NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Information on the study

Title	I**De**ntification of **Fac**tors predictive of **To**facitinib's survival in patient with rheumatoid arthritis in routine practice and impact of patients' behavioural strategies on clinical parameters: the DeFacTo study.
Protocol number	A3921313
Protocol version	2.0
Date of last version of protocol	21 december 2020
Active substance	Tofacitinib (a selective immunosuppressant, JAK inhibitor, and a targeted synthetic DMARD)
Medicinal product	XELJANZ®, Tofacitinib citrate
Question and objectives of the study	The primary objective of this study is to identify factors predictive of drug survival with Tofacitinib in RA patient. In addition to evaluation of effectiveness and tolerability, one of the secondary objectives is to evaluate the impact of patients' behavioural strategies on Tofacitinib drug survival and other clinical parameters in routine practice.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	Anti-citrullinated protein antibody
(e)CRF	electronic Case Report Form
ACR	American College of Rheumatology
AE(S)s	Adverse Events (Serious)
AEM	Adverse Event Monitoring
JIA	Juvenile Idiopathic Arthritis
ANSM	French National Agency for the Safety of Medicines and Health Products Safety
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CENGEPS	French National Centre for Management of Healthcare Product Trials
CNIL	National Commission on Data processing and Freedoms
CNOM	National Medical Council
CPP	Committee for the Protection of persons (Ethics Committee)
CRA	Clinical Research Associate
CRP	C Reactive Protein
CSQ	Coping Strategies Questionnaire
CYP	Cytochrome P450
DAS	Disease Activity Score
DMARD	Disease-Modifying Anti-Rheumatic Drug
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EULAR	EUropean League Against Rheumatism
EuroQoL EQ-5D-3L	EuroQoL EQ-5D-3L: 5-dimensions of health status questionnaire
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FiRST	Fibromyalgia Rapid Screening Tool
FPFV	First Patient First Visit
GVP	Guidelines on good pharmacovigilance practice
IL	Information Leaflet
LPLV	Last Patient Last Visit
MA	Market Authorisation
TJC	Tender Joint Count
SJC	Swollen Joint Count
PCS	Pain Catastrophising Scale
PhGA	Physician Global Assessesment
PtGA	Patient Global Assessesment
PV	Pharmacovigilance
QC	Quality Control
RA	Rheumatoid Arthritis
RF	Rheumatoid Factors
RMP	Risk Management Plan
SDAI	Simplified Disease Activity Index

SF-12	Short Form-12 Health Survey – 12-item quality of life questionnaire
SmPC	Summary of Product Characteristics
VAS	Visual Analogue Scale
WHO	World Health Organisation
WMA	World Medical Association

3. RESPONSIBLE PARTIES

Principal investigator(s) of the protocol

Name(s), diploma(s)	Position title	Institution	Address
Separated document			

Pfizer project team

Nom	Titre	Fonction	Adresse
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PPD	Doctor	PPD	PPD

Coordinator of the Scientific Committee

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4. SUMMARY

Study title	**ID**entification of **Fac**tors predictive of **To**facitinib's survival in patients with rheumatoid arthritis in routine practice and impact of patients' behavioural strategies on clinical parameters: the DeFacTo study. VERSION AND DATE: Version 2.0 – 21-DEC-2020 PROTOCOL NUMBER : A3921313
Sponsor	**Pfizer**
Scientific Committee	**Coordinator :** PPD **Expert :** • PPD
Investigator Coordinnator	PPD
Investigators	A total of 100 hospital and liberal rheumatologist investigators for rheumatoid arthritis patients and Xeljanz® prescribers will be recruited.
Rationale	Rheumatoid arthritis (RA) is an auto-immune disease characterised by inflammation and joint destruction which is at the origin of progressive incapacity and negative psychological effects [1, 2]. RA is a problem of public health, whether on the level of the individual or on society, in particular, regarding incapacity for work and resultant loss of productivity [3, 4]. According to the recent European League Against Rheumatism (EULAR) recommendations [5] and the current recommendations of the French Society of Rheumatology (SFR) [1], earlier diagnosis is leading to earlier therapeutic intervention with the goal of disease activity control, maintenance of physical function, optimization of quality of life and improvement of patient mindset [1]. "Treat-to-target" is defined as the basic therapeutic principle in order to reach a goal of sustained remission or low disease activity in every patient [1, 5]. Xeljanz® (Tofacitinib) is an orally targeted synthetic DMARDs (ts-DMARDs) of the new class called Janus kinase inhibitors (JAK-inhibitors). In combination with methotrexate (MTX), Tofacitinib has been approved in 2017 by the European Medicine Agency (EMA) [6] for the treatment of moderate-to-severe active rheumatoid arthritis in adult patient who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). Furthermore, Tofacitinib can also be administered as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate [7, 8] Tofacitinib efficacy and safety in the treatment of rheumatoid arthritis has been proven and tried not only across a wide clinical development plan including 7 phase III studies and 2 long-term extension studies [7, 9-15, 16], but also under real life conditions of use since its first approval in the United State in 2012 and

	subsequent years in other countries worldwide [17]. Although the efficacy and safety profile of Tofacitinib is currently well-documented in the clinical setting [7, 9-15, 16], many fields of research remain to be investigated regarding this drug of a novel therapeutic class, including outcomes in the real world setting. For example, nowadays it is recognized that treatment retention is an overall marker of treatment success depending on multiple factors including efficacy, safety, patients' and disease characteristics at baseline, patients' and physicians' confidence with the treatment [1, 5]. Survival rate is a standardized method for identifying predictive factors of drug survival. Existing data with biologic DMARDs in rheumatoid arthritis have identified a number of independent predictors for treatment continuation [18-23]. Regarding Tofacitinib, newly introduced on the market, few data on drug retention [24] and no data on the factors predictive of Tofacitinib drug survival in patients with RA are available. Therefore, the primary objective of the DeFacTo study will be to identify the factors predictive of Tofacitinib drug survival in patients with RA. Moreover, rheumatoid arthritis substantially affects quality of life. Different factors such as pain, disability or fatigue which are directly or indirectly the result of inflammation can have a negative impact on quality of life [1, 25]. Nevertheless, such quality of life is not governed solely by symptoms of the disease, but also by the behaviour of the patient, as well as by behavioural strategies which he/she evidences with regard to the disease. We often refer to catastrophisation [26-28] and coping [29-32] to evaluate these behavioural strategies. If catastrophisation is described as a distortion of the perception of pain involving a both emotional and cognitive component, pushing the patient to see only the worst [26-28], coping involves adaptive strategies by which the patient attempts to find solutions in order to better cope with his/her disease [29-32]. It has been demonstrated that such behavioural strategies can influence directly or indirectly the intensity of symptoms [33]. As secondary objectives, the impact of behavioural strategies on drug survival and other clinical parameters as well as Tofacitinib effectiveness and tolerability will be studied under real-life conditions of use in French patients with RA.
Study Objectives	**Primary objective:** - To identify factors predictive of drug survival with Tofacitinib **Secondary objectives:** - To evaluate the impact of behavioural strategies in patients with rheumatoid arthritis on Tofacitinib drug survival. - To study the correlation between behavioural strategies and effectiveness - To evaluate the effectiveness of Tofacitinib

<table>
<tr><td></td><td>- To evaluate the tolerability of Tofacitinib</td></tr>
<tr><td>EVALUATION END POINTS</td><td>
Primary endpoint

• Duration of Tofacitinib survival

Secondary endpoints

• Change from baseline in catastrophising behaviour adopted by the patient (PCS-Pain Catastrophising scale) [34, 35]
• Change from baseline in coping adaptive strategy adopted by the patient (CSQ - Coping Strategies Questionnaire) [29-32]
• Percentage of patients with low disease activity (LDA) as assessed by DAS28-4 ESR/CRP < 3.2, SDAI ≤11, CDAI ≤10 [36],
• Percentage of patients in remission as assessed by DAS28-4 ESR/CRP < 2.6, SDAI ≤3.3, CDAI ≤2.8, ACR-EULAR 2011 Boolean criteria (TJC ≤ 1 + SJC ≤ 1 + CRP ≤ 1 mg/dL + VAS patient ≤ 1) [36, 37]
• Change from baseline in DAS28-4 ESR/CRP and its components over time
• Evaluation of the response to treatment by considering outcome of DAS28 (EULAR criteria) [38]

Table 1: Evaluation of response to treatment considering outcome of DAS28 (EULAR criteria)

<table>
<tr><td>DAS28 at visit</td><td colspan="3">Decrease in DAS28 compared to V0</td></tr>
<tr><td></td><td>>1.2</td><td>>0.6 and ≤1.2</td><td>≤0.6</td></tr>
<tr><td>≤3.2</td><td>Good responder</td><td>Moderate responder</td><td>Non-responder</td></tr>
<tr><td>>3.2 and ≤5.1</td><td>Moderate responder</td><td>Moderate responder</td><td>Non-responder</td></tr>
<tr><td>>5.1</td><td>Moderate responder</td><td>Non-responder</td><td>Non-responder</td></tr>
</table>

• Change from baseline in the number of painful joints (TJC) over time
• Change from baseline in the number of swollen joints (SJC) over time
• Evaluation of the possible existence of fibromyalgia (FiRST questionnaire) [39, 40]
• Change from baseline in the duration of morning stiffness over time
• Change from baseline in patient compliance over time (GIRERD Questionnaire) [41]
• Change from baseline in overall health status over time (EuroQoL EQ-5D-3L questionnaire) [42-44]
• Change from baseline in quality of life over time (SF-12 questionnaire) [45]
• Change from baseline in fatigue over time (FACIT-Fatigue questionnaire) [46, 47]
• Evaluation of tolerability
</td></tr>
<tr><td>STUDIED</td><td>Patients eligible for this study can be included by the physician if they are</td></tr>
</table>

POPULATION	starting a treatment with Tofacitinib for RA according to usual clinical practice and satisfy all of the following criteria for inclusion. Patient treatment is independent from patient enrolment into the study. Criteria for inclusion: 1. Patient 18 years of age or older 2. Patient in whom the diagnosis of moderate-to-severe active rheumatoid arthritis has been confirmed by a rheumatologist 3. Patient for whom the rheumatologist decides to initiate treatment with Tofacitinib 4. Patient informed of the study Criteria for non-inclusion: 1. Patient participating in a randomised clinical trial. 2. Patient presenting with a contraindication to prescription of Tofacitinib 3. Patients who are investigational site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.
Study Type and Methodology	**STUDY TYPE** This is an observational, open-label, prospective, multi-centre, national study designed to evaluate the factors predictive of Tofacitinib's survival in patients with rheumatoid arthritis. The duration of this study will be approximately 48 months including a 24-month recruitment period and a 24-month patient follow-up period. Patients will be followed prospectively and follow-up visits will be conducted after the initial consultations. No visit or additional test is required by the protocol, since the study is observational: the modalities for follow-up and treatment will be left up to the sole judgement of the participating doctor. **ORIGIN AND NATURE OF THE DATA COLLECTED** Data will be recorded during the 24 months participation of each patient: at inclusion (V0), at 1 month (V1), at 3 months (V2), at 6 months (V3), at 12 months (V4), at 18 months (V5) and at 24 months (V6). In case of discontinuation of treatment with Tofacitinib, for whatever reason, clinical data will be collected as close as possible to the date of such a discontinuation. Likewise, in case of Tofacitinib discontinuation outside the 6 scheduled visits, an additional visit to collect clinical data as close as possible to the date of this discontinuation should be organised. **Eligible patients will be followed starting from the date of the first prescription of Tofacitinib during 24 months, whether they continue treatment with Tofacitinib or not.** All study data will be collected by the participating physician directly in the eCRF.

