NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz® (tofacitinib) Using an Administrative Healthcare Database in France
Protocol number	A3921403
Protocol version identifier	4.0
Date	26 February 2024
EU Post Authorization Study (PAS) register number	To be registered prior to the start of data collection
Active substance	Tofacitinib Anatomical Therapeutic Chemical code: L04AA29
Medicinal product	Tofacitinib (Xeljanz®)
Product reference	EU/1/17/1178/001014
Procedure number	EMEA/H/C/004214
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	Are prescribers in France adherent to the recommendations and limitations for use described in the tofacitinib additional risk minimisation measure (aRMM) materials? The primary objectives are as follows: 1. Describe the characteristics of patients treated with tofacitinib and by indication (i.e., rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC), and off-label use), in terms of: • Demographics (e.g., age and sex); and

	• Comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs for treating patients with RA, PsA or UC, specifically: • Adherence to the recommended posology per indication (average daily dose) and duration of use; • Adherence to recommendations for patient screening and laboratory monitoring prior to and during tofacitinib treatment; • Adherence to recommendations for limitations of use, including: • Contraindicated use; • Use with medications not compatible with tofacitinib. • Describe prescribing patterns over time: • Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically: • Use in patients with risk factors for venous thromboembolism (VTE); • Use in the patients aged 65 years and older; • Use in patients with risk factors for cardiovascular (CV); • Use in patients with risk factors for malignancy. • Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the JAKi 2022/2023 Article 20 referral, specifically:

	• UC maintenance treatment dosage for patients with CV and malignancy risk factors, in addition to VTE risk factors.
Country(-ies) of study	France
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Marketing Authorization Holder(s)

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	Average daily dose
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
aRMMs	Additional risk minimisation measures
BID	Twice daily
CABG	Coronary artery bypass graft
CCAM	Classification Commune des Actes médicaux
CNAM	Caisse nationale de l'Assurance Maladie
CNIL	National Commission on Informatics and Liberty
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CV	Cardiovascular
csDMARD(s)	Conventional synthetic disease-modifying antirheumatic drug(s)
DALY	Disability adjusted life year
DHPC	Direct healthcare professional communication
DMARD	Disease-modifying antirheumatic drug
DUS	Drug utilisation study
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HTLV	Human T-cell lymphotropic virus
HZ	Herpes zoster
ICD-10	International Classification of Disease, 10th Revision

Abbreviation	Definition
IEC	Independent ethics committee
IRB	Institutional review board
JAKi	Janus kinase inhibitors
LDL	Low-density lipoprotein
LTD	Long-term disease
MACE	Major adverse cardiovascular event
MAH	Marketing Authorisation Holder
MI	Myocardial infarction
MTX	Methotrexate
N	Number
N/A	Not applicable
NI	Non-interventional
NMSC	Non-melanoma skin cancer
OR	Odds ratio
PAS	Post-authorisation study
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PsA	Psoriatic arthritis
PRAC	Pharmacovigilance Risk Assessment Committee
PMSI	Programme de Médicalisation des Systèmes d'Information
QD	Once daily
RA	Rheumatoid arthritis
SAP	Statistical analysis plan
SD	Standard deviation
SLSP	System Level Security Policy
SmPC	Summary of Product Characteristics
SNDS	Système National des Données de Santé
SNIIRAM	Système National d'Informations Inter-Régimes de l'Assurance Maladie
TB	Tuberculosis
TG	Triglycerides
TNF	Tumour necrosis factor
UC	Ulcerative colitis
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz® (tofacitinib) Using an Administrative Healthcare Database in France

Protocol version 4.0, 26 February 2024

Main authors: Juan (Joanne) Wu, ScD, MS

Rationale and background: Tofacitinib citrate (Xeljanz®) is an oral Janus kinase inhibitor approved by the European Commission (EC) for the treatment of adults with moderate-to-severe rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC) and other indications (i.e., ankylosing spondylitis and juvenile idiopathic arthritis). To minimise important identified and potential risks associated with the use of tofacitinib, the Marketing Authorisation Holder (MAH) implemented additional risk minimisation measures (aRMMs). This protocol describes a drug utilisation study to assess prescribing patterns of tofacitinib and whether prescribers are adherent to the screening and monitoring recommendations and limitations for use included in the aRMM materials for patients prescribed tofacitinib, as well as any potential off-label use of tofacitinib, contraindicated use and use with concomitant medications not compatible with tofacitinib. Additionally, as a result of the 2019 benefit-risk reassessment requested by the EC pursuant to Article 20 of Regulation (EC) No 726/2004, the 2021 signal evaluation procedure, and the 2022/2023 Janus kinase inhibitors (JAKi) Article 20 referral, the MAH will evaluate healthcare professionals' adherence to the new Pharmacovigilance Risk Assessment Committee recommendations and limitations for use implemented after the 2019 Article 20 referral to minimise the risk of venous thromboembolism (VTE), use in elderly patients aged ≥65 years and mortality, after the signal evaluation procedure to assess use in patients with cardiovascular (CV) risk factors and use in patients with malignancy risk factors, and after the latest JAKi referral to assess the updated recommendations for use in patients with VTE, CV and malignancy risk factors.[1]

Research question and objectives: The research question is: Are prescribers in France adherent to the recommendations and limitations for use described in the tofacitinib aRMM materials?

The primary objectives are to:

1. Describe the characteristics of patients treated with tofacitinib and by indication (i.e., RA, PsA and UC; off-label indications), in terms of:

    - Demographics (e.g., age and sex); and

    - Comorbidities and prior and current medication use.

2. Evaluate prescribers' adherence to the tofacitinib aRMMs for treating patients with RA, PsA and UC, specifically:

    - Adherence to the recommended posology per indication (average daily dose [ADD]) and duration of use;
    - Adherence to recommendations for patient screening and laboratory monitoring prior to and during tofacitinib treatment;
    - Adherence to recommendations for limitations of use, including:
        - Contraindicated use;
        - Use with medications not compatible with tofacitinib.
    - Describe prescribing patterns over time:
        - Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically:
            - Use in patients with risk factors for VTE;
            - Use in patients aged 65 years and older;
            - Use in patients with risk factors for CV;
            - Use in patients with risk factors for malignancy.
        - Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the JAKi 2022/2023 Article 20 referral, specifically:
            - UC maintenance treatment dosage for patients with CV and malignancy risk factors, in addition to VTE risk factors.

Study design: This is a retrospective cohort study using administrative claims data to describe the utilisation of tofacitinib in routine clinical practice in France. The study observation period will be from 01 January 2017 to 31 December 2025 with an indexing period for identifying tofacitinib new initiators from 01 January 2018 to 31 December 2024. The indexing period will also be split into different reporting periods according to the timing of each updated aRMMs to contextualise the changes in the utilisation of tofacitinib.

Population: Patients of all ages who are new initiators of tofacitinib with at least one reimbursed prescription during the study indexing period will be included in this study. The

index date (defined as the date of first reimbursed prescription of tofacitinib) will be between 01 January 2018 (the earliest date of the full distribution of the original aRMM materials for RA indication) and 31 December 2024. Patients are also required to have at least 12 months of available medical history prior to the index date and a complete 12-month follow-up period after the index date to describe the use of tofacitinib.

Variables: Demographic characteristics (age and sex), diagnoses (indication [including off-label use]), comorbidities, contraindicated use, VTE risk factors, CV risk factors and malignancy risk factors), use of alternative therapy (i.e., biologics) prior to initiation of tofacitinib, prior and current medications, procedures (including screening and monitoring tests), ADD and duration of tofacitinib therapy will be examined to address the objectives.

Data source: The study population will be sourced from the French national health claims database, the Système National des Données de Santé (SNDS), which covers >99% (~65 million insures) of the French population from birth or immigration to death or emigration.

Study size: 480 to 1,062 patients per indication group (e.g., RA/PsA and UC) are needed to detect a minimum meaningful difference with 80% statistical power and a two-sided 5% significance level in the proportion of tofacitinib initiators with risk factors of interest across different reporting periods. In contrast, 240 to 426 patients per indication group are needed to detect a minimum meaningful difference with 80% statistical power and a two-sided 5% significance level in the composite risk factor scores. Based on preliminary assessment of data from the SNDS database, it is anticipated that approximately 8,000 RA or PsA and 2,000 UC patients who initiate tofacitinib will be captured through the end of the indexing period (e.g., December 2024).

Data analysis: The analysis will be conducted separately by indication of tofacitinib ("RA or PsA" and "UC," unless otherwise specified). Results will be provided as descriptive statistics such as count and proportion of patients having taken the recommended laboratory tests prior to initiating tofacitinib. Utilisation of tofacitinib in patients with VTE risk factors, patients 65 years and older, patients with CV risk factors and patients with malignancy risk factors will be stratified by reporting periods (VTE, CV and malignancy, and the JAKi reporting periods) in accordance with the distribution of the revised aRMM materials following the 2019 Article 20 referral, the 2021 signal procedure, and the 2022/2023 JAKi Article 20 referral to contextualise the changes in patterns of use. Comparative statistical analyses will be conducted to describe changes in the use of tofacitinib across reporting periods.

Milestones: Start of data collection is planned to occur on 31 August 2024 and the end of data collection on 01 September 2026. The interim study report will be submitted by 31 May 2025; the final study report will be submitted by 01 September 2027.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	08 May 2023	Cover page	• Updated protocol date and version number • Revised research question and objectives • Updated Pfizer address	Pharmacovigilance Risk Assessment Committee (PRAC) request to assess the effectiveness of updated aRMMs in France following 2022/2023 JAKi referral, recommendations and clarifications for A3921403 Protocol Version 1 (29 November 2022)
		2. List of Abbreviations	• Added new abbreviations	
		3. Responsible parties	• Updated Pfizer address • Updated Certara address	
		4. Abstract	• Added new rationale and background for JAKi referral • Added new objectives for evaluating JAKi referral, reorganized original objectives and removed secondary objectives • Extended study period by 12 months. Revised milestone dates for start and end of data collection, interim and final report	
		6. Milestones	• Extended study period by 12 months. Revised milestone dates for start and end of data collection, interim and final report	
		7. Rationale and Background	• Added new rationale and background for JAKi referral • Added the distribution date for updated aRMM materials per JAKi referral	
		8. Research Question and Objectives	• Added new objectives for evaluating JAKi referral, reorganized original objectives and removed secondary objectives	
		9.2.Setting	• Updated Figure 1 -4 to reflect the 12-month extension of study period • Added a new reporting period for JAKi referral and created a new Figure 5 for an overview of JAKi reporting periods	
		9.3 Variables	• Revised variables to enhance clarity per PRAC's recommendations • Added new variables to address new objectives related to JAKi referral • Added additional stratifications for average daily dose	

