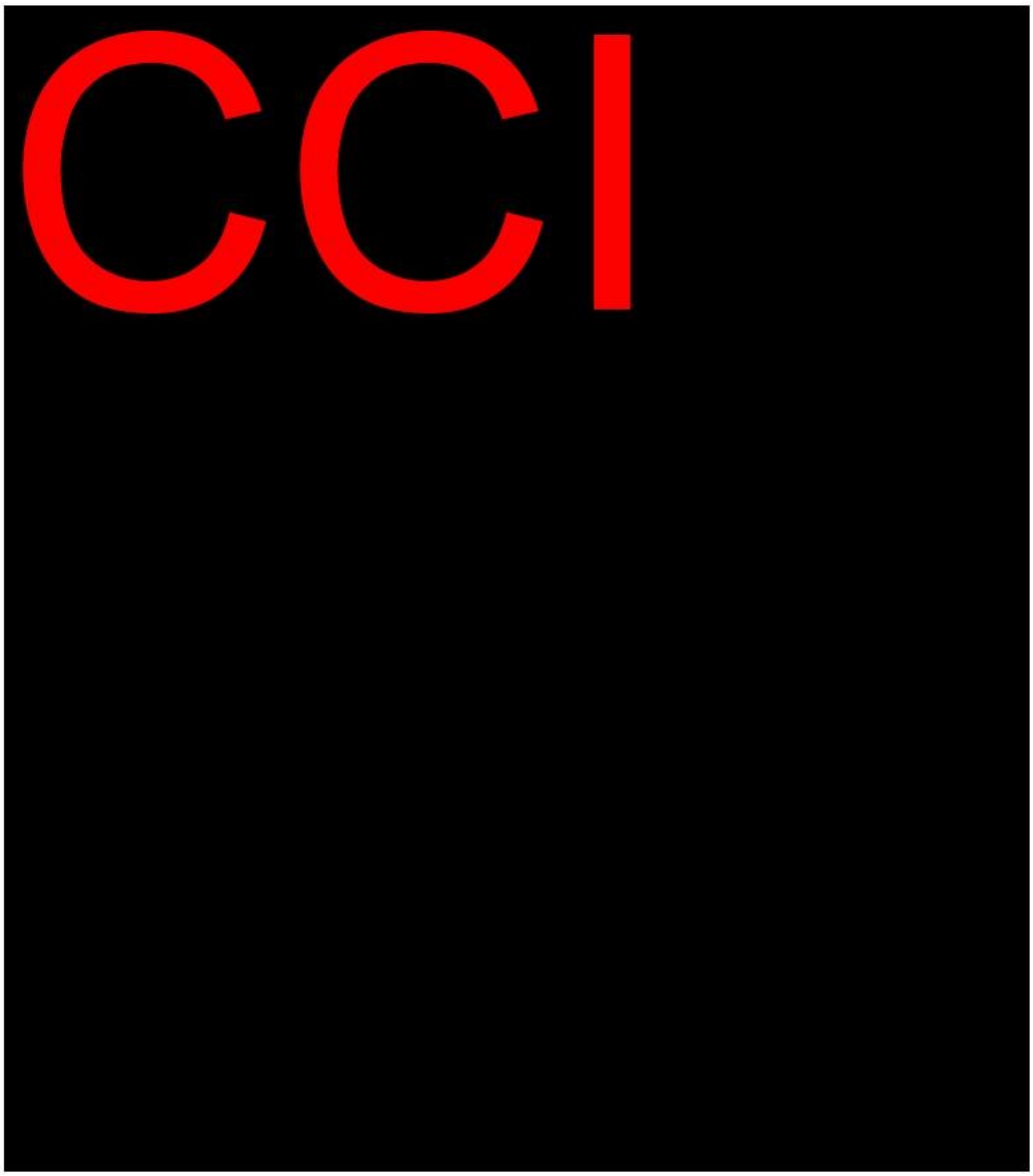
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