Study drug	XELJANZ®: the prescription, dose and duration of treatment are freely decided by the participating physician.
Study duration	• Total duration of study: 48 months • Length of inclusion period: 24 months • Follow-up time per patient: 24 months
Data Analysis	**STATISTICAL ANALYSES** The detailed methodology for conduct of the statistical analysis of data collected in the setting of this study will be documented in a Statistical Analysis Plan (SAP). Tofacitinib maintenance will be estimated by considering the date of initiation of treatment with Tofacitinib and the date of permanent discontinuation. The time of follow-up of patients not presenting with an event of interest (permanent discontinuation of treatment) will be censored at the date of the last visit. Drug survival with Tofacitinib will be described using the Kaplan-Meier method in a full analysis set. **Principal analysis** Factors predictive of drug survival will be investigated using a Cox model. A univariate analysis will first be conducted. All potential factors for which the p-value resulting from the univariate analysis is strictly less than 10% will be included in a multivariate Cox model. Predictive factors and their interactions will be selected according to a backward (step-down) selection method. Predictive factors retained in the model will be those with a p-value < 5%. **Key secondary analysis** The impact of behavioural strategies (catastrophisation and coping) on Tofacitinib drug survival will be evaluated in patients suffering from RA. A Cox proportional hazards model will be used with the 5 dimensions of the coping questionnaire and the catastrophisation score collected at the baseline visit included as independent variables.
Effectif	300 patients
Regulatory	RIPH de catégorie 3 CNIL : Méthodologie de référence MR003

5. AMENDMENT(S)

A substantial amendment is a change that is likely to have an impact on the safety or physical or mental integrity of study participants or that may affect the results of the study and their interpretation, e.g. changes in the primary or secondary objectives of the study, study population, study design, data sources, data collection method, sample size, definitions of primary exposure, results and confounding factors as well as the analytical design as described in the protocol.

Amendment number	**Date**		**Modified section(s) of protocol**	**Summary of amendment(s)**	**Reason**
Version 2.0	21- DEC -2020	Version 1.2 modified by version 2.0	Cover page Summary Section 6 Sections 9.2 et 9.5 Section 9.3.2.1 Section 9.6.3 Section 12 Section 13	Updated the protocol template used, in accordance with Pfizer Inc Standard Operating Procedures Modification of the Medical and Scientific Responsible Introduction of new tofacitinib dosage as per SmPC Adding study planned schedules (Section 6) Change in recruitment target Update the PCS Self Questionnaire Score Threshold – Pain Catastrophizing Scale Clarification on the secure-cover self-questionnaires transmission circuit Clarification on the publication of the study results Added a bibliographic reference following the update of the PCS questionnaire score	The target of 500 patients could not be achieved given the decline in visits this year due to the COVID-19 pandemic. The number of patients to be included was reduced, and the resulting hypotheses and sample calculation were adjusted accordingly.

6. STUDY MILESTONES

Table 2: Planned Study Schedule

Study milestone	**Expected date**
Selection of investigator sites	July 2018 – July 2019
Start of data collection	January 2019
End of data collection	January 2023

Final study report	January 2024

7. JUSTIFICATION AND CONTEXT

Rheumatoid arthritis (RA) is a chronic auto-immune disease characterised by inflammation and joint destruction which is at the origin of progressive incapacity and negative psychological effects [1, 2]. RA is a problem of public health, whether at the level of the individual or of society, in particular, regarding incapacity for work and resultant loss of productivity [3, 4].

Earlier diagnosis leading to earlier therapeutic intervention with the goal of disease activity control, maintenance of physical function, optimization of quality of life and improvement of patient mindset, is a universally recognized principle [1, 5].
The recent European League Against Rheumatism (EULAR) recommendations [5] and the current recommendations of the French Society of Rheumatology (SFR) [1] define treat-to-target as the basic therapeutic principle in order to reach a target of sustained remission or low disease activity in every patient. Conventional synthetic DMARDs, mainly methotrexate (MTX), in the absence of contraindication, constitute the first-line treatment approach of symptomatic RA patients [1, 5]. In case of inadequate or insufficient response to csDMARDs with persistent disease activity, treatment with biologic agents, like Tumor Necrosis Factor α (TNFα) blockers therapy or biologic agents with other mechanism of action should be offered. Biologic DMARDs have proven their efficacy on symptoms and signs of rheumatoid arthritis, quality of life, productivity and on reducing joint destruction [1, 5].

As recently, two orally targeted synthetic DMARDs (ts-DMARDs) of the new class called Janus kinase inhibitors (JAK-inhibitors) has been brought into the market in the European Union [6], the EULAR recommendations were expanded to include tsDMARDs : *"If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD or a tsDMARD should be considered"* [5].

XELJANZ® is one of these two ts-DMARDs [7, 8]. It is a selective and reversible inhibitor of Janus kinases JAK 1 and JAK 3, enzymes involved in the pathophysiology of RA through signal transduction of many cytokines [7, 8].
It has the specificity of being administered orally while the biological background treatments currently available are all administered by parenteral route. The recommended dosage is one Tofacitinib 5 mg tablet (immediate release tablets) twice daily or Tofacitinib 11 mg (extended release tablets) once a day, the transition from one formulation to another is possible according to the recommendations mentioned in the SmPC [7, 8].

Xeljanz® (Tofacitinib), in combination with methotrexate (MTX), obtained on 22 March 2017 Market Authorisation (MA) in the treatment of moderate-to-severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-Rheumatic drugs (DMARDs). Furthermore, Xeljanz® can also be administered as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate [7, 8]. The recommended dosage is 5 mg of Tofacitinib bid [7, 8].
In its opinion of 27 September 2017, the French Transparency Commission issued a favourable opinion to registration of XELJANZ® on the list of medicinal products reimbursable to social security beneficiaries and on the list medicinal products certified for use by communities in the indication and dosage of the Market Authorisation [7].

Evaluation of the efficacy and safety of Tofacitinib in the treatment of rheumatoid arthritis is based on a wide clinical development plan including 7 phase III studies and 2 long-term extension studies [7, 9-15, 16] which to date amount to a total of over 22,800 patient-years exposure to treatment [17].

In 2012, following market launch of XELJANZ® in the USA, post-marketing monitoring of patients exposed to Tofacitinib since November 2012 (FDA Market Authorisation), using the CORRONA US registry, was set up. To date, apart from Herpes Zoster, no specific safety signal has been demonstrated compared to other DMARDs [7].

Currently marketed in over 80 countries worldwide [6] with over 110,000 patients who have been or are under treatment with Tofacitinib [17], XELJANZ® has a clinical experience and post-marketing follow-up of over 9 years [16, 17].

Although the efficacy and safety profile of Tofacitinib is currently well-documented in the clinical setting [7, 9-15, 16], many fields of research remain to be investigated regarding this drug of a novel therapeutic class, including outcomes in the real world setting.

Nowadays it is recognized that treatment retention is an overall marker of treatment success depending on multiple factor including efficacy, safety, patients' and disease characteristics at baseline, patients' and physicians' confidence with the treatment [1, 5]. Survival rate is a standardized method for identifying predictive factors of drug survival. Existing data with biologic DMARDs in rheumatoid arthritis have identified a number of independent predictors for treatment continuation [18-23].

Regarding Tofacitinib, few data on drug retention in patients with rheumatoid are available [24]. Based on the data of the Swiss Clinical Quality Management Registry (SCQM), recent findings of Finckh A *et al.* [24] have shown that Tofacitinib drug retention is at least comparable to other available biologic DMARDs. Even more, after adjustment for potential confounders including age, gender, disease duration, seropositivity, BMI, smoking status, DAS28-CRP and the total number of previous biologic DMARDs, the adjusted analysis demonstrated a slightly higher hazard of drug discontinuation with TNF inhibitors compared to Tofacitinib (HR 1.27, 95%CI [1.02-1.57], p=0.04), while no difference was observed for biologic DMARDs with other mechanism of action and Tofacitinib (HR 1.03, 95%CI [0.83-1.28], p=0.76) [24].

And to date, no data exists on the factors predictive of Tofacitinib drug survival in the management of RA patients.

The DeFacTo observational study will therefore has as primary objective to identify the factors predictive of Tofacitinib drug survival in patients with RA.

Moreover, rheumatoid arthritis substantially affects quality of life. Different factors such as pain, disability or fatigue, which are directly or indirectly the result of inflammation, can have a negative influence on such quality of life [1, 25]. Nevertheless, this quality of life is not governed solely by symptoms of the disease, but also by the behaviour of the patient, as well as the behavioural strategies which he/she evidences with regard to his/her disease. We often refer to the term catastrophisation [26-28] or coping [29-32] to evaluate such behavioural strategies.

Catastrophisation is described as a distortion of the perception of pain involving a component that is both emotional and cognitive that pushes the patient to see only the worst [26-28]. It is often the translation of a persistent or transient pessimism, separate from depression.

On the contrary, coping corresponds to all processes by which a patient strives to "do the best" with his/her disease. Coping implies adaptive strategies where the patient tries to find solutions in order to deal successfully with his/her disease [29-32]. It has been demonstrated that such behavioural strategies can influence directly or indirectly the intensity of symptoms [33]. Both catastrophisation and coping can be evaluated and rated by a specific validated patient questionnaire, Catastrophizing Pain Scale [34, 35] and Coping Strategies Questionnaire [29-32] respectively.

To date, no data exists in the literature regarding the impact of behavioural strategies, whether catastrophisation or coping, on DMARDs drug survival and other clinical parameters in patients suffering from rheumatoid arthritis. Therefore it will be evaluated in this study as secondary objectives.

The DeFacTo study will also make it possible to collect data on effectiveness and tolerability of Tofacitinib under real-life conditions of use in French patients with rheumatoid arthritis.