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.7 Data analysis	• Added data analysis to describe changes in the utilisation of tofacitinib following JAKi referral • Revised data analysis to reflect integrating original secondary objective 2 into primary objective 2	
		9.9 Limitations of the research methods	• Further discussed the limitation related to the validity and completeness of SNDS claims data • Added other relevant publications using SNDS in context of safety or drug utilisation studies	
		13. References	• Added other relevant publications in context of safety or drug utilisation studies	
		15. List of figures	• Added Figure 5: overview of JAKi reporting periods	
		Annex 13	• Added a list of diagnosis codes for approved indications	
2	17 October 2023	Title page	• Updated protocol date and version number • Ensured alignment of lay-out of objectives with Research Question and Objectives.	Pharmacovigilance Risk Assessment Committee (PRAC) requested amendments and clarifications for A3921403 Protocol Version 2 (08 May 2023)
		4. Abstract	• Updated protocol date and version number • Added text relating to comparative statistical analyses. • Revised milestone dates for start of data collection and interim report	
		6. Milestones	• Revised milestone dates for start of data collection and interim report	
		9.3 Variables	• Added VTE, CV and malignancy risk factor score variables to Table 3.	
		9.4. Data Sources	• Added description of the long-term disease (LTD) registration database which is mentioned throughout protocol	
		9.7 Data analysis	• Added statistical analysis to formally compare changes in the utilisation of tofacitinib across reporting periods	
		9.3 Variables	• Updated age>50 as age ⩾ 65 as VTE risk factor • Removed "*appropriate*" and "*inappropriate*" terminology from the names of variables pertaining to	In alignment with current SmPC and aRMMs

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			continuation of tofacitinib after turning age 65	
		10.3 IRB/IEC	• Added specifics of IRB/IEC approval by CNIL, the independent national data protection authority in France	Enhanced clarity
3 (protocol version 4.0)	26 February 2024	6. Milestones	• Revised milestones for start of data collection and interim report	Revised timelines to account for additional time for protocol review by PRAC and new data release in July/August 2024
		4. Abstract	• Updated study size to reflect sample size required for detecting meaningful differences in comparative analyses	PRAC requested amendments and clarifications for A3921403 Protocol Version 3 (17 October 2023)
		9.5 Study size	• Updated study size to reflect sample size required for detecting meaningful differences in comparative analyses	

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	To be registered prior to the start of data collection
Start of data collection: first data release for interim study	31 August 2024
End of data collection [a]: final data release for overall study	01 September 2026
Interim report [b]	31 May 2025
Final study report [c]	01 September 2027

a End of data collection refers to the date in which the analytical dataset will be first completely available for the final report, due to the approximate 12-month data lag associated with the database.
b Interim study report 1 will cover data from 01 January 2017 through 31 December 2023.
c The final study report will cover data from 01 January 2017 through 31 December 2025.

7. RATIONALE AND BACKGROUND

Tofacitinib citrate (Xeljanz®) is an oral Janus kinase inhibitor approved by the European Commission (EC) in March 2017, as an immediate-release film-coated tablet (5 milligram [mg]), taken twice daily (BID), for the treatment of adults with moderate-to-severe active rheumatoid arthritis (RA) who have had inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).[1] The EC subsequently approved a prolonged-release film-coated tablet (11 mg), taken once daily (QD), in December 2019. RA is a chronic systemic autoimmune disease characterised by inflammation and progressive destruction of joints. Despite a number of treatment options available, many patients do not sustain remission.[2] In clinical trials, patients treated with 5 mg of tofacitinib BID, in combination with methotrexate (MTX), showed significantly reduced disease activity scores and improved physical functioning and general health status as compared to patients on placebo.[3] The approved dose of tofacitinib when used in combination with MTX for the treatment of moderate-to-severe active RA is 5 mg BID or prolonged-release 11 mg QD, which should not be exceeded; it may also be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.[4]

In June 2018, tofacitinib 5 mg tablet BID was approved by the EC, in combination with MTX, for the treatment of active psoriatic arthritis (PsA) in adults with inadequate response or intolerance to a prior DMARD therapy. PsA is an inflammatory arthritis occurring in between 6% and 42% of patients with psoriasis.[5] In clinical trials, patients treated with 5 mg of tofacitinib BID, in combination with a non-biologic DMARD, achieved significantly improved clinical response and physical functioning over the 6- and 12-month study periods.[3] The approved dose of tofacitinib for the treatment of active PsA is 5 mg BID or prolonged-release 11 mg QD, which should not be exceeded.[4]

Finally, in July 2018, tofacitinib 5 mg tablet BID and 10 mg tablet BID were approved by the EC for the treatment of moderately-to-severely active ulcerative colitis (UC) in patients with inadequate response, loss of response or intolerance to conventional therapy or a biologic agent. UC is a bowel disease characterised by inflammation and ulcers in the colon and rectum. In clinical trials, patients treated with 5 mg or 10 mg of tofacitinib BID were more likely to achieve and/or maintain a clinical response and remission of their condition as compared to patients in the placebo group.[3] At the time of initial approval, the doses of tofacitinib for the treatment of moderately-to-severely active UC were 10 mg BID for induction (up to a 16-week period) and 5 mg BID for maintenance, which should not be exceeded.[4]

Table 1 summarises the date tofacitinib was approved by the EC and the approved dose for each of the 3 approved indications.

Table 1. Summary of approved indications and dosages for tofacitinib

Indication	Date approved by the EC	Approved dose
RA	March 2017	5 mg immediate-release tablets BID
	December 2019	11 mg prolonged-release tablets QD
PsA	June 2018	5 mg immediate-release tablets BID
	July 2021	11 mg prolonged-release tablets QD
UC	July 2018	5 mg and 10 mg immediate-release tablets BID

Note: BID is an abbreviation for "bis in die," which in Latin means twice a day; QD is an abbreviation for "quaque die," which in Latin means once a day

In May 2019, the EC requested a reassessment of the benefit-risk of tofacitinib pursuant to Article 20 of Regulation (EC) No 726/2004 due to a signal for increased risks of pulmonary embolism (PE) and mortality arising in an ongoing Pfizer-sponsored Phase 3b/4 safety study (A3921133: *Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of Tofacitinib in Comparison to A Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis*) designed to evaluate the risk of malignancy and major adverse cardiac events in RA patients aged 50 years and older who had at least one cardiovascular (CV) risk factor. In November 2019, the Committee on Human Medicinal Products (CHMP) concluded that, based on a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC), patients treated with tofacitinib are at increased risk of venous thromboembolism (VTE) events, both for deep vein thrombosis (DVT) as well as PE, especially in patients with risk factors for VTE. The PRAC further concluded that the risk of VTE events is dose-dependent. To minimise this risk, the PRAC recommended that warnings be added to the Summary of Product Characteristics (SmPC) regarding the increased risk of VTE observed in patients taking tofacitinib, especially for patients with known risk factors for VTE. The PRAC also recommended that treatment with tofacitinib be discontinued in patients with suspected VTE and that tofacitinib 10 mg BID for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative therapy available. Clarifications on the posology were also added, particularly for UC patients in maintenance. Specifically, some patients (i.e., patients who failed to respond to alternative treatment options for UC such as TNF inhibitor treatment) who had a reduction in response to 5 mg BID maintenance treatment may benefit from an increase in maintenance dose to 10 mg BID; for these patients, the presence of known risk factors for VTE should be considered. However, tofacitinib 10 mg BID for maintenance treatment should be used for the shortest duration possible.[4]

The PRAC also concluded that, based on the interim analyses of Study A3921133, there is a potential increased risk of mortality. This was partly driven by an increased risk of serious infections among patients 65 years and older. As such, tofacitinib should be considered among patients 65 years and older only if no suitable alternative therapy is available. These conclusions and revisions to the SmPC were approved by the EC on 31 January 2020.

Additionally, in June 2021, as a result of a signal evaluation procedure (EPITT Number 19382) to assess increased incidence rate of major adverse cardiovascular events (MACE) and malignancies, excluding non-melanoma skin cancer (NMSC) in patients treated with RA for tofacitinib, the European Medicines Agency (EMA) concluded that myocardial infarction (MI), lung cancer and lymphoma were important identified risks. To minimise these risks, and the potential risk of MACE and malignancies excluding NMSC, the EMA recommended that the SmPC be updated to include restrictions on use of tofacitinib in patients over 65 years of age, patients who are current or past smokers, patients with other CV risk factors and patients with other malignancy risk factors (e.g., current malignancy or history of malignancy other than a successfully treated NMSC). In these patients, tofacitinib should only be used if no suitable treatment alternatives are available.

Recently, following the latest JAKi Article 20 referral in 2022/2023 (EMEA/H/A-20/1517), two recommendations have been updated relevant to tofacitinib, including: (1) updated recommendations on the UC maintenance treatment dosage for patients with MACE and malignancy risks, in addition to VTE risk factors. Specifically, tofacitinib 10 mg BID for maintenance treatment is not recommended in patients with UC who have known MACE and malignancy risk factors, in addition to VTE risk factors, unless there is no suitable alternative therapy available; (2) updated recommendations for cautious use in patients with VTE risk factors other than MACE or malignancy risk factors.

In conjunction with the initial authorisation in March 2017, to minimise important potential and identified risks associated with the use of tofacitinib and to continue to monitor important potential and identified risks, the Marketing Authorisation Holder (MAH) implemented an educational programme designed to increase awareness of the risks of tofacitinib in each member state of the European Union (EU). This programme consists of routine (SmPC and patient package insert) and additional risk minimisation measures (a prescriber brochure, checklists for treatment initiation and treatment maintenance and a patient alert card to distribute to patients). There is also a website where healthcare professionals (HCPs) can access the aRMM materials.

The content and messages for the initial aRMM materials were agreed upon with the National Competent Authority prior to the launch of tofacitinib in each member state and the distribution of these materials was implemented after April 2017. Since then, the aRMM materials have been periodically revised to reflect subsequently approved indications. One revision incorporated the PRAC/CHMP's recommendations following the re-evaluation of the benefit-risk of tofacitinib (e.g., minimising the risk of VTE events among patients treated with tofacitinib), with distribution of these "Article 20-VTE-revised aRMM materials" to France on 04 May 2020 (termed "VTE aRMM materials" hereafter; Table 2). A subsequent revision incorporated the PRAC/CHMP's recommendations following the re-evaluation of the benefit-risk of tofacitinib (e.g., minimising the risk of CV events and malignancy among patients treated with tofacitinib), with distribution of these "CV and Malignancy-revised aRMM materials" to France on 17 May 2022 (termed "2021 signal evaluation procedure

aRMM materials" hereafter; Table 2). The newly updated aRMMs following the JAKi Article 20 referral were distributed on 06 April 2023.