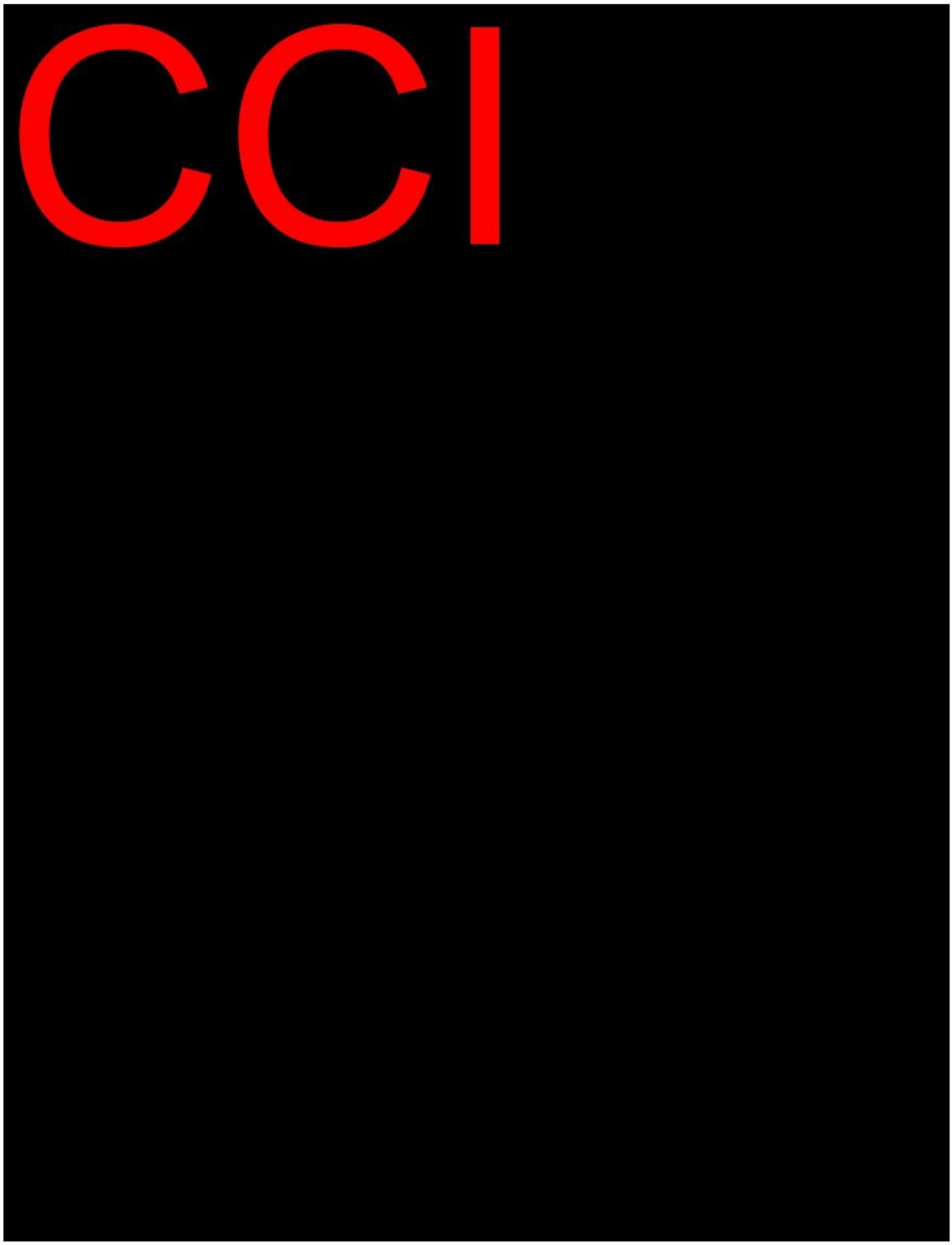
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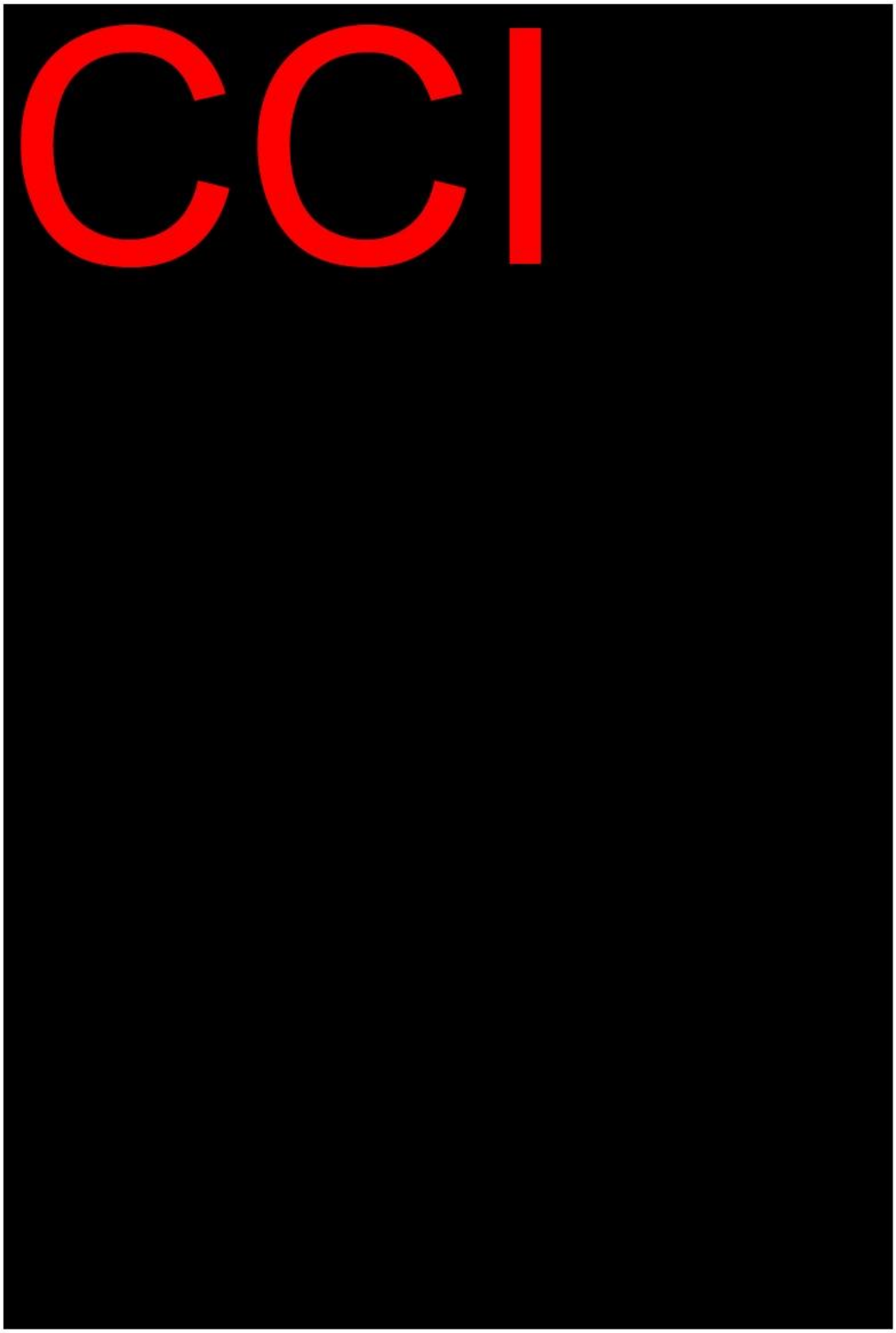