8. STUDY OBJECTIVES

Primary objective of the study

- To identify factors predictive of drug survival with Tofacitinib

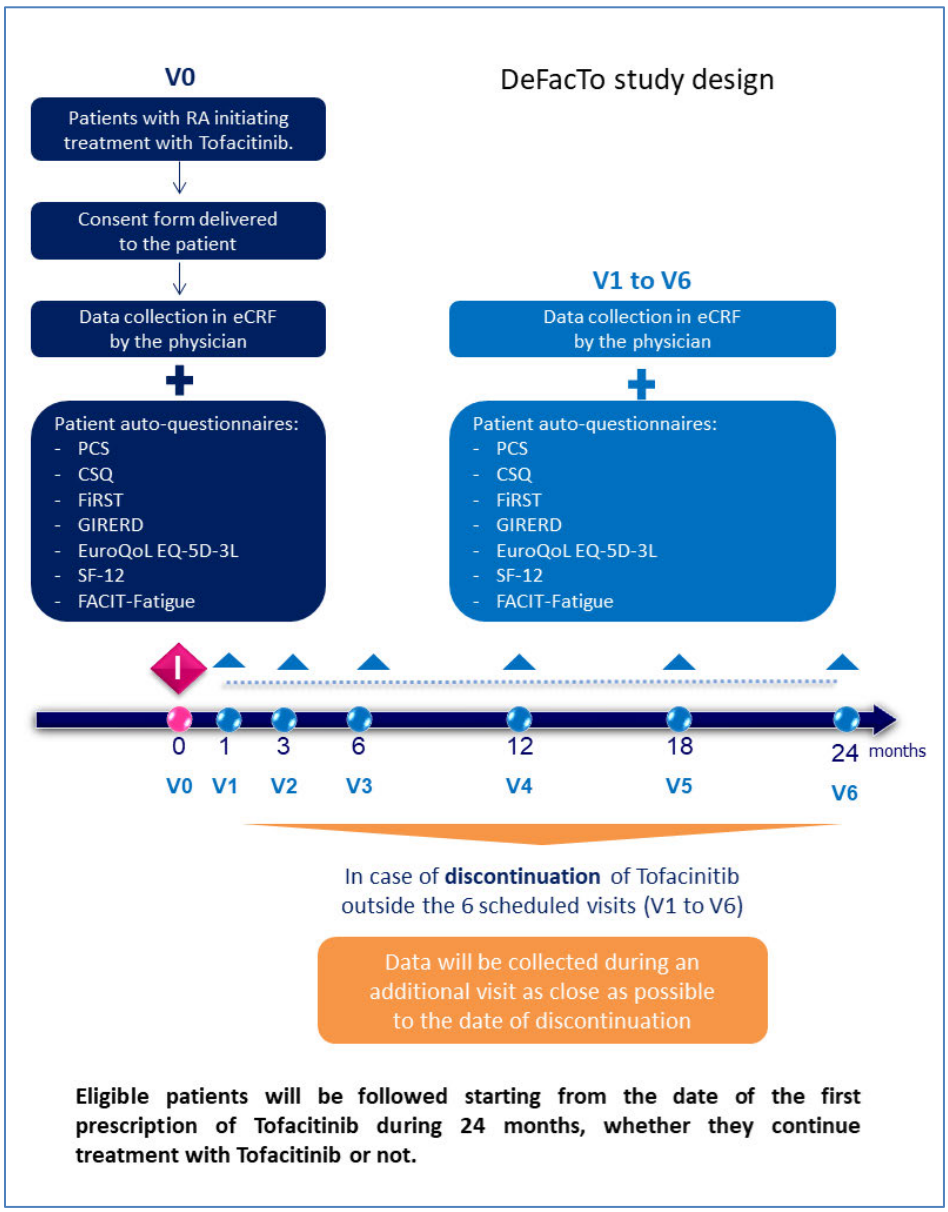
Secondary objectives

- To evaluate the impact of behavioural strategies in patient with rheumatoid arthritis on Tofacitinib drug survival
- To study the correlation between behavioural strategies and effectiveness
- To evaluate the effectiveness of Tofacitinib
- To evaluate the tolerability of Tofacitinib

9. METHODS
9.1. Study design
9.1.1. Study Schema

This is an observational, open-label, prospective, multi-centre, national study designed to identify factors predictive of Tofacitinib's survival in patients with RA. Additionally it will provide real world patient outcome in France. Furthermore, data from France will be compared and also pooled with data from other countries. Details will be included in a separate analysis plan for a pooled analysis.

Figure 1: Study schema



Patients can be enrolled in the study by their rheumatologist if they satisfy all of the following criteria for inclusion. All visits must be scheduled according to usual clinical practice. Medical follow-up of patients is independent of enrolment of patients in the study.

In the setting of this study, 6 visits can be documented. Data will be collected from the patient's medical dossier at V0 and at time of the 6 follow-up visits: at 1 month (V1), at 3 months (V2), at 6 months (V3), at 12 months (V4), at 18 months (V5) and at 24 months (V6). No sample will be collected specifically for this study. At each visit, patients will be subjected to management in compliance with healthcare standards. In order to collect comparable study data, visits 2 to 6 performed within ±14 days after planned date of the visit will be used for analysis of data.

In case of discontinuation of treatment with Tofacitinib, for whatever reason, clinical data will be collected as close as possible to the date of such a discontinuation.

Likewise, in case of Tofacitinib discontinuation outside the 6 scheduled visits, an additional visit to collect clinical data as close as possible to the date of this discontinuation should be organised.

Eligible patients will be followed starting from the date of the first prescription of Tofacitinib during 24 months, whether they continue treatment with Tofacitinib or not.

The dose and duration of treatment, as well as the frequency of follow-up of the patient must be based on clinical and individual needs and will be determined by the rheumatologist. To provide precise information on treatment, the initial dose of Tofacitinib and all changes and reasons for changes will be documented in the evaluation.

All AE spontaneously reported by the patient or observed by the participating physician during the study will be recorded on the AE page of the electronic case report form (eCRF).

9.1.2. Set up of centres

In order to ensure expected recruitment, the study will be conducted by about 100 rheumatologists. Participating physicians will be selected from among those all over France out of the total number of French health institutions which manage patients with rheumatoid arthritis.

In order to reach an objective of participation of 100 centres desired, the study will be offered to about 550 centres.

In a first phase, all centres which have the potential to participate in the study will be contacted by Pfizer to submit to them a questionnaire on feasibility which will be sent to them by email.

Physicians who accept to participate must return the “Participating physician” form to the centre for management of the study, attached to the email for proposal of the study. This will also enable them to choose the type of agreement to participate in this study.

Following receipt by Pfizer of this form, physicians who accepted to participate will receive their agreements for signature and final validation of their participation.

Physicians who do not respond after receipt of the invitation for participation will be contacted again in order to ensure that they do not wish to participate.

Physicians who did not return their signed agreement within two weeks after its dispatch will also be reminded up until obtainment of the expected number of participating doctors.

Once the agreement has been validated by Pfizer, the physician will be contacted by Pfizer in order to organise the set up of the centre. The latter will take place by Teleconference (TC) for each of the participating physicians involved in the study. During this TC, the study protocol, the logistics and pharmacovigilance will be presented.

Each set up will result in distribution of access codes to the study eCRF.

The study eCRF will include all documents necessary for perfect knowledge of the project and of its conduct:

- opinion of the CPP,
- authorisation of the CNIL (if applicable),

- opinion from the CNOM[2],
- the study protocol,
- the information leaflet,
- the physician questionnaires (CRF),
- the patient questionnaires.

In order to enable constant contact between participating physicians and Pfizer, a green phone number (free phone) will be available.

9.1.3. Visit for inclusion: Establishment of the cohort and collection of data

Each physician will include consecutively all adult patients with rheumatoid arthritis and initiating treatment with Tofacinitib, seen in a consultation in a centre participating in the study.

Each patient then must be informed about the principle of the study with the information leaflet, and if the patient accepts to participate in the study, the physician then must do the following:

- provide the patient with the signed information leaflet,
- complete the questionnaire corresponding to the visit for inclusion,
- give his or her patient the PCS, CSQ, FiRST, GIRERD, EuroQoL EQ-5D-3L,
- SF-12, FACIT-Fatigue questionnaires that the patient must complete and give back to his/her physician for return to the logistics centre of the study.

Patient paper questionnaires will be recovered by a carrier who will deliver them to Pfizer and will be transferred by Pfizer electronically via a secure website to the firm in charge of data management for data entry.

Starting with the first inclusion and up to the date of end of inclusions, participating physicians make a commitment for comprehensive collection of data from all adult patients with rheumatoid arthritis and initiating treatment with Tofacinitib.

Constitution of the cohort will take about 24 months.

9.1.4. Follow-up visits of patients

Patients will be followed in the setting of the study over a maximum 24-month duration or up to their early withdrawal from the study for whatever reason.

At each follow-up visit (1 month (V1), 3 months (V2), 6 months (V3), 12 months (V4), 18 months (V5), 24 months (V6) and at time of withdrawal from the study), the physician must do the following:

- complete the questionnaire corresponding to the follow-up visit,
- give the patient the PCS, CSQ, FiRST, GIRERD, EuroQoL EQ-5D-3L, SF-12, FACIT-Fatigue questionnaires.

The patient must complete these questionnaires and give them back to his/her physician at the end of each visit.

The patient paper questionnaires will be recovered by a carrier who will deliver them to Pfizer and they will be transferred by Pfizer electronically via a secure website to the firm in charge of data management for data entry. During this period, physicians make a commitment for comprehensive and regular collection of follow-up data for each patient enrolled.

Total duration of follow-up for a patient will be a maximum of **24 months**.

Total duration of the study will be **48 months**.

9.1.5. Withdrawal of a patient from the study

Withdrawals from the study before the planned end of follow-up will be classified according to the following categories:

- Patient lost to follow-up (if yes, specify measures taken to find patient)
- Non compliance with study procedure (if yes, specify the cause)
- Withdrawal from study desired by patient/doctor (if yes, specify the reason given)
- Withdrawal from study because of an adverse event (if yes, specify the type)
- Serious adverse event (if yes, specify the type)
- Death (cause and date)
- Other reason (if yes, specify)

9.1.6. Endpoints

9.1.6.1. Primary endpoint

- Duration of Tofacitinib survival

9.1.6.2. Secondary endpoints

- Change from baseline in catastrophising behaviour adopted by the patient (PCS-Pain Catastrophising Scale) [34, 35]
- Change from baseline in coping adaptive strategy adopted by the patient (CSQ-Coping Strategies Questionnaire) [29-32]
- Percentage of patients with low disease activity (LDA) as assessed by DAS28-4 ESR/CRP < 3.2, SDAI ≤ 11, CDAI ≤ 10 [36],
- Percentage of patients in remission as assessed by DAS28-4 ESR/CRP < 2.6, SDAI ≤ 3.3, CDAI ≤ 2.8, ACR-EULAR 2011 Boolean criteria (TJC ≤ 1 + SJC ≤ 1 + CRP ≤ 1 mg/dL + VAS patient ≤ 1) [36, 37]
  Change from baseline in score DAS28 ESR/CRP and in its components over time
- Evaluation of response to treatment considering outcome of the DAS28 (EULAR criteria) [38]

Table 1: Evaluation of response to treatment considering outcome of DAS28 (EULAR criteria)

DAS28 at visit	Decrease in DAS28 compared to V0		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good responder	Moderate responder	Non-responder
>3.2 and ≤5.1	Moderate responder	Moderate responder	Non-responder
>5.1	Moderate responder	Non-responder	Non-responder

- Change from baseline in the number of painful joints (TJC) over time
- Change from baseline in the number of swollen joints (SJC) over time
- Evaluation of the possible existence of fibromyalgia (FiRST questionnaire) [39, 40]
- Change from baseline in the duration of morning stiffness over time
- Change from baseline in patient compliance over time (GIRERD Questionnaire) [41]
- Change from baseline in overall health status over time (EuroQoL EQ-5D-3L questionnaire) [42-44]
- Change from baseline in quality of life over time (SF-12 questionnaire) [45]
- Change from baseline in fatigue over time (FACIT-Fatigue questionnaire) [46, 47]
- Evaluation of tolerability

9.2. Context

The duration of this study will be approximately 48 months including a 24-month recruitment period and a 24-month patient follow-up period.