Table 2. Dates for full reimbursement of tofacitinib and full distribution of the original, VTE aRMM materials, 2021 signal evaluation procedure aRMM materials and 2022/2023 JAKi referral aRMM materials in France

Country	Indication	Date of full reimbursement	Date of full distribution of the original aRMM materials	Start date of distribution of the VTE aRMM materials	Start date of distribution of the 2021 signal evaluation procedure aRMM materials	Start date of distribution of the 2022/2023 JAKi referral aRMM materials
France	RA	September 2017	January 2018	04 May 2020	17 May 2022	06 April 2023
	PsA	December 2018	May 2019			
	UC	February 2019	May 2019			

A comprehensive plan was proposed to assess the effectiveness of the aRMM programme, which consists of the following 2 components:

1. Process indicators (i.e., HCPs' receipt and understanding of the aRMM materials); and

2. Outcome indicators (i.e., prescribing and clinical practice behaviours with respect to recommendations).

To assess these 2 components, the MAH proposed the following post-authorisation safety studies with the aim of evaluating the effectiveness of the aRMM programme:

1. A survey of tofacitinib prescribers to address component 1 (A3921334, completed); and

2. A drug utilisation study (DUS) (Study A3921321) to address component 2 that will assess prescribing patterns of tofacitinib and whether prescribers are adherent to the screening and monitoring recommendations and limitations for use included in the aRMM materials for patients prescribed tofacitinib.

As a result of the Article 20 benefit-risk reassessment, the MAH will additionally evaluate HCPs' adherence to the new PRAC recommendations and limitations for use to minimise the risk of VTE across all approved indications (i.e., tofacitinib should be used with caution in patients with known VTE risk factors regardless of indication and dosage), with additional focus on the use of tofacitinib 10 mg BID as a maintenance treatment for patients with UC, and use and prior treatments among patients aged 65 years and older treated with tofacitinib. The MAH will also examine tofacitinib prescribing patterns over time, as well as changes in the utilisation of tofacitinib among patients with VTE risk factors and among elderly patients aged ≥65 years following the updated recommendations and limitations for use. As a result of the 2021 signal evaluation procedure, the MAH will also assess HCPs' adherence to the

new EMA recommendations and limitations for use related to tofacitinib use in patients with CV risk factors and use in patients with malignancy risk factors. Similar to above, the MAH will also examine tofacitinib prescribing patterns over time in the context of the 2021 signal evaluation procedure outcome. As a result of the 2022/2023 JAKi Article 20 referral, the MAH will assess HCPs' adherence to the updated recommendations and limitations for use related to tofacitinib use in patients with VTE, CV or malignancy risk factors.

Study A3921321 is an ongoing DUS (i.e., component 2 described above) using secondary data from Sweden, Hungary, Germany and the Netherlands. This protocol (A3921403) describes another drug utilisation study in France that will complement Study A3921321. Data from the 2 DUS studies, together with the findings from the tofacitinib prescriber survey (A3921334), will be used to assess whether the aRMM materials are effective or not. This non-interventional study is designated as a post-authorisation safety study and is conducted by the MAH as a Category 3 commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is: Are prescribers in France adherent to the recommendations and limitations for use described in the tofacitinib aRMM materials?

The primary objectives are to:

1. Describe the characteristics of patients treated with tofacitinib and by indication (i.e., RA, PsA and UC; off-label use), in terms of:
    - Demographics (e.g., age and sex);
    - Comorbidities and prior and current medication use.
2. Evaluate prescribers' adherence to the tofacitinib aRMMs for treating patients with RA, PsA or UC, specifically:
    - Adherence to the recommended posology per indication (average daily dose [ADD]) and duration of use;
    - Adherence to recommendations for patient screening and laboratory monitoring prior to and during tofacitinib treatment;
    - Adherence to recommendations for limitations of use, including:
        - Contraindicated use;
        - Use with medications not compatible with tofacitinib.

- Describe prescribing patterns over time:
  - Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically:
    - Use in patients with risk factors for VTE;
    - Use in patients aged 65 years and older;
    - Use in patients with risk factors for CV;
    - Use in patients with risk factors for malignancy.
  - Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the JAKi 2022/2023 Article 20 referral, specifically:
    - UC maintenance treatment dosage for patients with CV and malignancy risk factors, in addition to VTE risk factors.

9. RESEARCH METHODS

9.1. Study design

This is a retrospective cohort study to provide real-world evidence on the utilisation of tofacitinib in France.

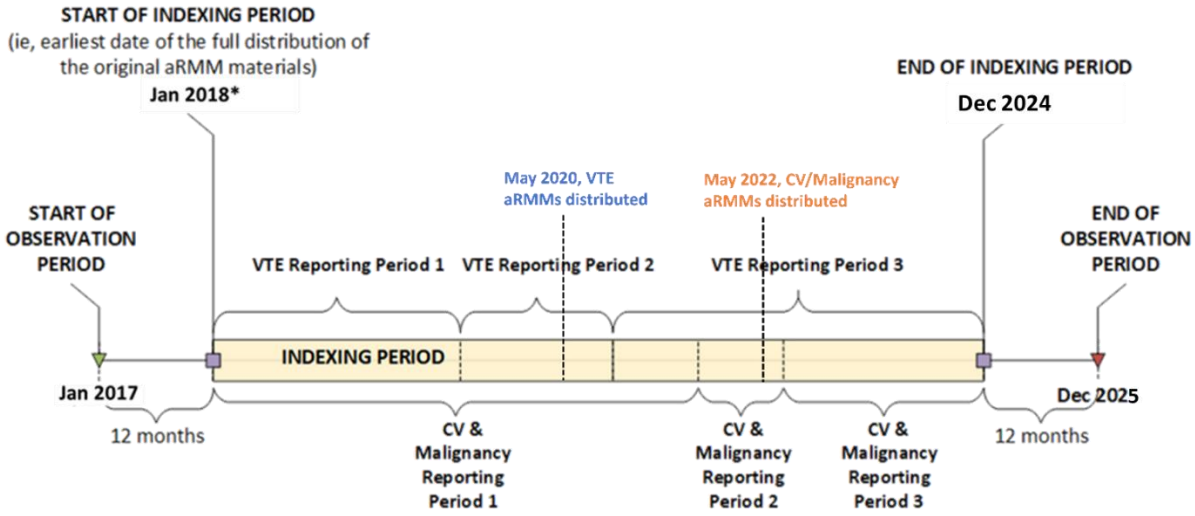
The study presents a number of strengths, which include the prospectively collected electronic health data, the richness of data available in the Système National des Données de Santé (SNDS) and near-complete coverage of the French population (>99%) with minimal loss to follow-up.

9.2. Setting

The study population will be sourced from the French SNDS database. SNDS contains healthcare utilisation data, including pharmacy data, with a coverage of 99% of the population in France. Further details about this data source are provided in Section 9.4. The study population will consist of patients of all ages who newly initiated tofacitinib in French routine clinical setting.

See Figure 1 for an overview of the study observation period (Section 9.2.3), including the indexing period, the VTE Reporting Periods 1-3 (Section 9.2.4), the CV and Malignancy Reporting Periods 1-3 (Section 9.2.5) and the JAKi Reporting Periods 1-3 (Section 9.2.6).

Figure 1. Overview of the study observation period



*Aligned with the first reimbursed prescription record in the French database

9.2.1. Inclusion criteria

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

- Have their first reimbursed prescription of tofacitinib (Anatomical Therapeutic Chemical [ATC] code L04AA29) during the indexing period;
- Have 12 months of available medical history *prior to* the index tofacitinib dispensing; and
- Have 12 months of available medical data *after* the index tofacitinib dispensing.

9.2.2. Exclusion criteria

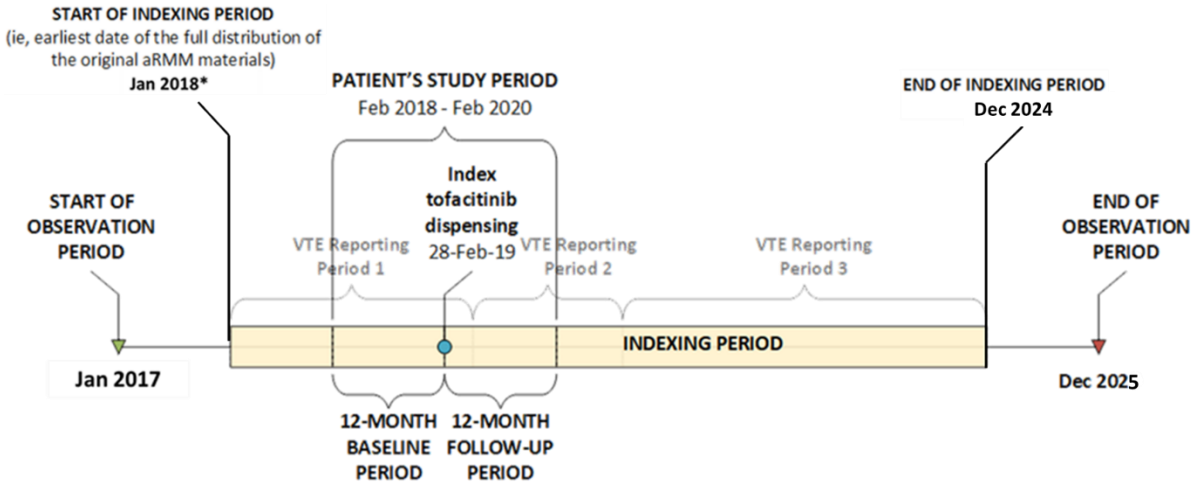
Patients meeting any of the following criteria will not be included in the study:

- Have ≥1 reimbursed prescription of tofacitinib in the 12 months prior to the indexing date; or
- Patients with an index tofacitinib reimbursed prescription for an approved indication for which the original aRMM materials for that indication were not yet distributed or for an approved indication not examined as part of this study (i.e., ankylosing spondylitis and juvenile idiopathic arthritis).
    - For example, if a patient indexes with a tofacitinib reimbursed prescription for UC in France prior to May 2019 (the date of full distribution of the original aRMM materials for UC indication), he or she will be excluded from the study.

9.2.3. Study period

The study period will be from 01 January 2017 to 31 December 2025. The **indexing period** will begin on 01 January 2018 (the earliest date of the full distribution of the original aRMM materials for France [RA], aligned with the first reimbursed prescription record in the French database), will end on 31 December 2024, and will be used to identify patients who newly initiated tofacitinib. The date of a patient's first reimbursed prescription of tofacitinib during the indexing period will be considered the patient's **index date (**Figure 2**)**.

Figure 2. Example index tofacitinib dispensing and patient-specific study period against the Venous Thromboembolism Reporting Periods



* Aligned with the first reimbursed prescription record in the French database

The 12-month **baseline period** will immediately precede the index date and will be used to ascertain indication (including off-label use), comorbidities, prior and current medications, potential contraindicated use of tofacitinib, VTE risk factors, CV risk factors, malignancy risk factors, use in patients aged 65 years and older and whether there is evidence that prescribers are following the recommended screenings in the aRMM materials that should occur *prior to* initiation of tofacitinib.

The 12-month **follow-up period** will begin on the patient's index date. Variables that will be ascertained during the follow-up period include comorbidities, comedications, adherence to the recommended posology per indication (ADD) and duration of tofacitinib treatment, potential contraindicated use of tofacitinib, VTE, CV or malignancy risk factors, use with concomitant medications not compatible with tofacitinib and whether there is evidence that prescribers are following the recommended monitoring in the aRMM materials that should occur *after* initiation of tofacitinib.