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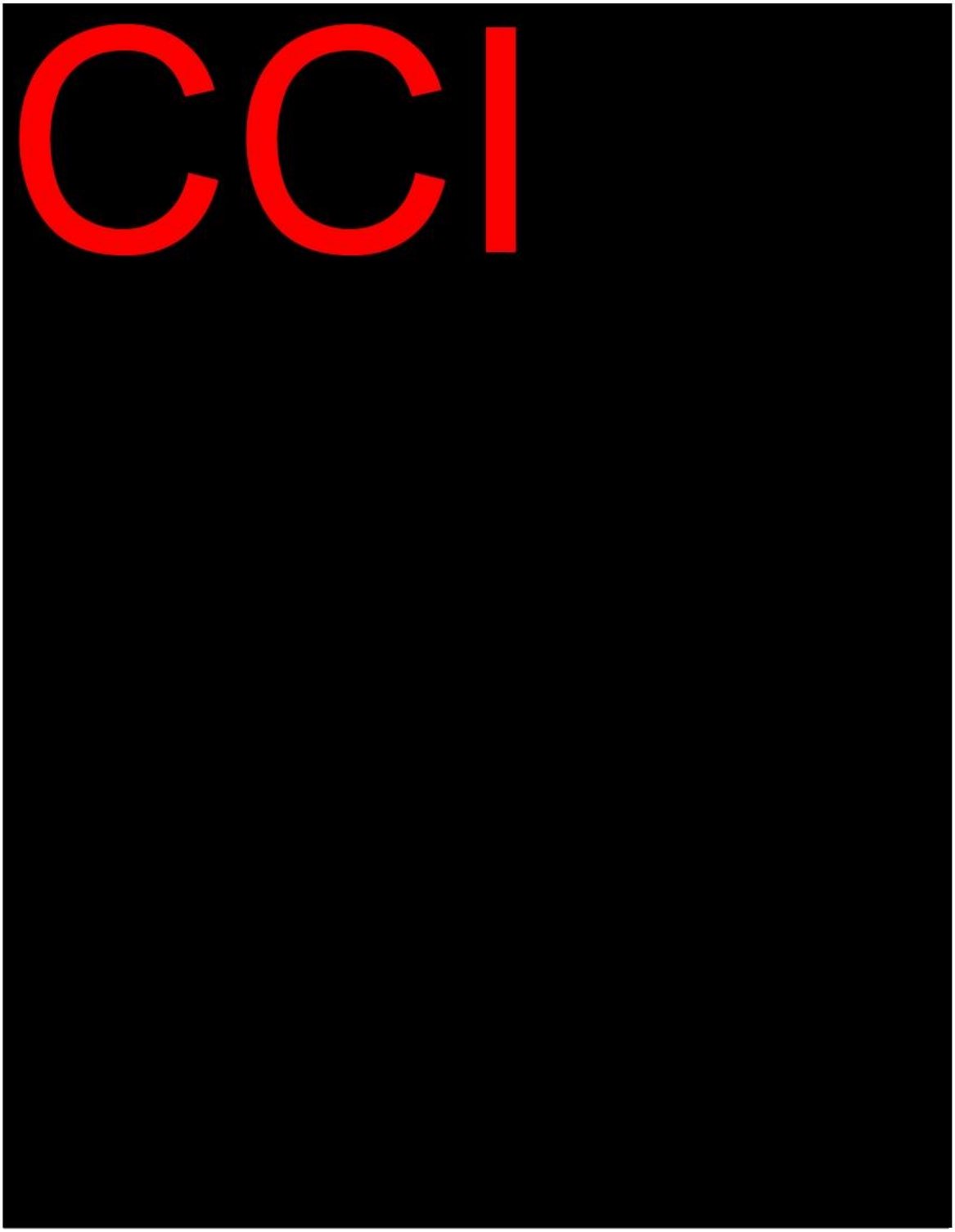
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ANNEX 2. ADDITIONAL INFORMATION

Not applicable.