Patients will be followed prospectively and follow-up visits will follow up on regular visits. No additional visits or examinations are required by the protocol, as the study is observational: follow-up and treatment arrangements will be at the sole discretion of the participating physician.

Population of physicians

Physicians participating in this study will be hospital rheumatologists and rheumatologists with a combined activity (private practice and hospital practice), representative of French hospital rheumatologists managing patients treated with biologic medicinal products or targeted synthetic DMARD for RA.

A list of 550 hospital centres geographically divided over all of France has been pre-established in order to recruit 300 patients in approximatively 100 centres (about 5 patients per centre).

Population of patients

Patients eligible for this study can be included by the physician if they are starting a treatment with Tofacitinib for RA according to usual clinical practice and satisfy all of the following criteria for inclusion. Patient treatment is independent from patient enrolment into the study.

Patients who are eligible but not enrolled in the study will be recorded in a non-inclusion registry with minimum collection of information.

9.2.1. Criteria for inclusion

Patients will be eligible for this study if they satisfy all the following criteria for inclusion:

1. Patient 18 years of age or older
2. Patient in whom the diagnosis of moderate to severe active rheumatoid arthritis has been confirmed by a rheumatologist
3. Patient for whom the rheumatologist decides to initiate treatment with Tofacitinib
4. Patient informed of the study

   The delivery of an informative notice must be personally dated and signed by the doctor to indicate that the patient has been informed of all relevant aspects of the study.

9.2.2. Criteria for non-inclusion

Patients who satisfy one of the following criteria will not be enrolled in the study:

1. Patient participating in a randomised clinical trial.
2. Patient presenting with a contraindication to prescription of Tofacitinib
3. Patients who are investigational site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.

9.3. Variables

The Case Report Form describes the data to be collected by doctors and patients during the different stages of the study.

Only data *available in the patients' medical records will be collected.*

The following variables will be collected for the purposes of the study at all visits:

9.3.1. Data collected by sites

Table 2: Patients data collected

	Inclusion visit Initiation of treatment	**Follow-up visit**						**Additional visit in case of discontinuation of Tofacitinib outside the 6 scheduled visits**
		At 1 month (V1)	**At 3 months (V2)**	**At 6 months (V3)**	**At 12 months (V4)**	**At 18 months (V5)**	**At 24 months (V6)**	
Patient information	X							
Verification of eligibility criteria	X							
Demographic characteristics								
Age, gender	X							
Weight, height, BMI	X							
Smoking status	X							
Alcohol intake (excessive use M>3 glasses wine/day, F>2 glasses wine/day)	X							
socio-educational status lives alone (Y/N)	X							
Status with respect to hepatitis B Status with respect to hepatitis C Status with respect to tuberculosis	X							

	Inclusion visit Initiation of treatment	Follow-up visit						Additional visit in case of discontinuation of Tofacitinib outside the 6 scheduled visits
		At 1 month (V1)	At 3 months (V2)	At 6 months (V3)	At 12 months (V4)	At 18 months (V5)	At 24 months (V6)	
Vaccine status - Pneumococcus - Herpes zoster History of chickenpox (Y/N)	X							
Biological parameters at inclusion								
Haemoglobin (g/dl)	X							
Mean corpuscular volume (μ^3)	X							
Lymphocyte absolute count (cells/mm^3)	X							
Neutrophil absolute count (cells/mm^3)	X							
Characteristics of RA								
Date of initial diagnosis	X							
Age at time of diagnosis of disease	X							
Erosions at time of diagnosis (Y/N)	X							
Rheumatoid nodules (previous or current): Y/N	X							
Secondary Sjögren Syndrome (Y/N)	X							
RF (negative, positive < 3x N, positive + ≥ 3x N)	X							
ACPA (negative, positive < 3x N, positive + ≥ 3x N)	X							
Previous treatments of RA (treatment line)	X							
If MTX as 1st line treatment (just before prescription of Tofacitinib), dosage and route of administration (PO /SC)	X							
Evaluation of RA								
Existence of comorbidities: - CV disease - Cancers - Infection - Gastro-intestinal disease - Osteoporosis - Depression - Diabetes	X							
Chronic low back pain (Y/N)	X							
Existence of fibromyalgia (FiRST questionnaire)	X	X	X	X	X	X	X	X
ESR (min/hour)	X	X	X	X	X	X	X	X
CRP (mg/mL)	X	X	X	X	X	X	X	X
PtGA (patient)	X	X	X	X	X	X	X	X
PhGA (physician)	X	X	X	X	X	X	X	X
Evaluation of pain by the patient	X	X	X	X	X	X	X	X
Duration of morning stiffness	X	X	X	X	X	X	X	X
TJC (28)	X	X	X	X	X	X	X	X
SJC (28)	X	X	X	X	X	X	X	X

	Inclusion visit Initiation of treatment	Follow-up visit						Additional visit in case of discontinuation of Tofacitinib outside the 6 scheduled visits
		At 1 month (V1)	At 3 months (V2)	At 6 months (V3)	At 12 months (V4)	At 18 months (V5)	At 24 months (V6)	
PCS Questionnaire	X	X	X	X	X	X	X	X
CSQ Questionnaire	X	X	X	X	X	X	X	X
GIRERD Questionnaire	X	X	X	X	X	X	X	X
Euro QoL EQ-5D-3L Questionnaire	X	X	X	X	X	X	X	X
SF-12 Questionnaire	X	X	X	X	X	X	X	X
FACIT-fatigue Questionnaire	X	X	X	X	X	X	X	X
Administration of Tofacitinib								
Reason for initiation of Tofacitinib (problem of tolerability to previous treatment, primary failure (absence of significant improvement), secondary failure (significant improvement and then loss of efficacy), patient choice, other	X							
Dosage	X	X	X	X	X	X	X	X
Concomitant treatments								
Conventional synthetic DMARD: INN, dosage, date of start	X	X	X	X	X	X	X	X
Corticosteroid therapy: dose, p.o./bolus dose	X	X	X	X	X	X	X	X
Psychotropic treatment (antidepressant, BZD, BZD hypnotic)	X	X	X	X	X	X	X	X
Changes to treatment with Tofacitinib								
- Y/N - If yes: date of change, dosage, reasons for change		X	X	X	X	X	X	X
Discontinuation of treatment with Tofacitinib								
- Y/N, - If yes: date of discontinuation and reasons for discontinuation - Prescription of a biologic treatment or tsDMARD: Y/N. If yes: INN, dosage and date of start		X	X	X	X	X	X	X
Safety								
Collection of AEs		X	X	X	X	X	X	X

9.3.2. Patient Reported Outcomes

9.3.2.1. PCS questionnaire PCS – *Pain Catastrophizing Scale* (Annexe 3.1):

Catastrophisation of pain affects the manner in which patients perceive pain. In this questionnaire, patients will be asked to describe the type of thoughts and of emotions that they experience when faced with pain [34, 35].

The PCS is a 13-item questionnaire (13 thoughts or feelings at time of pain onset) which provides an overall score resulting from the sum of three subscale scores evaluating rumination, exaggeration and helplessness.

The scores for each item are calculated on a 5-point rating scale (0 point for "not at all", up to 4 points for "all the time").

PCS total scores range from 0 to 52.

An overall score greater than or equal 20 indicates a clinically relevant level of catastrophisation [34, 35,53].

9.3.2.2. CSQ questionnaire– Coping Strategies Questionnaire (Annex 3.2):

The Coping Strategies Questionnaire (CSQ) evaluates use by the patient of this coping strategy to best deal with and best live with disease/pain [29-32]. In its French version, five factors of cognitive coping are evaluated in it: "Distraction", "Dramatisation", "Unawareness of painful sensation", "Reinterpretation" and "Prayer" [32].

9.3.2.3. GIRERD questionnaire (Annex 3.3):

The GIRERD questionnaire [41], consisting of 6 questions, is used to evaluate compliance with a medical treatment. The patient is invited to reply "yes" or "no" to each of 6 questions relating to compliance with a prescribed treatment.

- If the patient responds "no" to all questions, he is considered as a good complier.
- If the patient responds "yes" once or twice, he is considered as a minor complier.
- If the patient responds "yes" three times or more, he is considered as a non-complier.

9.3.2.4. FiRST questionnaire -Fibromyalgia Rapid Screening Tool (Annex 3.4):

The FiRST questionnaire (Fibromyalgia Rapid Screening Tool) is a tool for detecting fibromyalgia in patients with diffuse rheumatic pain.

Six items are evaluated: (1) diffuse pain, (2) painful symptoms, (3) fatigue, (4) sleep and cognitive disorders, (5) nonpainful abnormal sensations, (6) functional somatic symptoms. A score of 5 positive items out of 6 items in the questionnaire (Yes/No responses) makes it possible to detect fibromyalgia with a sensitivity of 90.5% and a specificity of 85.7% [39-40].

9.3.2.5. Euro QoL EQ-5D -3L questionnaire (Annex 3.5):

The EuroQol EQ-5D Health State Profile [42-44] 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.

9.3.2.6. SF-12 questionnaire – Short Form Survey (Annex 3.6):

The short form version of the "Medical Outcomes Study Short-Form General Health Survey" (SF-36) contains only 12 questions out of 36. The SF-12 makes it possible to measure the physical and mental quality of the life score. It evaluates eight aspects of quality of life using the WHO definition of quality of life: overall and mental health status, physical and social functioning, physical and emotional health, pain and vitality [(45)].

Physical and mental scores, between 0 and 100, are calculated by means of an algorithm:

- A score greater than 50 corresponds to average quality of life,
- A score of between 40 and 49 translates mild incapacity,
- A score of between 30 and 39, moderate incapacity,
- A score of less than 30, to severe incapacity.

9.3.2.7. FACIT-F questionnaire - Functional Assessment of Chronic Illness Therapy-Fatigue (Annex 3.7):

The FACIT-Fatigue questionnaire (Functional Assessment of Chronic Illness Therapy Fatigue scale) measures the impact of fatigue on quality of life of patients who have cancer or a chronic disease [(46)]. It is a score validated in RA [(47)]. In consists of 4 dimensions: physical, social, family, emotional, functional [(47)]. The self-evaluation is performed with a 13-item questionnaire. Each response is scored from 0 to 4.

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, with higher scores representing better patient status (less fatigue) [(47)].

9.4. Sources of data Each patient with RA in whom the rheumatologist decides to initiate treatment with Tofacitinib, seen in a consultation or in a centre participating in the study, will be informed orally and in writing of the study modalities, its objectives and its duration.
Patients who volunteer to participate in the study will provide their oral consent prior to their enrolment in the study and to completion by the participating doctor of at least one of the items in the eCRF.
The doctor will indicate this agreement in the patient's source dossier (hospital medical dossier) in compliance with rules of good practice.
A case report form will be used for recording of data. In the setting of this protocol, the term "case report form" refers to the collection of medical data in electronic format or on paper medium.
Data will be collected using two methods:
- By physicians in an electronic case report form (eCRF)

- By patients in questionnaires on paper format

The data of interest will be reported in an electronic observation book (eCRF) by the investigating site, based on the data available in the patient's medical record if available. A Clinical Studies Technician (TEC) will be available to assist the investigator in the entry of

patient data into the eCRF. For each patient included, it is suggested that the investigator collect the data in the eCRF during the inclusion visit and throughout the treatment with Xeljanz®.