9.2.4. Venous Thromboembolism Reporting Periods

For analyses evaluating changes in the use of tofacitinib in patients with VTE risk factors, the indexing period will be split into the following 3 periods:

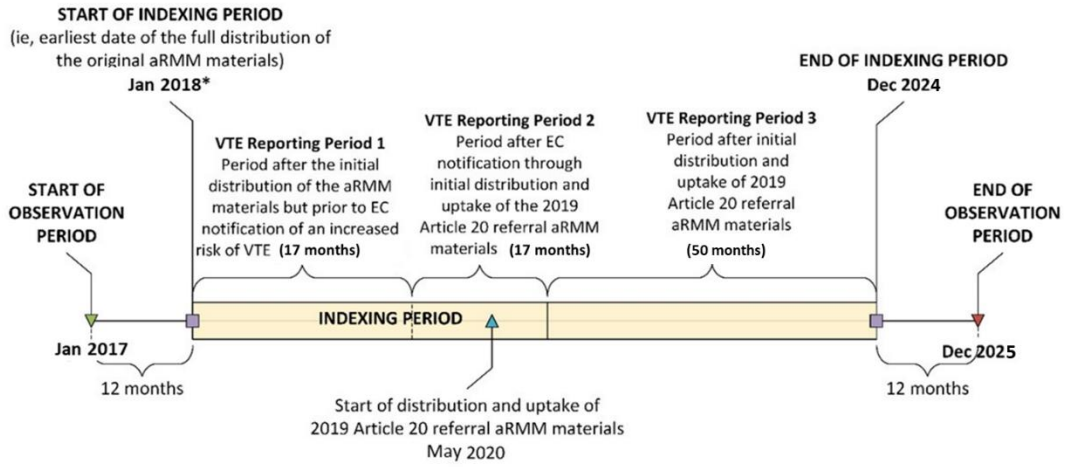
- **Reporting Period 1**, which will cover the 17-month period after the initial distribution of the aRMM materials but *prior to* the PRAC/CHMP's notification of an increased risk of VTE among patients already at high risk (01 January 2018 through 31 May 2019, to allow for dissemination of DHPC letters following announcement of the provisional measures);

- **Reporting Period 2**, which will cover the 17-month period after the PRAC/CHMP's notification of an increased risk of VTE and mortality, through initial distribution and uptake of the 2019 Article 20 referral aRMM materials (01 June 2019 through 31 October 2020); and

- **Reporting Period 3**, which will cover the 50-month period after the period of initial distribution and uptake of the 2019 Article 20 referral aRMM materials (01 November 2020 through 31 December 2024).

See Figure 3 for an overview of the VTE Reporting Periods 1-3.

Figure 3. Overview of the Venous Thromboembolism Reporting Periods



*Aligned with the first reimbursed prescription record in SNDS

9.2.5. Cardiovascular and Malignancy Reporting Periods

For analyses evaluating changes in the use of tofacitinib in patients with CV risk factors and patients with malignancy risk factors, the indexing period will be split into the following 3 periods:

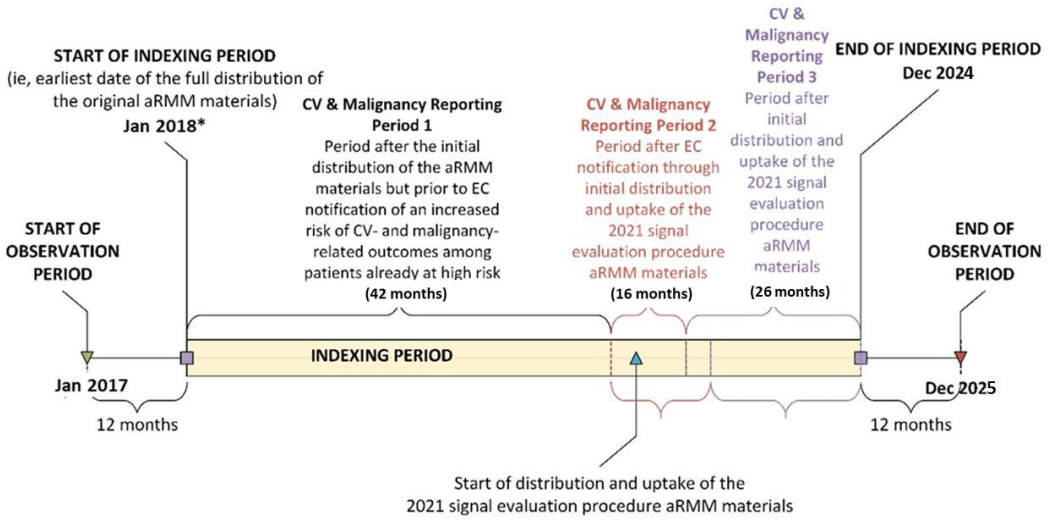
- **Reporting Period 1**, which will cover the 42-month period after the initial distribution of the aRMM materials but *prior to* the PRAC/CHMP's notification of an increased risk of CV-related outcomes and malignancy-related outcomes among patients already at high risk (01 January 2018 through 30 June 2021, to allow for dissemination of DHPC letters);

- **Reporting Period 2**, which will cover the 16-month period of and after the PRAC/CHMP's notification of restrictions on use in the context of increased risk of CV-related outcomes and malignancy-related outcomes, through initial distribution and uptake of the 2021 signal evaluation procedure aRMM materials (01 July 2021 through 31 October 2022); and

- **Reporting Period 3**, which will cover the 26-month period *after* the period of initial distribution and uptake of the 2021 signal evaluation procedure aRMM materials (01 November 2022 through 31 December 2024).

See Figure 4 for an overview of the CV and Malignancy Reporting Periods 1-3.

Figure 4. Overview of the Cardiovascular and Malignancy Reporting Periods



*Aligned with the first reimbursed prescription record in the French database

9.2.6. JAKi Reporting Periods

For analyses evaluating changes in the use of tofacitinib according to updated recommendations in the JAKi 2022/2023 Article 20 referral, the indexing period will be split into the following 3 periods:

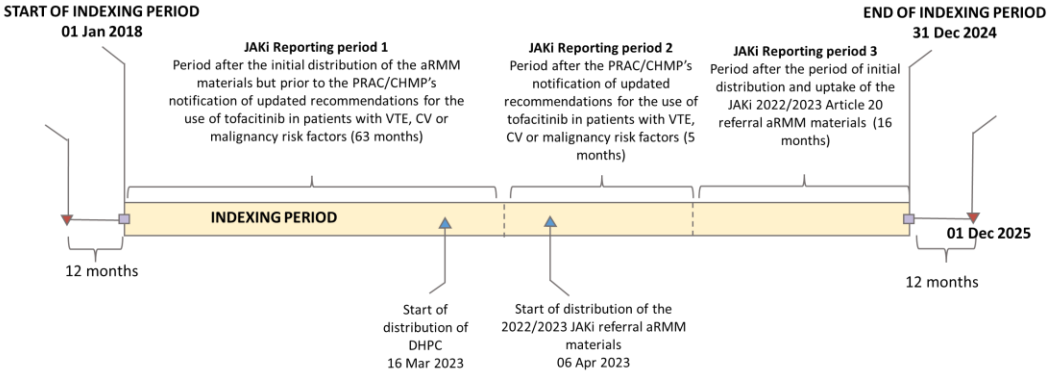
- **Reporting period 1**: which will cover the 63-month period after the initial distribution of the aRMM materials but prior to the PRAC/CHMP's notification of the JAKi referral (01 January 2018 through 31 March 2023, to allow for dissemination of DHPC letters);

- **Reporting Period 2**, which will cover the 5-month period after the PRAC/CHMP's notification of the JAKi referral, through initial distribution and uptake of the JAKi referral aRMM materials (01 April 2023 through 31 August 2023); and

- **Reporting Period 3**, which will cover the 16-month period after the period of initial distribution and uptake of the JAKi referral aRMM materials (01 September 2023 through 31 December 2024).

See Figure 5 for an overview of the JAKi Reporting Periods 1-3.

Figure 5. Overview of the JAKi Reporting Periods



9.3. Variables

9.3.1. Variables and definitions

Table 3 summarises and defines the study variables to be collected and analysed in SNDS. Unless otherwise specified, these variables will be assessed during each patient's entire study period (baseline period and follow-up period).

This study will use code-based algorithms from the literature and/or other code lists to identify study variables. Published validated algorithms will be used where available.[6, 7] All code-based algorithms and code lists will be reviewed and/or approved by Pfizer prior to