Pfizer in charge of the study data management is responsible for the creation and maintenance of the eCRFs.

No directly nominative data will be collected. When setting up the investigation centre individually, Pfizer will assign a 4-digit code to each centre: this code corresponds to the centre number.

The patient number will consist of the centre number (out of 4 digits) followed by a 3-digit code assigned in ascending order of inclusions: for example, patient number 0009-002 corresponds to the second patient of the center 9. The data collected will be confidential and covered by medical confidentiality.

In addition, quality of life and compliance questionnaires will be completed by patients on paper forms before being returned by secure T-envelopes to the service provider in charge of data processing.

9.5. Sample size

The primary objective of this study is to identify factors predictive of drug survival. This will be investigated using a multivariate Cox regression model. A review of the literature suggests that such an analysis requires at least 10 events (discontinuation of treatment) per variable proposed in a multivariate regression model [48]. The minimum number of subjects to include in the study can then be estimated using the following formula:

$$N = 10\ k / p$$

Where p is the smallest of the proportion of positive cases (cases that reached the endpoint) and negative cases (cases that did not reach the endpoint) in the population and k the number of predictor variables.

Assuming a drug survival of 50% at 24 months [24] and also that 30% of the potential predictive factors will pass the univariate selection, it will be necessary to observe 150 events (i.e. 50 x0,3 variables x10 events) in approximately 300 patients (i.e. 150 events/0.50).

9.6. Data management

All information in the study will be collected by the participating doctor directly in an eCRF.

The databases and eCRFs will be created by the clinical research organisation under contract (CRO) in charge of Data Management of the study.

The eCRF will be the tool usually used by the CRO for this type of study. All Data Management operations will be carried out in agreement with requirements of Pfizer and according to the standard operating procedures (SOP) of the CRO.

The data management plan will be designed and will describe in a detailed manner the specifications of the eCRF and the controls which will be executed for each variable, as well as a list of obvious authorised corrections

The eCRF and the database specific for the study will be created, tested and validated before start of data entry of information by the scientific committee. All study participants will be trained in knowledge of the study and in the tools (eCRF) before their account is activated.

E-CRFs allow the use of pretests (on-line consistency tests which allow the investigators to immediately correct any discrepancies) in order to reduce the number of correction requests.

Once the pages are entered and monitored, the Data Manager will start the programmed consistency tests and any discrepancies will be resolved online by the participating investigator sites.

Once any corrections are made on the database, the Data Management report drafted by the Data Manager and a database lock authorization request will be sent to the Sponsor. Once the database has been locked, the final version of the Data Management Report and the database lock certificate will be sent to the Sponsor.

The frozen database will be transferred to Pfizer and the firm in charge of conduct of statistical analysis by Pfizer.

AEs reported during the study will be coded using the latest version of the "Medical Dictionary for Regulatory Activities" (MedDRA) available at time of the first coding. The codes and decodes associated with the "lower lowest term" (LLT), "preferred term" (PT) and "system organ class" (SOC) will be entered into the database. Ongoing treatments at V0 and received during the study will be coded with the latest available version of the "World Health Organization Drug Reference List" dictionary (WHODRL) available at time of the first coding. The codes and decodes associated with "anatomic therapeutic class" (ATC) and WHO code will be entered into the database.

9.6.1. Electronic Case Report Forms (e-CRF)

As it is used in this protocol, the term Electronic Case Report Form (e-CRF) must be understood as referring to an electronic record of data, based on the method of collection of the data used in this study.

The eCRF will be completed by the investigator site.

Data of interest will be reported in an electronic Case Report Form (eCRF).

A e-CRF is required and must be filled in for each included patient. The completed original e-CRFs are the sole property of Pfizer and must not be disclosed to any third party, whatever their form, except for the authorized representatives of Pfizer or the appropriate regulatory authorities, without the written authorization of Pfizer. The investigator must make sure that the e-CRFs are kept in a secure manner on the study site in encrypted electronic or paper form and are protected by a password or securely kept in a locked room to prevent any access by unauthorized third parties.

The investigator is ultimately responsible for the collection and notification of all the clinical, safety and laboratory data recorded in the e-CRFs and on any other data collection medium (source documents) and for ensuring that they are accurate, authentic/original, traceable, complete, consistent, readable and available if necessary. The *e-CRFs* must be signed by the investigator or an authorized member of the research team in order to guarantee the

authenticity of the data captured in them. Any correction made to the entries in the *e-CRF* or source documents must be dated, accompanied by the author's initials and an explanation (if necessary), and must not mask the original data.

In most cases, the source documents comprise the hospital or doctor's records. In this case, the data collected in the e-CRF must correspond to these records.

In certain cases, the e-CRF can also be used as source document. In this case, a document, available at the investigator site or at Pfizer, must clearly identify the data that were recorded in the e-CRF, and for which the e-CRF constitutes the source document.

9.6.2. Record Keeping

To allow for evaluations and/or inspections/audits from regulatory authorities or Pfizer, participating doctors accept to keep the files, including the identity of all of the participating patient (sufficient information to make a link between the files, for example CRFs and hospital files), all of the original signed information documents, the copies of all of the CRFs, the notification forms for tolerance of use, the source documents, the detailed documents for distribution of treatments and appropriate documentation of any pertinent correspondence (for example, letters, minutes from meetings and reports from phone calls).

The files must be kept by the participating doctors in compliance with the local regulations or according to the specifications of the Study Convention (SE), depending on which has the longest duration. Participating doctors must ensure that the files continue to be stocked securely for as long as they must be kept.

If the participating doctor is no longer able to keep the study files for the required period for whatever reason (for example, retirement, transfer), Pfizer must be notified in advance. The study files must be transferred to a third person, designated by Pfizer, for example another participating doctor, another institution or an independent third party named by Pfizer.

The files of the participating doctor must be kept for a minimal duration of 15 years after the end or the interruption of the study or longer if required by the local regulations in force.

The participating doctor must obtain written authorization from Pfizer before divulging any files, even if the record keeping requirements have been satisfied.

9.6.3. Circuit des CRF

The data collected by the investigator from the inclusion of patients and throughout the study will be directly recorded by the investigator site on the study eCRF.

Adverse events will be collected using the eCRF by the investigator sites during the usual follow-up visits, for all the study patients. Where applicable, requests for additional information from the Pfizer pharmacovigilance department will be sent to the person who reported the event (investigator or another member of the investigator team). All the reports (initial and follow-up reports) will be collected using a site number and the patient number.

Patient self-questionnaires may be directly completed in electronic format by the patients on the study ePRO.

Hard copies of the completed patient self-questionnaires will be sent to Pfizer by the investigator site using secure follow-up envelopes. They will then be sent electronically by Pfizer via a secure site to the data management for entry.

9.6.4. Database construction

The database and eCRFs will be created by the clinical research organisation under contract (CRO) in charge of Data Management of the study.

The eCRF will be the tool usually used by the CRO for this type of study. All Data Management operations will be carried out in agreement with requirements of Pfizer and according to the standard operating procedures (SOP) of the CRO.

An annotated questionnaire will be drawn up by Pfizer giving the name of the tables and name of the variables. Each variable will be associated with its type, length and where applicable, its format. The annotated questionnaire will be submitted to Pfizer for validation.

Pfizer will then construct a database using its own software. The structure of the database will be documented and verified on listings by comparing the attributes of the database variables with the specifications noted on the annotated questionnaire.

Before any entry of real data, the structure of the database and data entry screens will be tested and validated according to the Standard Operating Procedures of Pfizer. Fictitious questionnaires will be filled in and entered for these tests. Validation will be performed by printing out the data in listings and comparing them with the data noted in the questionnaires. A validation report will be drafted by Pfizer. The final structure of the database must be submitted for validation to Pfizer before the entry of any real data.

An audit file will be created to record all the modifications made to the database. The original data, modified data, date and time of the change, the person who made the change and the reason for the change will be recorded in the audit file. The functioning of the audit file will be tested by changing the fictitious data. A report will be drafted by the CRO.

9.6.5. Data control

A list of consistency tests used to detect discrepancies and aberrant responses in the questionnaires will be published by the CRO in charge of datamanagement. These tests will be programmed with CRO's own software and then tested with fictitious data. This fictitious data and documents about the tests will be kept in the study file by Pfizer and available for review.

After entry, the data will be continuously controlled and a specific request for each discrepancy will be electronically generated by the data control system. In order to reduce the number of requests submitted to investigators, a guide of self-evident corrections may be prepared by the CRO.

The CRO will make the data control documents available to Pfizer on simple request. Periodic data monitoring progress reports will be published by the CRO.

9.6.6. Access to data

The databases and servers on which the data are saved will be located in locked rooms. Only personnel dedicated to the study will have access to the databases**.**

9.6.7. Database lock

The database will only be locked once data entry, monitoring and, where applicable, coding have been completed by Pfizer. The database will be locked using the Pfizer procedure and the CRO's Standard Operating Procedures. After validation by Pfizer, the database will be locked and ready for statistical analysis.

9.6.8. Data management report

A data management report will be drafted by Pfizer after database lock.

9.7. Data analysis

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

A descriptive statistical analysis will be carried out including the number of cases, missing data, and the mean, standard deviation, median, first and third quartiles, minimum and maximum, or frequency tables according to the nature of the parameter.

All tests will be two-sided and the type I error (α) will be set at 5% for the entire study, except for the screening of predictive factors of drug survival using an univariate analysis (see the following) where a type I error will be set at 10%. No adjustment for multiplicity will be used. Two-sided 95% confidence intervals will be provided whenever this is relevant.

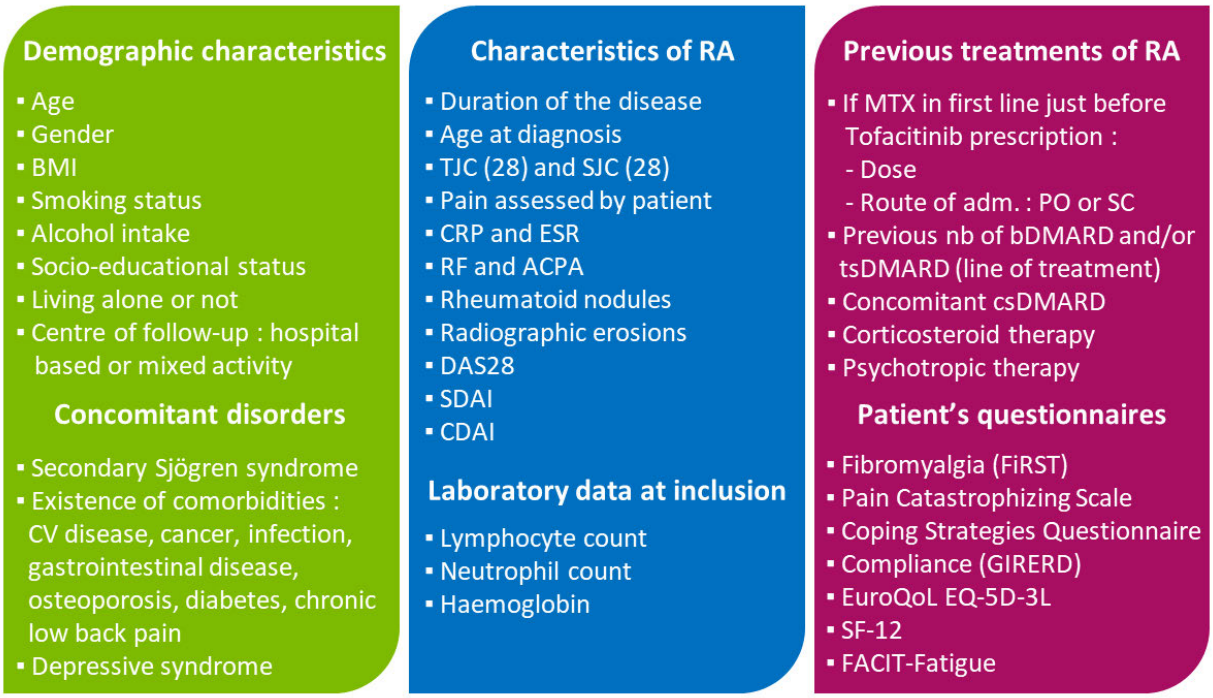
A Full Analysis Set is defined as patients who receive at least one dose of Tofacitinib and have at least one set of post-baseline measurements. This population will be used for all efficacy analysis. The population for analysis of tolerability will be comprised of all patients enrolled, who received at least one dose of Tofacitinib.