study initiation. Preliminary algorithms and/or codes are proposed in the following (Table 3); see also Annexes). Final algorithms and/or code lists may be refined as part of the statistical analysis plan (SAP) development. It is also to be noted that while laboratory tests performed are captured, results of laboratory tests are not available in the SNDS database.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Exposure		
Tofacitinib treatment	Exposure	Defined as having ≥1 ATC code (L04AA29) for a reimbursed prescription of tofacitinib during the indexing period. *Index date* is defined as the date of the first reimbursed prescription of tofacitinib.
Indication		
Indication	Indication (including off-label use)	Reported in the following categories: RA, PsA, UC and off-label/unknown based on hospital discharge diagnoses and active registration for diagnoses reported in the long-term disease (LTD) database for outpatients in the relevant time period. If there are no diagnosis codes for RA, PsA or UC, it will be categorised as off-label/unknown indications. Details will be further developed in the SAP. List of diagnoses codes for indications in ANNEX 13. LIST OF DIAGNOSIS CODES FOR INDICATIONS.
Primary Objective 1: Demographics, comorbidities and prior and current medications List of comorbidity codes in ANNEX 11. LIST OF CODES FOR COMORBIDITIES, unless otherwise specified		
Age at tofacitinib initiation	Demographic	Calculated as the date of tofacitinib initiation minus the patient's month and year of birth and reported in the following categories: <18 years, 18-29 years and 30-39 years; 40-49 years; 50-59 years; 60-69 years; 70-79 years; ≥80 years; and <65 years and ≥65 years.
Sex	Demographic	Reported in the following categories: Male, Female and Unknown. Assessed on the date of the index tofacitinib prescription dispensing.
Hepatic impairment	Comorbidity	Defined as ≥1 International Classification of Disease, 10th Revision (ICD-10) diagnosis code for hepatic impairment.
Hepatic impairment, mild or moderate	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for mild or moderate hepatic impairment.
Hepatic impairment, severe	Comorbidity	Defined as ≥1 ICD-10 diagnosis code or procedure code for severe hepatic impairment.
Renal impairment	Comorbidity	Defined as ≥1 ICD-10 diagnosis code or procedure code for renal impairment
Renal impairment, mild	Comorbidity	Defined as ≥1 ICD-10 diagnosis code or procedure code for mild renal impairment
Renal impairment, moderate	Comorbidity	Defined as ≥1 ICD-10 diagnosis code or procedures code for moderate renal impairment
Renal impairment, severe	Comorbidity	Defined as ≥1 ICD-10 diagnosis code or procedure code for severe renal impairment
Herpes zoster (HZ)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for HZ.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Human immunodeficiency virus (HIV)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for HIV.
Tuberculosis (TB), including both active and latent TB	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for TB.
Viral hepatitis B or C	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for viral hepatitis B or C.
Serious and opportunistic infections of interest (including HIV, HZ, TB and viral hepatitis B and C)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for a serious and/or opportunistic infection of interest. Complete list in ANNEX 3. LIST OF DIAGNOSIS CODES FOR SELECT INFECTIONS OF INTEREST
Diverticulitis	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for diverticulitis.
Malignancy (non-metastatic and metastatic, excluding NMSC)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for a malignancy (excluding NMSC).
NMSC	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for NMSC.
Gastrointestinal perforation	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for gastrointestinal perforation.
Interstitial lung disease	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for interstitial lung disease. Complete list in ANNEX 6. LIST OF DIAGNOSIS AND PROCEDURE CODES FOR INTERSTITIAL LUNG DISEASE
Diabetes	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for diabetes or ≥3 (or at least 2 in case of large pack sizes) prescription dispensing of oral antidiabetic agents and/or insulin (identified by ATC codes).
Immunodeficiencies of interest	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for immunodeficiency. Complete list in ANNEX 5. LIST OF DIAGNOSIS CODES FOR SELECT IMMUNODEFICIENCIES OF INTEREST.
Prior use of corticosteroids	Medication history	Defined as ≥1 prescription dispensing of a corticosteroid (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST
Prior use of statins	Medication history	Defined as ≥1 prescription dispensing of a statin (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Prior use of any biologic	Medication history	Defined as ≥1 prescription dispensing of a biologic (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Prior use of conventional synthetic DMARDs (csDMARDs)/ Immunomodulators	Medication history	Defined as ≥1 prescription dispensing of a csDMARD/ Immunomodulators (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Prior use of MTX	Medication history	Defined as ≥1 prescription dispensing of MTX (as identified by ATC code L04AX03) in the 12 months prior to the index tofacitinib dispensing.
Prior use of anti-TB therapy	Medication history	Defined as ≥1 prescription dispensing of anti-TB therapy (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing.
Prior vaccination	Medication history	Defined as ≥1 procedure code, ≥1 ICD-10 code and/or ≥1 reimbursed prescription (as identified by ATC code[s]) for a vaccination, overall and stratified by live and non-live vaccinations (if available) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.
Concomitant use of a contraindicated potent immunosuppressants	Comedication	Defined as ≥30 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for a contraindicated potent immunosuppressants (as identified by ATC code[s]) during the follow-up period. Days of supply in SNDS will be approximated by reimbursed package size and per recommended posology. Duration of tofacitinib therapy defined in Section 9.3.2.
Concomitant use of MTX	Comedication	Defined as ≥30 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for MTX during the follow-up period.
Concomitant use of a corticosteroid	Comedication	Defined as ≥30 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for a corticosteroid (as identified by ATC code[s]) during the follow-up period.
Concomitant use of anti-TB therapy	Comedication	Defined as ≥30 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for anti-TB therapy (as identified by ATC code[s]) during the follow-up period.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs		
Adherence to the recommended posology per indication and duration of use		
Duration of tofacitinib therapy	Outcome: Adherence to recommended posology	Defined in Section 9.3.2. Assessed during the follow-up period.
ADD	Outcome: Adherence to recommended posology	Defined in Section 9.3.3. Assessed during the follow-up period.
A patient with an ADD of >11 mg during any of the 8-week intervals and no evidence of a diagnosis for UC	Outcome: Adherence to recommended posology	Among RA/PsA patients is defined as 0 ICD-10 diagnosis code for UC during baseline or follow-up period and an ADD of >11 mg during any of the 8-week intervals.
A patient with an ADD of ≥15 mg in Weeks 17-24, Weeks 25-32, Weeks 33-40 or Weeks 41-48 of follow-up and with evidence of a diagnosis for UC but no use of an alternative therapy (i.e., biologic) prior to tofacitinib initiation	Outcome: Adherence to recommended posology	*Among UC patients*, is defined as ≥1 prescription dispensing for a biologic (as identified by ATC codes) prior to the index tofacitinib dispensing and an ADD ≥15 mg in any of the intervals: Weeks 17-24, Weeks 25-32, Weeks 33-40 or Weeks 41-48 of follow-up. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB **Note:** This definition will miss those who have one 10 mg BID prescription and the remaining prescriptions are 5 mg BID.
A patient who has known VTE, CV or malignancy risk factors with an ADD of >10 mg in Weeks 17-24, Weeks 25-32, Weeks 33-40 or Weeks 41-48 of follow-up and with evidence of a diagnosis for UC but no use of an alternative therapy (i.e., biologic) prior to tofacitinib initiation	Outcome: Adherence to recommended posology	*Among UC patients*, is defined as ≥1 prescription dispensing for a biologic (as identified by ATC codes) prior to the index tofacitinib dispensing and an ADD >10 mg in any of the intervals: Weeks 17-24, Weeks 25-32, Weeks 33-40 or Weeks 41-48 of follow-up and ≥1 VTE, CV or malignancy risk factors from baseline to Week 16. An ADD ≥ 15 mg in the definition above will be used in a sensitivity analysis.
Adherence to patient screening and laboratory monitoring prior to and during tofacitinib treatment		
The following recommended screenings and monitoring will be assessed in the following time frames: • In the 30 days prior to and including the day of tofacitinib initiation; • In the 31 to 60 days prior to tofacitinib initiation;		

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
• In the 61 to 90 days prior to tofacitinib initiation; and • In the 91 to 180 days prior to tofacitinib initiation; For patients with at least 6 months of tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.2): • In the 60 days after the day of tofacitinib initiation; • In the 61 to 120 days after tofacitinib initiation; and • In the 121 to 180 days after tofacitinib initiation. For patients with 12 months of tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.2): • In the 181 to 240 days after tofacitinib initiation; • In the 241 to 300 days after tofacitinib initiation; and • In the 301 to 360 days after tofacitinib initiation. For analyses, 1 month will be defined as 30 days and 1 year will be defined as 360 days. List of laboratory codes in ANNEX 10. LIST OF LABORATORY TEST CODES.		
Creatinine (serum or urine) laboratory testing	Outcome: Screening	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for a creatinine (serum or urine) laboratory test.
TB screening	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for TB (active and latent) screening.
Viral hepatitis B and C screening	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for viral hepatitis B and C screening.
Absolute lymphocyte count (ALC) laboratory testing	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for ALC laboratory testing.
Absolute neutrophil count (ANC) laboratory testing	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for ANC laboratory testing.
Haemoglobin laboratory testing	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for haemoglobin laboratory testing.
Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) laboratory testing	Outcome: Screening Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for ALT and/or AST laboratory testing.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Lipid panel (i.e., total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG)) laboratory testing	Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for lipid panel laboratory testing.
Describe prescribing patterns over time: Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use after the 2019 Article 20 referral, the 2021 signal evaluation procedure, and the 2022/2023 JAKi Article 20 referral		
Adherence to recommendations for limitations of use in patients with VTE risk factors (will be stratified by VTE reporting period 1, 2, 3)		
Assessment of VTE risk factors prior to initiation of tofacitinib		
Prior VTE	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for VTE in the 12 months prior to the index tofacitinib dispensing. List of VTE codes in ANNEX 12. LIST OF DIAGNOSIS CODES FOR VTE.
History of surgery, major	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 procedure code for a major surgery in the 3 months prior to the index tofacitinib dispensing.
Prior MI	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for an MI in the 3 months prior to the index tofacitinib dispensing.
History of heart failure	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for heart failure in the 12 months prior to the index tofacitinib dispensing.
History of combined hormonal contraceptives or hormonal replacement therapy	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 reimbursed prescription of a combined hormonal contraceptives and/or hormonal replacement therapy (as identified by ATC codes) in the 12 months prior to the index tofacitinib dispensing.
History of inherited coagulation disorder	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for inherited coagulation disorder in the 12 months prior to the index tofacitinib dispensing.
History of malignancy (non-metastatic and metastatic, excluding NMSC)	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding NMSC) in the 12 months prior to the index tofacitinib dispensing.
Age ≥65 years	Outcome: changes in use in patients with VTE risk factors	Defined as age at tofacitinib initiation ≥65 years.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
History of diabetes	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for diabetes or ≥3 (or at least 2 in case of large pack sizes) prescription dispensing of oral antidiabetic agents and/or insulin (identified by ATC codes) in the 12 months prior to the index tofacitinib dispensing.
History of hypertension	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for hypertension or ≥3 (or at least 2 in case of large pack sizes) prescription dispensing of antihypertensive agents (identified by ATC codes) in the 12 months prior to the index tofacitinib dispensing. ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES
Initiating tofacitinib with ≥1 VTE risk factor(s)	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 VTE risk factor(s) (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 VTE risk factors other than CV or malignancy risk factors	Outcome: changes in use in patients with VTE risk factors	The same definition as above but only limited to VTE risk factors other than CV or malignancy risk factors.
VTE risk factor scores	Outcome: changes in use in patients with VTE risk factors	Calculated as the sum of the number of VTE risk factors (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing. Weighting of VTE risk factors may be considered as a sensitivity analysis to reflect the potential different importance of each risk factor.
Number of UC patients with: ≥1 VTE risk factor; no prior alternative therapy (i.e., biologic); and an ADD >10 mg in Weeks 17-24, Weeks 25-32, Weeks 33-40 or Weeks 41-48 of follow-up	Outcome: changes in use in patients with VTE risk factors	Defined as an UC patient meeting all of the following criteria: ≥1 VTE risk factor(s) (as listed and defined above) 12 months prior to the index tofacitinib prescription dispensing; 0 prescription medication dispensing for a biologic (as identified by ATC codes) in the 12 months prior to the index tofacitinib prescription dispensing; and an ADD of >10 mg in any of the intervals: Weeks 17-24, Weeks 25-32, Weeks 33-40 and Weeks 41-48 of follow-up (ADD defined in Section 9.3.3). Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Assessment of VTE risk factors while receiving tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.2)		
VTE	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for VTE while receiving tofacitinib therapy. List of VTE codes in ANNEX 12. LIST OF DIAGNOSIS CODES FOR VTE