Tofacitinib maintenance will be estimated by considering the date of initiation of treatment with Tofacitinib and the date of permanent discontinuation of this same treatment. The follow-up time of patients not presenting with an event of interest (permanent discontinuation of a patient) will be censored at the date of the last visit. Drug survival with Tofacitinib will be described with the Kaplan-Meier method. Survival function S(t) (probability that an event of interest does not occur before the date (t) will be depicted graphically by a survival curve with 95% confidence intervals estimated with the Klein and Moeschberger method [(49)]. An estimate of drug survival with Tofacitinib at 12 and 24 months will be provided.

Principal analysis

Factors predictive of drug survival will be investigated using a Cox model.
The potential predictive factors of drug survival are as follows:

Figure 2 : Potential predictive factors of drug survival



First, the effect of each factor on drug survival will be tested with a univariate Cox model. Thus, the hazard-ratios calculated are called "raw". They will be presented with their 95% confidence interval and their associated p-value. Then, all potential factors for which the p-value resulting from univariate analysis is strictly less than 10% will be included in a multivariate Cox model. 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 < 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. The adjusted hazards-ratios thus obtained will be presented with their 95% confidence interval and their associated p-value.

Missing data will be managed using a method based on missing data indicators [50, 51]. This method is not a method of imputation of missing data. A fixed value will be assigned to missing observations, and a dummy variable (1/0) will be added to the multivariate model in order to indicate if the value of this variable is missing or not. If more than 10% of the patients have missing baseline covariates, a complete case analysis will also be performed as a sensitivity analysis. Additional methods for handling missing data may also be used. Further details will be provided in the statistical analysis plan as appropriate.

Secondary analyses

The impact of behavioural strategies (catastrophisation and coping) on Tofacitinib drug survival will be evaluated in patients suffering from RA. A Cox proportional hazards model will be used with the 5 dimensions in the coping questionnaire and the catastrophisation score collected at the baseline visit included as independent variables.

In a second phase and in a similar manner, a Cox model will be used to estimate the impact of the adaptive strategies under treatment. Therefore, the last evaluation available before discontinuation of treatment (or the last visit if a patient does not permanently discontinue treatment) and the change between this latter evaluation and the baseline value will be taken into account in separate models.

The correlation between behavioural strategies and effectiveness will be studied with Pearson's or Spearman's coefficient according to the nature of variables compared.

Interim analysis

Interim descriptive analyses will be conducted annually.

In general, additional analyses, in relation to the objectives of the study, may be carried out in agreement with the Scientific Committee of the study, for publication purposes.

Pooled analysis within a programme of studies conducted by Pfizer

This study falls within a programme of studies conducted by Pfizer across different countries (Germany, Turkey, Greece, Spain, Czech Republic, Israel, etc.) in order to create a database of patients treated under real-life conditions with Tofacitinib in rheumatoid arthritis. This database is based on EULAR 2017 recommendations for a core data set to support observational research in RA [52].

Data collected from this French study will be compared to and pool-analysed with data from other countries in order to evaluate the long-term effectiveness and tolerability of Tofacitinib in a broader population of RA patients.

9.8. Quality control

9.8.1. Data entry in centres

The physician has the responsibility of collecting and of recording data in the eCRF. He/she must ensure that data are entered completely and accurately, and that they are consistent with source data.

Centres may request the aid of a TEC (study technician) in the setting of the study in order to help them for data entry in the eCRF. During these data entry visits, the TEC will be in charge of reporting in the case report forms data on patients enrolled by the centre and to report AEs to the Pfizer pharmacovigilance department.

9.8.2. Quality control

Follow-up, quality control, data entry and analysis of data will be carried out by the CRO specialising in follow-up, management and processing of data from observational studies according to good practice in force under contract with Pfizer S.A.S.

Requests for additional information and/or requests for corrections may be sent (by dispatch in electronic format) to participating physicians, requesting missing or inconsistent information based on the data validation plan.

Throughout this study, doctors will be contacted by staff especially trained under contract with Pfizer to ensure comprehension of the protocol and of the electronic questionnaire by the physician, and compliance with the protocol. All these contacts will be documented.

The quality of the data collected during the study will be ensured by:

- The training of investigator teams during study set-up (objectives and conduct of the study, protocol and eCRF, logistics, pharmacovigilance procedures etc.)
- Regular follow-up of investigators during the study (by telephone calls and emails)
- Online control of data captured in the eCRF (automated on-line control for key data and additional correction requests). All of these controls will be described in the Data Management Plan.

Key indicators of the good conduct of the study (number of active sites, number of included patients, number of follow-ups performed etc.) will be generated from the study database. This database can be used to edit study progress reports in order in order to manage site reminders.

Data quality control will be performed on site on a sample of 10% of active centres. Screening of active centres for quality control will be performed by randomisation at the end of the enrolment period.

9.9. Limits of the methods of research

This protocol was designed in such a way as to best meet the objectives defined for this observational study. However it has certain limitations which must be discussed and which must be taken into account during the implementation of the study and processing of the results.

The study has methodological limitations that are inherent to its non-interventional design.

To minimise potential selection bias, patients enrolled in the study will be so enrolled according to a consecutive method (study proposed systematically to all patients who satisfy eligibility criteria seen in a consultation during the period of enrolment). In addition, in order to verify the absence of a selection bias, characteristic of patients enrolled in the study will be compared to those of patients who have refused to participate in the study; characteristics of these patients will be collected in a non-inclusion registry with a minimum collection of information.

9.10. Other aspects

Pfizer will ensure, by its study assistants, regular administrative follow-up of participating sites.

Pfizer may make available to sites, a TEC in order to assist doctors with data entry in the eCRF.

The CRO responsible for data management will ensure the parameterisation of the eCRF, and printing of requests for correction.

The firm responsible for statistical analyses will ensure drafting of the statistical analysis plan, the statistical report and the clinical report of this study.

9.10.1. Logistical follow-up

Follow-up of participating physicians will be carried out by a team of Pfizer study assistants especially trained for the study. This follow-up may be performed in different manners: phone calls, email, a specific letter and newsletter. This follow-up consists of dispatch via mailing to participators in the study, collection of regulatory documents and fee payments.

The quality of these contacts will be preferred in light of the fact that it will promote involvement and work quality performed by participating physicians. Each one will be followed insofar as possible by the same study assistant, from the time of his/her recruitment up to closure of the study.

The research assistants will perform follow-up of incomplete or inconsistent data (control of inconsistencies, non-responses and omissions) and will be in constant contact with participating physicians. During the patient screening process and depending on number of inactive participating doctors (no patient selected), the research assistants may decide to send reminders to the latter.

Furthermore, a free phone number (green phone number) specific for the study will be set up targeting participating physicians in order to respond immediately to their questions throughout the study.

In terms of traceability, all “entering” calls via the green phone number and “outgoing” calls (call for screening, reminders, etc.) will be the subject of a written report (date, purpose of call, measures to be taken, etc.) and will be recorded in the panel of operating indicators.

9.10.2. Data collection

After signing the contract and the set-up visit, the investigators and each person participating at the site must send the Pfizer Post-MA Study department: the protocol acknowledgement form, the eCRF training certificate and the pharmacovigilance training certificate. Participating doctors will then receive the link with their identifier and their access code to the e-CRF.

These codes are personal, and all the persons trained and involved in the study at the site will receive their identifier and code.

The investigator sites will complete the questionnaire for each included patient during the scheduled regular visits.

If a patient drops out of the study during follow-up, the investigator site will fill in the end-of-study questionnaire and give the reason for withdrawal.

The investigators undertake to exhaustively collect the data for each patient.

9.10.3. Archiving

The investigators will keep the questionnaires for up to 15 years after the last visit of the last patient. All the documents will then be returned to the study sponsor**.**

The study management center will keep all study-related documentation until 15 years after the last patient's visit.

10. PROTECTION OF PATIENTS

10.1. Information and protection of patients

All the parties shall comply with current legislation and in particular the laws concerning the implementation of technical and organizational measures for ensuring the protection of the patients' personal data. These measures comprise the omission of the patients' names or other data making it possible to identify them directly in all reports, publications and other communications, except where required by current legislation.
Personal data will be kept at the study site in encrypted electronic/or paper form and will be protected by a password or secured in a locked room in order to ensure that only approved study personnel has access to it. The study site will set up the appropriate technical and organizational measures to ensure that personal data can be recovered in the event of loss or damage. In the event of a potential personal data breach, the study site will assume responsibility for determining whether the breach has actually occurred and, if so, for making the notifications required by law.

To protect the rights and freedoms of individuals with regard to the processing of personal data, when the study data are compiled for transfer to Pfizer and the other approved parties, patients' names will be removed and replaced by a specific unique numeric code, on the basis of the numbering system defined by Pfizer. All the other data allowing the identification of patients and transferred to Pfizer or other approved parties will be identified using this specific unique code for each patient. The investigator site will keep a confidential list of the patients taking part in the study, with the link between the numeric codes of each patient and the real identity of each of them. When data are transferred, Pfizer will maintain high standards of confidentiality and protection of the patients' personal data, in accordance with the provisions of the study agreement and applicable privacy protection laws.

10.2. Patient Information Leaflet

The information documents and all the materials intended for the recruitment of patients must comply with local regulatory and legislative requirements and in particular the current laws concerning the respect of privacy.
The documents used during the consent process for data collection and all the materials allowing patient recruitment must be examined and approved by Pfizer and approved by the Committee for the Protection of Persons (CPP) before their use, and must be available for inspection.
The investigator must make sure that all the study patients or their legal representatives are fully informed about the nature and objectives of the study, the disclosure of study-related data and any risks associated with their participation, in particular the risks associated with the processing of patients' personal data. The investigator must also make sure that all the study patients or their legal representatives are fully informed about their rights to access and correct their personal data and withdraw their consent for the processing of their personal data.

The investigator will provide exhaustive information and hand over the information sheet to each patient or admissible legal representative before the conduct of any study-specific activity, in particular with regard to the collection of data about the patient.
Investigators will keep in the medical records the information sheets that they signed certifying that they adequately informed and gave the patients and/or their legal representatives the information sheet before inclusion in the study.
Note that only the principal investigator or co-investigators trained in the study can sign the information sheet.

10.3. Withdrawal of the patient

Patients can withdraw from the study at any time at their own request, or can be withdrawn at any time at the investigator's or sponsor's discretion for pharmacovigilance, behavioral or administrative reasons. In all circumstances and where applicable, every effort should be made to document patient outcomes. Investigators will obtain information about the reason for withdrawal and the follow-up of the patient after all unresolved adverse events.

If the patient withdraws from the study, and opposes the disclosure of future information, no other evaluation may be carried out, and no other data must be collected. The sponsor can keep and continue to use all the data collected before his/her voluntary withdrawal from the study.

10.4. Ethics Committee (CPP)

This is a non-interventional study that does not modify in any way the usual medical management of the persons entering the study, or compromise their physical or mental integrity or require any particular follow-up visit for the persons entering the study. All procedures are performed and all products used in a usual way, without any additional or unusual diagnostic or monitoring procedure.

Under these conditions, this study comes within the scope of application of Ordinance No. 2016-800 of 16 June 2016 for research, article L1121-1, and the project must therefore be declared to the French National Agency for Medicines and Health Products Safety (ANSM), and a submission made to the Committee for the Protection of Persons (CPP).

The sponsor must obtain prior authorization for the study protocol, protocol amendments and patient information sheets, and all other significant documents (for example, advert to obtain recruits), where necessary, from the CPP.

All correspondence with the CPP must be kept by the investigator.

10.5. National Medical Council (CNOM)

In application of article L4113-6 of the Public Health Code and articles R4113-104 and R4113-105 of the Public Health Code, the following documents have been sent by the sponsor of the study to the CNOM:

- Final study protocol
- Questionnaire for collection of data
- List of physicians participating in the study and members of the scientific committee

- Financial agreement proposed to doctors participating and to members of the scientific committee
- Information letter for patients

The sponsor of the study must inform the CNOM by registered letter of all financial aspects between the sponsor, members of the scientific committee and doctors participating in the study.

Non-response 2 months after receipt of the dossier by the CNOM signifies a favourable opinion. A copy of the opinion of receipt will be sent to each participating physician by the Sponsor. It is the responsibility of each participating physician then to send a copy of this opinion of receipt and the financial agreement signed by the Departmental Medical Council (CDO) to which he is attached by articles L4113-9, L4113-10 and L4163-10 of the Public Health Code.

In the setting of this study, CENGEPPS contracts are not applicable and may be used only for payment of hospital extra costs paid directly to the institution to which the participating doctor is attached.

10.6. Protection of data: National Data Processing Commission "CNIL"

In accordance with law No. 78-17 of 6 January 1978 on Data Processing, Data Files and Civil Liberties, amended by law 2004-801 of 6 August 2004 concerning the protection of individuals with regard to the processing of personal data, this protocol will be subject to a declaration of compliance with a reference method to the French Data Protection Agency (CNIL).

Taking into account the fact that the study comes within the scope of MR003, the compliance commitment of Pfizer allows us to start without the opinion of the French Data Protection Agency (CNIL).

10.7. Ethical conduct of the study

The study will be conducted in conformity with legal and juridical requirements, as well as the objective, value and scientific rigor and in compliance with generally accepted practices of research described in recommendations on pharmacoepidemiologic good practice (GPP) published by the International Society for Pharmacoepidemiology (ISPE), recommendations of good epidemiological practice (GEP) published by the International Epidemiological Association (IEA), good practice of research on results published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the international ethical recommendations for epidemiological research published by the Council for International Organizations of Medical Sciences (CIOMS), the European network of pharmacoepidemiology and pharmacovigilance centres (ENCePP) of the European Medicines Agency (EMA), the guide of methodological standards in pharmacoepidemiology and FDA guidelines for industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA guidelines for industry and for FDA staff: Good Practice of Conduct and Reporting of Pharmacoepidemiologic Safety Studies using all electronic medical data, and guide lines for industry: measures of change noted by the patient; use in development of medicinal products in support of labelling and/or equivalent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

11.1. Single reference document on safety of use

The current French Summary of Product Characteristics (SmPC) will be the single reference safety document during the study. It will be used by Pfizer pharmacovigilance department to evaluate any safety event reported to the Pfizer pharmacovigilance department by the investigator during this study.

This single safety reference document should be used by the investigator for prescribing information and recommendations.

11.2. Requirements in terms of pharmacovigilance

The following table summarises the requirements for recording of adverse events in the electronic case report and for reporting adverse events via the Adverse Event Reporting Form for noninterventional studies to Pfizer pharmacovigilance (NIS AEM Report Form). These requirements are defined by three types of events:

(1) serious adverse events (SAE)
(2) non-serious adverse events (AE) (if applicable), and
(3) situations involving exposure to a medicinal product including exposure in pregnancy, exposure in a breastfeeding mother, medicinal product errors, overdoses, misuse, extravasation and occupational-related exposure.

These events are defined in the section entitled “Definition of an adverse event”.

	Recorded in the study electronic CRF	**Reported via NIS AEM *Report Form* to Pfizer Pharmacovigilance within 24H following the awareness of the event**
SAE	All	All
Non-serious AE	All	***Potential risk (RMP XELJANZ in force) :*** - 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 - Higher incidence and severity of adverse events in the elderly
Situations involving exposure to a study medicinal product including exposure in pregnancy, exposure in a breastfeeding mother, medicinal product errors, an overdose, misuse, extravasation, lack of efficacy and occupational exposure	All (indepedently of existence of a concomitant AE), **except for occupational exposure**	All (independently of existence of a concomitant AE)

For each AE, the participating physician must look for and obtain sufficient information, both in order to determine the outcome of the adverse event and to evaluate if it satisfies criteria for classification as an SAE (see section entitled “serious adverse events” below).

Adverse events must be reported to Pfizer within 24 hours following awareness of the event by the participating physician, whether the event has been considered as related to the study medicinal product or not by the participating physician.

In particular, if a serious adverse event is fatal or life-threatening, reporting to Pfizer must be done immediately, whatever the information available on the adverse event. This time period also applies to all new information (follow-up) relating to reporting of adverse events forwarded previously. In rare cases where the participating physician is not immediately informed of occurrence of an adverse event, the participating physician must report the event within 24 hours after he becomes aware of it and complete the information at time when he became aware of this adverse event for the first time.

For adverse events considered as serious or identified in the right-hand column of the abovementioned table which are to be reported to Pfizer within 24 hours following awareness of them, the participating physician is required to look for and to provide all further information to Pfizer in conformity with this 24h time period. Furthermore, Pfizer can request that a participating physician obtain in an urgent manner specific further information on follow-up. This information can be more detailed than that recorded in the study case report form. Generally, this information will include a sufficiently detailed description of the adverse event in order to enable complete medical evaluation of the case and the independent determination of a possible causal relationship. All relevant information regarding the event, such as concomitant treatments or disorders, must be provided. If a patient dies, a summary of available results of an autopsy must be forwarded as soon as possible to Pfizer or to its certified representative.

Period of reporting

For each patient, the period of reporting of adverse events starts from the time the patient received the first dose of the study medicinal product or from the date on which the patient provided his/her informed consent if he/she has previously been exposed to the study medicinal products, and ends at end of the study period of observation which should include at least a period of 28 calendar days after the last administration of the study medicinal product; a report must be sent to the PFIZER Pharmacovigilance department or to its certified representative for all types of adverse events listed in the abovementioned table and occurring during this period. If the patient receives the study medicinal product on last day of the observational period, the reporting period will be extended by 28 calendar days after the end of the observational period.

In the event that the patient provides his/her consent but was never enrolled in the study (for example, the patient changed his/her mind on participation; failure in terms of screening criteria), the period of reporting ends on date of decision for non-inclusion of the patient.

If the participating physician becomes aware of a serious adverse event which occurred at any time after the end of the observational period, and he/she considers it related to a study medicinal product, this serious adverse event must also be reported to the Pfizer Pharmacovigilance department.

Evaluation of causal relationship

The participating physician must evaluate and record the causal relationship. For all adverse events, sufficient information must be obtained by the participating physician in order to determine the causal relation of each adverse event. For AE considered as related to a study medicinal product, the participating physician is required to perform follow-up up until resolution or stabilisation of the event and/or of its sequelae at a level considered acceptable by the participating doctor and that Pfizer is in agreement with this evaluation.

Evaluation of the causal relationship by the participating physician is the determination of the fact that a reasonable possibility exists that a study medicinal product has caused or has contributed to an adverse event. If the final determination of a causal relation is "unknown" and that the participating physician cannot determine if a study medicinal product has caused an event, then the event must be reported within 24 hours.

If the participating physician cannot determine the aetiology of the event but that he/she has determined that no study medicinal product was the cause of the event, information on this must be clearly provided in the case report form and in the adverse event reporting form for noninterventional studies.

Definition of an adverse event

Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. It is not necessary that the event have a causal relationship with the treatment or use. Examples of adverse events include, without this list being exhaustive, the following:

a. Abnormal test results (see the following for circumstances in which an abnormal test result constitutes an AE);
b. Clinically significant symptoms and signs;
c. Changes to results of the clinical examination;
d. Hypersensitivity; lack of efficacy; abuse of a medicinal product;
e. Pharmacodependence.

Furthermore, for medicinal products, they can include resultant signs or symptoms:

a. Of an overdose;
b. Of withdrawal;
c. Of misuse;
d. Of off-label use (Off-Label of MA);
e. Of medicinal product interactions;
f. Of extravasation;
g. Of exposure during pregnancy;
h. Of exposure during breastfeeding;
i. Of a medicinal product error;
j. Of occupational exposure.

Abnormal test results

Criteria enabling to determine if an abnormal result of an objective test must be reported as an adverse event are as follows:

- The test result is associated with symptoms, and/or
- The test result requires further diagnostic investigations or a medical/surgical intervention, and/or
- The test result leads to a change in dosage or to withdrawal of a patient from the study, to administration of a significant additional concomitant treatment, or to another treatment, and/or
- The test result is considered as an adverse event by the participating doctor or the sponsor.

The simple repetition of an abnormal test result, in the absence of one of the aforementioned conditions, does not constitute an adverse event. All abnormal test results which prove to result from an error do not need to be reported as adverse events.

Serious adverse events

A serious adverse event is defined as any untoward medical occurrence in a patient receiving a medicinal product or a nutritional product, whatever the dose, or using a medical device, and that:

- Causes death;
- Is life-threatening;
- Requires hospitalisation of the patient or results in prolongation of hospitalisation (see below for circumstances in which this does not constitute an adverse event);
- Results in permanent or important disability or incapacity (important deterioration of ability to accomplish actions of daily living);
- Results in a congenital anomaly or a malformation.

Progression of a malignancy during the study (including signs and symptoms of progression) must not be reported as a serious adverse event unless its outcome is fatal during the study or during the period of reporting of adverse events. Hospitalisation due to signs and symptoms of progression of the disease must not be reported as a serious adverse event. If a malignancy has a fatal outcome during the study or during the period of reporting of adverse events, then the event leading to death must be recorded as an adverse event, and as a grade 5 serious adverse event.