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Surgery, major	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 procedure code for a major surgery while receiving tofacitinib therapy.
MI	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for an MI while receiving tofacitinib therapy.
Heart failure	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for heart failure while receiving tofacitinib therapy.
Use of combined hormonal contraceptives or hormonal replacement therapy	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 prescription dispensing of a combined hormonal contraceptives and/or hormonal replacement therapy (as identified by ATC codes) while receiving tofacitinib therapy.
Inherited coagulation disorder	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for inherited coagulation disorder while receiving tofacitinib therapy.
Malignancy (non-metastatic and metastatic, excluding NMSC)	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding NMSC) while receiving tofacitinib therapy.
Age ≥ 65 years	Outcome: changes in use in patients with VTE risk factors	Defined as age ≥65 years while receiving tofacitinib.
Diabetes	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for diabetes or ≥3 (or at least 2 in case of large pack sizes) prescription dispensing of oral antidiabetic agents and/or insulin (identified by ATC codes) while receiving tofacitinib therapy.
Hypertension	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 ICD-10 diagnosis code for hypertension or ≥3 (or at least 2 in case of large pack sizes) prescription dispensing of antihypertensive agents (identified by ATC codes) while receiving tofacitinib therapy.
Discontinuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 VTE risk factor(s) while receiving tofacitinib therapy (as listed and defined above) plus 0 prescription dispensing for tofacitinib within a specific time window after the code for the first VTE risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the VTE risk factor(s) acquired while receiving tofacitinib therapy and will be operationalised during SAP development. Duration of tofacitinib therapy defined in Section 9.3.2.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Discontinuation of tofacitinib after developing ≥1 VTE risk factors other than CV or malignancy risk factors while taking tofacitinib	Outcome: changes in use in patients with VTE risk factors	The same definition as above but only limited to VTE risk factors other than CV or malignancy risk factors.
Continuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: changes in use in patients with VTE risk factors	Defined as ≥1 VTE risk factor(s) while receiving tofacitinib therapy (as listed and defined above) plus ≥1 prescription dispensing for tofacitinib within a specific time window after the code for the first VTE risk factor.
Continuation of tofacitinib after developing ≥1 VTE risk factors other than CV or malignancy risk factors while taking tofacitinib	Outcome: changes in use in patients with VTE risk factors	The same definition as above but only limited to VTE risk factors other than CV or malignancy risk factors
Adherence to recommendations for limitations of use in patients aged 65 years and older (will be stratified by VTE reporting period 1, 2, 3 and CV and malignancy report period 1, 2, 3)		
Initiating tofacitinib with no prior use of an alternative therapy (i.e., biologic) among patients 65 years of age and older	Outcome: changes in use in patients aged 65 years and older	Defined as patients who are 65 years and older on the date of the index tofacitinib dispensing with 0 prescription dispensing for an alternative therapy (i.e., biologic) in the 12 months prior. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Discontinuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: changes in use in patients aged 65 years and older	Defined as patients aged <65 years when initiating tofacitinib and discontinue tofacitinib after turning 65 years old. **Note:** Patients may not discontinue tofacitinib immediately after turning 65 years and need time to be seen by their healthcare providers. Specific algorithm will be developed during SAP.
Continuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib with no prior use of alternative therapies	Outcome: changes in use in patients aged 65 years and older	Defined as patients aged <65 years when initiating tofacitinib, who have ≥1 prescription dispensing of tofacitinib within a specific time window after turning 65 years and 0 prescription dispensing for an alternative therapy (i.e., biologic) prior to index tofacitinib prescription dispensing. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB..

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Continuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib with prior use of alternative therapies	Outcome: changes in use in patients aged 65 years and older	Defined as patients aged <65 years when initiating tofacitinib, who have ≥1 prescription dispensing of tofacitinib within a specific time window after turning 65 years and ≥1 prescription dispensing for an alternative therapy (i.e., biologic) prior to index tofacitinib prescription dispensing.
Adherence to recommendations for limitations of use in patients with CV risk factors (will be stratified by sex and age (≥65 years versus < 65 years), and CV and malignancy report period 1, 2, 3)		
Assessment of CV risk factors prior to initiation of tofacitinib		
History of hyperlipidaemia	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for hyperlipidaemia or ≥1 prescription dispensing (as identified by ATC code[s]) for a statin or other antihyperlipidaemic in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 9. LIST OF ATC CODES FOR ANTIHYPERLIPIDAEMICS.
Age ≥65 years	Outcome: changes in use in patients with CV risk factors	Defined as age at tofacitinib initiation ≥65 years
History of coronary artery disease (defined as MI, stroke, coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI])	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for MI or stroke or ≥1 procedure code for CABG or PCI in the 12 months prior to the index tofacitinib dispensing.
History of stable angina pectoris	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 code for stable angina pectoris in the 12 months prior to the index tofacitinib dispensing.
Current or past smoker[1]	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for tobacco use disorder or ≥1 procedure code for counselling visits for smoking or ≥1 prescription dispensing (as identified by ATC code[s]) for a nicotine replacement product in the 12 months prior to the index tofacitinib dispensing.
History of diabetes	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for diabetes or at least 3 reimbursements (or at least 2 in case of large pack sizes) of oral antidiabetic agents and/or insulin in the 12 months prior to the index tofacitinib dispensing.
History of hypertension	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for hypertension or ≥1 prescription dispensing (as identified by ATC code[s]) for an antihypertensive in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES.

[1] Potential for very low sensitivity leading to misclassification. This variable will be reported if feasible

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
History of chronic kidney disease	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for chronic kidney disease in the 12 months prior to the index tofacitinib dispensing.
CV risk factor scores	Outcome: changes in use in patients with CV risk factors	Calculated as the sum of the number of CV risk factors (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing. Weighting of CV risk factors may be considered as a sensitivity analysis to reflect the potential different importance of each risk factor.
Initiating tofacitinib with ≥1 CV risk factor (s)	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 CV risk factor(s) (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing (unless otherwise specified).
Initiating tofacitinib with ≥1 CV risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 CV risk factor (as listed and defined above) identified in the 12 months prior to the day of the index tofacitinib dispensing and 0 prescription medication dispensing for an alternative therapy (i.e., biologic) in the 12 months prior to the date of the index tofacitinib prescription dispensing. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Assessment of CV risk factors while receiving tofacitinib therapy (will be stratified by sex and age (≥65 years versus < 65 years))		
Hyperlipidaemia	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for hyperlipidaemia or ≥1 prescription dispensing (as identified by ATC code[s]) for a statin or other antihyperlipidaemic while receiving tofacitinib. Complete list in ANNEX 9. LIST OF ATC CODES FOR ANTIHYPERLIPIDAEMICS.
Age ≥65 years	Outcome: changes in use in patients with CV risk factors	Defined as age ≥65 years while receiving tofacitinib.
Current smoker	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for tobacco use disorder or ≥1 procedure code for counselling visits for smoking or ≥1 prescription dispensing (as identified by ATC code[s]) for a nicotine replacement product while receiving tofacitinib.
Coronary artery disease (defined as MI, stroke, CABG or PCI)	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for MI or stroke or ≥1 procedure code for CABG or PCI while receiving tofacitinib therapy.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Stable angina pectoris	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for stable angina pectoris while receiving tofacitinib therapy.
Diabetes	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for diabetes while receiving tofacitinib therapy.
Hypertension	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for hypertension or ≥1 prescription dispensing (as identified by ATC code[s]) for an antihypertensive while receiving tofacitinib. Complete list in ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES.
Chronic kidney disease	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 ICD-10 diagnosis code for chronic kidney disease while receiving tofacitinib.
Discontinuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 CV risk factor(s) while receiving tofacitinib therapy (as listed and defined above) plus 0 prescription dispensing for tofacitinib within a specific time window after the code for the first CV risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the CV risk factor(s) acquired while receiving tofacitinib therapy and will be operationalised during SAP development. Duration of tofacitinib therapy defined in Section 9.3.2.
Continuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: changes in use in patients with CV risk factors	Defined as ≥1 CV risk factor(s) while receiving tofacitinib therapy (as listed and defined above) plus ≥1 prescription dispensing for tofacitinib within a specific time window after the code for the first CV risk factor.
Adherence to recommendations for limitations of use in patients with malignancy risk factors (will be stratified by age (≥65 years versus < 65 years), and CV and malignancy report period 1, 2, 3)		
Assessment of malignancy risk factors prior to initiation of tofacitinib		
Age ≥65 years	Outcome: changes in use in patients with malignancy risk factors	Defined as age at tofacitinib initiation ≥65 years.
History of malignancy (non-metastatic and metastatic, excluding NMSC)	Outcome: changes in use in patients with malignancy risk factors	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding NMSC) in the 12 months prior to the index tofacitinib dispensing.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Current or past smoker	Outcome: changes in use in patients with malignancy risk factors	Defined as ≥1 ICD-10 diagnosis code for tobacco use disorder or ≥1 procedure code for counselling visits for smoking or ≥1 prescription dispensing (as identified by ATC code[s]) for a nicotine replacement product in the 12 months prior to the index tofacitinib dispensing.
Malignancy risk factor scores	Outcome: changes in use in patients with malignancy risk factors	Calculated as the sum of the number of malignancy risk factors (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing. Weighting of malignancy risk factors may be considered as a sensitivity analysis to reflect the potential different importance of each risk factor.
Initiating tofacitinib with ≥1 malignancy risk factor	Outcome: changes in use in patients with malignancy risk factors	Defined as ≥1 malignancy risk factor(s) (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 malignancy risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: changes in use in patients with malignancy risk factors	Defined as ≥1 malignancy risk factor (as listed and defined above) identified in the 12 months prior to the index tofacitinib dispensing and 0 prescription medication dispensing for a biologic (as identified by ATC code) in the 12 months prior to the index tofacitinib prescription dispensing. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Assessment of malignancy risk factors while receiving tofacitinib therapy (will be stratified by age (≥65 years versus < 65 years))		
Age ≥65 years	Outcome: changes in use in patients with malignancy risk factors	Defined as age ≥65 years while receiving tofacitinib.
Malignancy (non-metastatic and metastatic, excluding NMSC)	Outcome: changes in use in patients with malignancy risk factor	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding NMSC) while receiving tofacitinib therapy.
Current smoker	Outcome: changes in use in patients with malignancy risk factor	Defined as ≥1 ICD-10 diagnosis code for tobacco use disorder or ≥1 procedure code for counselling visits for smoking or ≥1 prescription dispensing (as identified by ATC code[s]) for a nicotine replacement product while receiving tofacitinib.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Discontinuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: changes in use in patients with malignancy risk factor	Defined as ≥1 malignancy risk factor while receiving tofacitinib therapy (as listed and defined above) plus 0 prescription dispensing for tofacitinib within a specific time window after the code for the first malignancy risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the malignancy risk factor acquired while receiving tofacitinib therapy and will be operationalised during SAP development.
Continuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: changes in use in patients with malignancy risk factor	Defined as ≥1 malignancy risk factor while receiving tofacitinib therapy (as listed and defined above) plus ≥1 prescription dispensing for tofacitinib within a specific time window after the code for the first malignancy risk factor.
Adherence to recommendations for limitations of use in the JAKi referral (will be stratified by the JAKi report period 1, 2, 3)		
A patient with CV or malignancy risk factors, an ADD of >10 mg in Weeks 17-24, Weeks 25-32, Weeks 33-40 and/or Weeks 41-48 of follow-up and evidence of a diagnosis for UC	Outcome: changes in use of tofacitinib following updated recommendations following the JAKi referral	Defined as an UC patient having ≥1 CV or malignancy risk factor(s) (as listed and defined above) from baseline to week 16 and an ADD of >10 mg in any of the intervals: Weeks 17-24, Weeks 25-32, Weeks 33-40 and Weeks 41-48 of follow-up while receiving tofacitinib therapy. This variable will be stratified by use of an alternative therapy (i.e., biologic) in the 12 months prior.
Adherence to recommendations for limitations of contraindicated use		
Initiating tofacitinib with severe hepatic impairment	Outcome: Contraindicated use	Defined as ≥1 ICD-10 diagnosis code for severe hepatic impairment in the 12 months prior to tofacitinib initiation.
Initiating tofacitinib while pregnant	Outcome: Contraindicated use	Defined as tofacitinib initiation (i.e., the index date) occurring between the beginning and end of a pregnancy, using SNDS-specific algorithms developed. Complete list of pregnancy codes in ANNEX 11. LIST OF CODES FOR COMORBIDITIES
Receiving tofacitinib while pregnant	Outcome: Contraindicated use	Defined as evidence of a pregnancy while receiving tofacitinib therapy using SNDS-specific algorithms.
Initiating tofacitinib while having TB (active or latent)	Outcome: Contraindicated use	Defined as ≥1 ICD-10 diagnosis code for TB in the 60 days prior to tofacitinib initiation.