An event will be defined as medically important based on medical and scientific judgement. A medically important event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is established that the event can be life-threatening for the patient and/or require an intervention in order to prevent one of the outcomes stated in the above, the medically important event must be reported as serious.

Events, for example, that enter into this category of medically important events are allergic bronchospasm requiring intensive care in the emergency room (ER) or at home, coagulation disorders, seizures which have not resulted in hospitalisation, or development of pharmacodependence or medicinal product abuse.

Furthermore, all suspected transmission of an infectious agent, pathogenic or not, by a Pfizer product is considered as a serious adverse event. Such event can be suspected by clinical symptoms or test results indicating an infection in a patient exposed to a Pfizer product. The terms “suspicion of transmission” and “transmission” are considered synonymous.

These cases are considered as unexpected and must be managed as serious cases by the Pfizer Pharmacovigilance Department. These cases can also be reported as product defect, if applicable.

Hospitalisation

Hospitalisation is defined as any initial admission to hospital (even for a duration less than 24 hours) into a health institution or any prolongation of an admission.

The admission also includes transfer within the hospital to an intensive care unit ICU (for example, from a psychiatric ward to a medical ward, from a medical ward to a coronary intensive care unit, from a neurology ward to a unit for treatment of tuberculosis).

A visit to the ER is not necessarily a hospitalisation; however, an event which leads to a visit to the ER must be evaluated as medically important.

Hospitalisation in the absence of an adverse event is not an adverse event in itself and does not require reporting. For example, the following reasons for hospitalisation without an AE are not to be reported:

- A social admission (for example, patient does not have a place to sleep)
- Administrative admission (for example, for an annual check-up)
- An optional admission not associated with a triggering AE (for example, for a scheduled cosmetic surgery procedure)
- Hospitalisation for observation in the absence of an AE
- Admission for treatment of a pre-existing condition not associated with development of another AE nor with worsening of a pre-existing disorder (for example, for an assessment following persistence of abnormal laboratory test data existing prior to the treatment)
- Planned admission by the protocol during the clinical study (for example, for a procedure required by the study protocol).

Situations requiring reporting to Pfizer Pharmacovigilance within 24 hours:

Situations involving exposure in pregnancy, exposure during breastfeeding, a medicinal product error, an overdose, misuse, extravasation, lack of efficacy, occupational exposure are described in the following.

Exposure in pregnancy (or exposure in utero)

An exposure during pregnancy occurs if:

A woman becomes pregnant or it turns out that she is pregnant while she is receiving or is exposed to a study medicinal product (for example, environmental exposure) or a woman becomes pregnant or it turns out that she is pregnant after having discontinued or having been exposed to a study medicinal product (maternal exposure);

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

A man has been exposed, in the setting of treatment or of environmental exposure, to a study medicinal product before or around the period of conception and/or has been exposed during pregnancy of his partner (paternal exposure).

Generally, cases of prospective and retrospective exposure in pregnancy, whatever the source, are to be reported, whether an adverse event is present or not, according to the procedure for reporting serious adverse events.

If a female patient in the study or the partner of a study patient becomes pregnant or it turns out that she is pregnant during treatment of a male patient in the study with the study medicinal product, the participating doctor must report this information to Pfizer, whether an adverse event has occurred or not, by completing the adverse event reporting form for noninterventional studies, as well as the additional form entitled “Exposure during pregnancy”.

Furthermore, information relating to environmental exposure to a medicinal product by a pregnant woman (for example, a female patient reports that she is pregnant and reports that she has been exposed to a cytotoxic product by inhalation or after having accidentally spilled it) must be reported to Pfizer, whether an adverse event has occurred or not, by completing the adverse event report form for noninterventional studies, as well as the additional form “Exposure during pregnancy”.

The information forwarded must include the planned date of term of the pregnancy (see the following for information on term of pregnancy).

Follow-up must be implemented to obtain general information on the pregnancy.

Furthermore, follow-up must be implemented to obtain information on the outcome of the pregnancy for all cases which are the subject of reporting of exposure in pregnancy whose outcome is unknown.

A pregnancy must be followed up to its end or up to termination of the pregnancy (for example, voluntary termination of pregnancy) and Pfizer must be informed of its outcome.

This information will be provided in the setting of follow-up of the initial report of exposure during pregnancy. In case of a birth, the structural integrity of the neonate can be evaluated at time of birth.

In case of a termination of pregnancy, the reason must be specified and, if possible clinically, the structural integrity of the foetus must be evaluated by a visual inspection (at least that the results of tests performed before the procedure have concluded in a congenital anomaly and that these results have been reported).

If the outcome of the pregnancy corresponds to criteria of an SAE (for example, an ectopic pregnancy, a spontaneous abortion, a foetal death in utero, a neonatal death or a congenital anomaly [for a viable baby, an aborted foetus, foetal death in utero or neonatal death]), procedures for reporting of SAE must be followed.

Further information on the outcome of pregnancy which are reported as an SAE are as follows:

A spontaneous abortion which includes a miscarriage and non-expulsion of the foetus;

Neonatal deaths which occur during the month following the childbirth must be reported, whatever the causal relationship, as SAEs. Furthermore, death of a baby after one month of age must be reported as an SAE whenever the participating doctor evaluates the death of the child of a young age as related or possibly related to exposure to the study product.

Further information on exposure in pregnancy can be requested. Follow-up on outcome at time of childbirth will be treated on a case-by-case basis (for example, follow-up in children born before full term, of a young age, in order to identify developmental retardation).

In case of paternal exposure, a form for communication of information intended for pregnant partners will be given to the male patient participating in the study for his partner. It must be documented that this document has been given to the patient participating in the study for transmission to his partner.

Exposure during breastfeeding

Situations of exposure during breastfeeding must be reported independently of existence of a concomitant AE.

A report of exposure during breastfeeding must not be filed with a Pfizer product specifically indicated for use in a pregnant woman (for example, vitamins) administered in agreement with the MA.

However, if a toddler presents an AE associated with administration of such a medicinal product, the AE must be reported as with exposure during breastfeeding.

A medicinal product error

A medicinal product error means any unintentional error in prescribing, dispensing or administration of a medicinal product, which can cause or lead to inappropriate use of a medicinal product or to harm for the patient, even though it is under the control of a health professional, the patient or of a consumer. Such events can be related to professional practice, products, procedure, and to systems in particular; prescribing; transmission of an order; product information, packaging and nomenclature of a product; composition; dispensing; distribution; administration; training in use of the product; monitoring and use.

Medicinal product errors include the following:

Near-accidents involving or not a patient directly (for example, administration by inadvertence or error, which is an accidental use of a product outside of indication of prescription by a healthcare professional or a patient/consumer);

Confusion concerning the name of a product (for example, marketing name and trade name).

The participating doctor must report the following medicinal product errors to Pfizer, independently of existence of an associate AE/SAE:

Medicinal product errors involving exposure of a patient to a product, whether the medicinal product error is accompanied by an adverse event or not.

Medicinal product errors not involving a patient directly (for example, potential medicinal product errors or near-accidents). Whenever a medicinal product error does not involve exposure of a patient to a product, the following minimal criteria constitute a case of medicinal product error:

The notifier is identifiable;

A suspect product;

Medicinal product error.

Overdose, Misuse, Extravasation

Cases of an overdose, misuse and extravasation associated with use of a Pfizer product must be reported to Pfizer by the participating doctor, independently of existence of a concomitant AE/SAE.

Lack of efficacy

Cases of lack of efficacy of a Pfizer product must be reported to Pfizer by the participating physician independently of existence of a concomitant AE/SAE; or indication of a Pfizer product.

Occupational exposure

Cases of occupational exposure to a Pfizer product must be reported to Pfizer by the participating physician, independently of existence of a concomitant AE/SAE.

12. PLANS FOR COMMUNICATION OF STUDY RESULTS

Pfizer and the scientific committee undertake to send the study results to all the doctors participating in the study.

At least one communication and one publication are planned at the end of the study.

12.1. Scientific Committee

A qualified scientific committee was set up for this study. It is composed of 2 doctors specialized in gastroenterology, who participated in drafting the protocol and its validation, and who will take part in the validation of the statistical analysis plan and drafting the clinical report. The scientific committee is also responsible for proposing and/or validating changes to the protocol once the study is underway.

12.2. Access to source data

A source document is any original document or object that proves the existence or accuracy of a data or fact recorded during the research and in particular the medical records of included patients.

The investigators will make available the documents and individual data strictly necessary for data collection during the study, study monitoring, quality control and auditing of the study, to the persons with access to these documents in accordance with legislative and regulatory provisions (Articles L.1121-3 and R.5121-13 of the Code of Public Health).

12.3. Confidentiality

Pursuant to current legislation (Articles L.1121-3 and R.5121-13 of the Code of Public Health), persons with direct access to source data must take all the necessary precautions to ensure the confidentiality of information about the experimental drugs, the research and participating subjects, in particular as regards their identity and the results obtained. These persons and the investigators themselves are subject to professional secrecy.

During the study or after its completion, the data collected on the participants and sent to the sponsor by the investigators (or any other specialized persons involved) will be made anonymous. They should in no case show the names of the persons concerned or their address.

No nominative data about the patient will be collected.

The sponsor (or its representative) must ensure that each person participating in the research gives his/her agreement for access to his/her personal data which are strictly necessary for the quality control of the research.

12.4. Data ownership

PFIZER will retain ownership of all the case report forms, data analysis, and reports resulting from this study.

12.5. Communication and publication

All the information obtained from this study will be considered confidential, until Pfizer and the members of the scientific committee have carried out its analysis and final review.

The study results may be published or presented by the members of the scientific committee after revision and approval by Pfizer, who will ensure that confidential information or industrial property are not disclosed. Before publication or presentation, a copy of the final text should be sent by the member(s) of the scientific committee to Pfizer, for comment. Such comments aim to ensure the scientific content of the proposed publications and/or presentations and make sure that the data and the material referring to Pfizer products and activities receive a fair, accurate, and reasonable presentation.

12.6. Communication of problems

If a prohibition or restriction is imposed (for example, the suspension of the study) by a responsible competent authority in any region of the world, or if the investigator becomes aware of any new information that could affect the evaluation of the benefits and risks of a Pfizer product, Pfizer must be immediately informed.

Moreover, the investigator shall immediately inform Pfizer about all the urgent safety measures taken by the investigator to protect study patients from any immediate danger, and from all the serious breaches of this non-interventional study protocol about which the investigator is aware.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF INDEPENDENT DOCUMENTS

Numéro	Numéro de référence du document	Date	Titre
1	1.2	09-NOV-2018	Patient Information Leaflet
2	2.0	21-DEC-2020	Case Report Form including non-inclusion log and adverse event reporting form
3.1	PCS		PCS – Pain Catastrophizing Scale
3.2	CSQ		CSQ – Coping Strategies Questionnaire
3.3	GIRERD		GIRERD
3.4	FIRST		FiRST-Fibromyalgia Rapid Screening Tool
3.5	Euro QoL		Euro QoL EQ-5D -3L
3.6	SF-12 (Version 2)		SF-12 (Version 2)
3.7	FACIT-F		FACIT-F - Functional Assessment of Chronic Illness Therapy-Fatigue
4	NA	08-DEC-2020	Sites list

ANNEX 2. ADDITIONNAL INFORMATION

Not Applicable