Table 3. Operational definitions of study variables in Système National des Données de Santé

Variable	Role	Operational definition
Initiating tofacitinib while having a serious and/or opportunistic infection	Outcome: Contraindicated use	Defined as ≥1 ICD-10 diagnosis code for a serious and/or opportunistic infection in the 60 days prior to tofacitinib initiation. Complete list of serious and/or opportunistic infections in ANNEX 3. LIST OF DIAGNOSIS CODES FOR SELECT INFECTIONS OF INTEREST
Adherence to recommendations for limitations of use with concomitant medications not compatible with tofacitinib Variables will be presented overall and may be stratified by patients with and without ≥2 tofacitinib prescription reimbursements during the follow-up period (where the second prescription is reimbursed within 15 days of the last day of the days' supply [or the equivalent] of the first prescription), pending sufficient sample size.		
Use of biologics approved to treat RA, PsA or UC while taking tofacitinib	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥30 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for a biologic approved to treat RA, PsA or UC (as identified by ATC code[s]) during the follow-up period. Complete list of biologics in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Use of selected potent immunosuppressants while taking tofacitinib	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥30 overlapping days' supply of a tofacitinib prescription reimbursement and a prescription reimbursed for the selected potent immunosuppressants azathioprine, 6-mercaptopurine, cyclosporine or tacrolimus (as identified by ATC code[s]) during the follow-up period. Complete list of selected potent immunosuppressants in ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Receipt of a live vaccination while taking tofacitinib	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥1 CCAM procedure code or ≥1 ICD 10 code and/or ≥1 prescription reimbursement (as identified by ATC code[s]) for a live vaccination (as available) while receiving tofacitinib therapy in the follow-up period. Complete list of vaccinations in ANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTERESTANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.

9.3.2. Duration of tofacitinib therapy

Duration of tofacitinib therapy will be defined as the time from the date of the index tofacitinib dispensing to the date of discontinuation of tofacitinib. The operational definitions for duration of tofacitinib therapy will be further elaborated in the SAP. For example, the following proxy may be used to estimate duration, that is, time between 2 prescription dispensing of tofacitinib, allowing for a grace period of a pre-determined length (e.g., 90 days) before being considered to have discontinued tofacitinib. The length of the grace period will be determined during development of the SAP.

9.3.3. Average daily dose

Drug reimbursement data will be utilised to estimate tofacitinib ADD (in mg per day) for each patient and duration of treatment. ADD will be described in each 8-week period, based on the posology and recommended duration of use in the SmPC, during the follow-up period for a total of six 8-week periods.

ADD will be calculated by total dose dispensed during an 8-week period divided by the length of the 8-week period, 56 days. Dose per prescription will be determined by the dose per tablet multiplied by the number tablets on packaging. Total dose dispensed is the sum of doses from all prescriptions in an 8-week period. If a prescription spans across 2 or more 8-week periods, the dose of the prescription will be prorated across periods.

ADD will be calculated from Week 1 through Week 48. For each 8-week period, ADD will be described as a continuous and categorical variable as below:

- Up to 5 mg ADD;
- >5 mg to 11 mg ADD;
- >11 mg to 15 mg ADD;
- >15 to 20 mg ADD; and
- >20 mg ADD.

ADD may be further stratified by (pending sufficient sample size):

- Approved indication, or by the indication groups: “PsA or RA” and “UC”;
- Presence of ≥1 major VTE risk factors prior to tofacitinib initiation;
- Use of an alternative therapy (i.e., biologic) in the 12 months prior to tofacitinib initiation; and
- VTE Reporting Period (1, 2, and 3), depending on the objective.

- The operational definitions for ADD will be further elaborated in the SAP.

9.4. Data sources

Data for this study will be obtained from SNDS database, which covers >99% (~ 65 million insures) of the French population from birth or immigration to death or emigration. The SNDS includes longitudinal claims data for inpatient and outpatient encounters by combining 3 main databases: the national hospital discharge database (PMSI), the health insurance claims database (Système National d'Informations Inter-Régimes de l'Assurance Maladie, SNIIRAM) and the national death registry. The PMSI was established in 2006 and captures information relating to inpatient or ambulatory care admissions to a public or private hospital in France. The SNIIRAM database captures data on socioeconomic characteristics and medical claims for medications, procedures and laboratory tests since 2003. The SNIIRAM database also includes the LTD registration data which captures information on the presence of LTD for which patients are eligible for 100% reimbursement of healthcare for the given disease. Data in the SNDS are updated bi-annually. Only variables relevant to this study, and available in the SNDS database, will be extracted.

As per the General Data Protection Regulation policy, only aggregated data with sample sizes >5 patients will be used for communications.

Details on the Health Insurance Data system, SNDS, are provided below in Table 4.

Table 4. Summary of Système National des Données de Santé database

Characteristics	SNDS
Database type	Claims
Country population	Over 65 million
Overall representativeness	Approximately 99% of the French population
Physician population	All
Expected number of tofacitinib patients by the end of 2019	About 5,300 [a]
Lag in data availability	12 months [b]

a Based on tofacitinib data from 2017-2019 that were obtained using the publicly available tools for querying the French national health registers
b Data are updated once a year, usually by the end of August

9.5. Study size

Comparative analyses for the changes in the proportions of patients with risk factors

For the comparative analyses, the study will assess changes in the proportion of tofacitinib initiators with risk factors of interest (e.g., VTE, elderly, CV, and malignancy) over different reporting periods (Section 9.2.4-9.2.6). The primary comparison of interest will be the proportion of tofacitinib initiators with risk factors during reporting period 3 (when full implementation of the updated aRMMs is expected) against that during reporting period 1 (baseline before implementation or notification of updated aRMMs). Secondary comparisons

of interest will be between reporting period 1 and reporting period 2, as well as reporting period 2 and reporting period 3 to assess any intermediate changes.

Sample size required for evaluating changes in the proportion of patients with risk factors across reporting periods was calculated using the following formula based on two independent sample *z*-test for proportions:[8]

$$N = \frac{(z_{\alpha/2} + z_{\beta})^2 (p_1(1-p_1) + p_2(1-p_2))}{\epsilon^2}$$

Preliminary data from the first interim report of the ongoing DUS study (A3921321) suggests that 30 to 80% of tofacitinib initiators had one or more risk factors of interest at baseline (e.g., during reporting period 1). Sample size was calculated across a range of possible baseline proportions and meaningful differences between any two reporting periods. Given the challenges in defining minimum meaningful differences and the lack of scientific guidance or validated thresholds, Chen et al.'s rule of thumb for classifying the magnitude of effect size based on odds ratios (OR) (e.g., small effect) is used to inform the minimum meaningful difference.[9] Minimum sample size is determined based on the smallest sample size needed to detect a minimum meaningful difference per scenario of baseline proportion. It is thus estimated that 160 to 354 patients per reporting period (480 to 1,062 total patients) per indication group (e.g., RA/PsA and UC) are needed to detect a minimum meaningful difference with 80% statistical power ($\beta = 0.20$) and a two-sided 5% significance level ($\alpha = 0.05$) (Table 1**Error! Reference source not found.**). Sample size needed varies based on the baseline proportion and point percent difference between reporting periods. The required sample size is irrespective of the length of the reporting period.

Table 5. Sample size for comparing changes in the proportion of patients with risk factors of interest across reporting periods

Percentage of patients with at least one risk factors at baseline	Point percent difference between any two reporting periods	Effect size classification for the difference based on OR [a]	Number of patients needed per reporting period [b]	Total number of patients needed for the entire study period per indication group [b, c]
80%	**10%**	**Small**	**291**	**873**
70%	10%	Small	354	1,062
70%	**15%**	**Small**	**160**	**480**
60%	10%	Small	385	1,155
60%	**15%**	**Small**	**171**	**513**
50%	10%	Small	385	1,155
50%	**15%**	**Small**	**167**	**501**
40%	**10%**	**Small**	**354**	**1,062**
30%	**10%**	**Small**	**291**	**873**

Odds ratio = VTE reporting period X odds of outcome / VTE reporting period Y odds of outcome;
Classified effect sizes as weak (1≤OR<1.5), small (1.5≤OR<2), medium (2≤OR<3) and large (≥3).
[a] References:[9, 10]
[b] Assuming equal sample size across reporting period
[c] Bolded rows indicate minimum sample size required per scenario of proportions

Comparative analyses for the changes in composite risk factor scores

For the comparative analyses that assess changes in the composite risk factor scores (e.g., mean number of risk factors per patient where each risk factor receives a score of 1) across reporting periods, the sample size was calculated using the following formula based on two independent sample *t*-test[8]:

$$N = \frac{2(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{\epsilon^2}$$

Preliminary data from the first interim report of the ongoing DUS study (A3921321) suggests the standard deviation for the mean number of risk factors per patient had a wide range but frequently centred around 0.6 to 0.8 at baseline (e.g., reporting period 1). Sample size was calculated across a range of standard deviations and differences in the mean number of risk factors per patient assuming equal sample sizes and variances between any two reporting periods. Given the challenges in defining minimum meaningful differences and the lack of scientific guidance or validated thresholds for the composite risk factor scores, Cohen's *d* effect size of 0.2 to <0.5 (small effect) was used to inform the minimum meaningful difference.[10] Minimum sample size is determined based on the smallest sample size needed to detect a minimum meaningful difference per scenario of baseline variance. It is estimated that 80 to 142 patients per reporting period (240 to 426 total patients) per indication group (e.g., RA/PsA and UC) are needed to detect a minimum meaningful difference with 80%

statistical power (β = 0.20) and a two-sided 5% significance level (α = 0.05) (Table 6). Sample size needed varies based on the baseline variance and difference in the mean number of risk factors between reporting periods. The required sample size is irrespective of the length of the reporting period.

Table 6. Sample size for comparing changes in the mean number of risk factors per patient across reporting periods

Standard deviation for the mean number of risk factors per patient	Difference in the mean number of risk factors between any two reporting periods	Cohen's *d* effect size [a]	Number of patients needed per reporting period [b]	Total number of patients needed for the entire study period per indication group [b, c]
1.3	-0.20	Small	664	1992
1.3	-0.25	Small	425	1275
1.3	-0.30	Small	295	885
1.3	-0.35	Small	217	651
1.3	-0.40	Small	166	498
1.3	-0.45	Small	132	396
1.3	-0.50	Small	107	321
1.3	**-0.55**	**Small**	**88**	**264**
1.2	-0.20	Small	566	1698
1.2	-0.25	Small	362	1086
1.2	-0.30	Small	252	756
1.2	-0.35	Small	185	555
1.2	-0.40	Small	142	426
1.2	-0.45	Small	112	336
1.2	**-0.50**	**Small**	**91**	**273**
1.1	-0.20	Small	475	1425
1.1	-0.25	Small	304	912
1.1	-0.30	Small	212	636
1.1	-0.35	Small	156	468
1.1	-0.40	Small	119	357
1.1	**-0.45**	**Small**	**94**	**282**
1.0	-0.15	Small	698	2094
1.0	-0.20	Small	393	1179
1.0	-0.25	Small	252	756
1.0	-0.30	Small	175	525
1.0	-0.35	Small	129	387
1.0	**-0.40**	**Small**	**99**	**297**

Table 6. Sample size for comparing changes in the mean number of risk factors per patient across reporting periods

Standard deviation for the mean number of risk factors per patient	Difference in the mean number of risk factors between any two reporting periods	Cohen's *d* effect size [a]	Number of patients needed per reporting period [b]	Total number of patients needed for the entire study period per indication group [b, c]
0.9	-0.15	Small	566	1698
0.9	-0.20	Small	318	954
0.9	-0.25	Small	204	612
0.9	-0.30	Small	142	426
0.9	-0.35	Small	104	312
0.9	**-0.40**	**Small**	**80**	**240**
0.8	-0.15	Small	447	1341
0.8	-0.20	Small	252	756
0.8	-0.25	Small	161	483
0.8	-0.30	Small	112	336
0.8	**-0.35**	**Small**	**83**	**249**
0.7	-0.15	Small	342	1026
0.7	-0.20	Small	193	579
0.7	-0.25	Small	124	372
0.7	**-0.30**	**Small**	**86**	**258**
0.6	-0.10	Small	566	1698
0.6	-0.15	Small	252	756
0.6	-0.20	Small	142	426
0.6	**-0.25**	**Small**	**91**	**273**
0.5	-0.10	Small	393	1179
0.5	-0.15	Small	175	525
0.5	**-0.20**	**Small**	**99**	**297**
0.4	-0.10	Small	252	756
0.4	**-0.15**	**Small**	**112**	**336**
0.3	**-0.10**	**Small**	**142**	**426**

a. Reference:[10]
b. Assuming equal sample size across reporting period
c. Bolded rows indicate minimum sample size required per scenario of baseline variance

Through a preliminary assessment, the SNDS database holds records for approximately 4,000 RA or PsA patients and 1,000 UC patients who initiated tofacitinib between January 2018 (start of indexing period) and December 2020. It is projected that approximately 8,000

RA or PsA and 2,000 UC patients who initiate tofacitinib will be captured through the end of the indexing period (e.g., December 2024).

Based on these estimated numbers of patients during the entire study period and sample size calculation, the study is anticipated to have sufficient sample size to detect meaningful differences in the use of tofacitinib among patients with risk factors between the pre- and post-implementation period of updated aRMMs. All eligible patients during the study period will be included in the analysis. The number of patients will be actively monitored during the course of the study and the MAH will provide timely notification to the EMA if sufficient sample size is not reached during the planned study period.

9.6. Data management

Based on the extraction criteria provided by Certara France, the Caisse nationale de l'Assurance Maladie (CNAM) statisticians will search for patients within the SNDS and will develop the relevant targeting algorithm to meet this study's needs. After validation of this algorithm with Certara France, the CNAM will extract the data required for this study. As this is an extraction from the SNDS database, no specific data are collected from patients or doctors.

The data for the study will be made available to the Certara France project team in a dedicated project area on the SNDS portal (subject to the favourable opinion of the relevant committees). Only authorised Certara France users will be able to access data extracted from the portal. Certara France is committed to strictly respecting the benchmark determining the criteria of confidentiality, expertise and independence for research laboratories and design offices provided for by the decree of 17 July 2017.

The data will be kept for the number of years authorised for the conduct of the study and the publication of the results, then they will be permanently deleted.

The data will be received from SNDS in text format according to the selection criteria of the study. SAS® software (SAS Institute Inc., Cary, North Carolina, United States) or R or other appropriate analytical software will be used to process the data, including its management and analysis, manage the analytic datasets and conduct data analysis. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation guidelines for data management. In addition, the data will be checked for consistency in terms of range of values, units of measurement and relevance of clinical information (e.g., a pregnancy diagnosis for a male patient).

9.7. Data analysis

Descriptive statistics will be provided for all results. Categorical variables will be reported using frequency distributions. Ordinal variables will be reported using frequency distributions, means, standard deviations (SDs), minimums, 25th percentiles, medians, 75th percentiles and maximums, unless otherwise specified. Continuous variables will be reported

using means, SDs, minimums, 25th percentiles, medians, 75th percentiles and maximums, unless otherwise specified. When relevant, 95% CIs will be calculated for the study outcomes outlined in Section 9.3.1 (Outcomes) and Table 3. All analyses will be stratified by the approved indication or indication groups ("RA or PsA" and "UC"), unless otherwise specified. In addition, for the objective of "Describe prescribing patterns over time", comparative statistical analyses will be conducted to describe changes in the use of tofacitinib across reporting periods to assess the statistical significance of reductions in the use of tofacitinib among patients with risk factors (see below for further details). P-value < 0.05 indicates statistical significance.

Missing values will be reported as missing and no imputation will be undertaken. Results will be summarised in tables and figures in Microsoft® Excel and/or Word format.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Primary objective 1: Demographics, comorbidities and prior and current medications

The proportion of patients treated with tofacitinib with approved indications and off-label use will be described and tabulated.

The demographic, comorbid and medication variables listed in Table 3 will be described and tabulated in the relevant time period as specified. Additional stratifications may be considered during the SAP development, pending sufficient sample size.

9.7.2. Primary objective 2: Prescribers' adherence to the tofacitinib additional risk minimisation measures

9.7.2.1. Adherence to the recommended posology per indication and duration of use

Average daily dose, as listed in Table 3 and defined in Section 9.3.3, will be reported for each of the pre-specified time intervals as a continuous and categorical variable and may be stratified by presence of ≥1 major VTE risk factor(s) in the 12 months prior to tofacitinib initiation, pending sufficient sample size.

Duration of tofacitinib therapy, as listed in Table 3 and defined in Section 9.3.2, will also be described, tabulated and stratified by approved indication group ("RA or PsA" and "UC") and age (i.e., <65 and ≥65 years).

The variables listed under 'Outcome: Adherence to recommended posology' in Table 3 will be described and tabulated.

9.7.2.2. Adherence to patient screening and laboratory monitoring prior to and during tofacitinib treatment

The proportion of patients with evidence of having received the recommended screenings prior to initiation of tofacitinib and recommended monitoring after initiation of tofacitinib, as listed in Table 3, will be described and tabulated.

9.7.2.3. Adherence to recommendations for limitations of use

9.7.2.3.1. Potential contraindicated use of tofacitinib

The proportion of patients treated with tofacitinib with potential contraindicated use will be described and reported by type of contraindication, as follows:

Contraindicated use, as measured by:

- A patient *initiating* tofacitinib therapy if they have severe hepatic impairment;
- A woman *initiating* tofacitinib therapy if she is pregnant;[11, 12]
- A patient *initiating* tofacitinib therapy if they have or have had TB in the prior 2 months;
- A patient *initiating* tofacitinib therapy if they have or have had a serious and/or opportunistic infection in the prior 2 months; and
- A woman *receiving* tofacitinib therapy during her pregnancy.[11, 12]
- Note that patients may be captured in more than one type of contraindicated use category.

9.7.2.3.2. Use with medications not compatible with tofacitinib

The proportion of tofacitinib patients with concomitant use of medications not compatible with tofacitinib will be reported overall and by patients with and without ≥2 tofacitinib prescription dispensing and measured by:

- The proportion of patients receiving biologics and/or potent immunosuppressants *while taking* tofacitinib; and
- The proportion of patients receiving a live vaccination *while taking* tofacitinib.

Additionally, the number of overlapping days' supply of the biologic or selected potent immunosuppressant with the tofacitinib prescription dispensing will be summarised.

9.7.2.4. Describe prescribing patterns over time: Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure

9.7.2.4.1. Patients with venous thromboembolism risk factors

To describe changes in the utilisation of tofacitinib, this analysis will be stratified by the VTE reporting periods 1, 2 and 3.

The proportion of patients with one or more risk factors for VTE, identified prior to tofacitinib initiation, will be described and tabulated overall and by individual VTE risk factor (e.g., prior VTE and recent MI).

Logistic regression analyses will be used to calculate odds ratios along with their corresponding 95% confidence intervals and p values to formally compare the proportion of patients with VTE risk factors across VTE reporting periods 1, 2 and 3.

To enhance statistical power in detecting changes, a composite score for the VTE risk factors will also be generated by summing the individual VTE risk factors. Linear regression analyses will be employed to compare the VTE composite score across the VTE reporting periods. In addition to the summed composite score, the same analysis using a composite score weighting the risk factors may be considered in an exploratory fashion (weights will be developed and described in the SAP). Regression coefficients with their 95% confidence intervals and p values will be generated.

The proportion of patients diagnosed with UC, one or more VTE risk factors identified prior to tofacitinib initiation and no use of alternative therapy (i.e., biologic) prior to tofacitinib initiation whose ADD in Week 17 through Week 24, Week 25 through Week 32, Week 33 through Week 40 or Week 41 through Week 48 was >10 mg will be described and tabulated.

The proportion of patients who discontinue or continue tofacitinib after developing one or more VTE risk factors while taking tofacitinib will be described separately.

9.7.2.4.2. Patients aged 65 years and older

To describe changes in the utilisation of tofacitinib among patients aged 65 years and older, analyses will be stratified by the VTE reporting periods 1, 2 and 3 and CV and malignancy reporting periods 1, 2 and 3. The following outcomes will be described:

- The proportion of patients aged 65 years and older initiating tofacitinib on the index date without prior alternative therapies (defined as ≥1 biologic in the 12 months prior to index date) will be described and tabulated.

- The proportion of patients who discontinue tofacitinib after turning 65 years old while receiving tofacitinib will be described and tabulated.

- The proportion of patients who continue tofacitinib after turning 65 years old while receiving tofacitinib, overall and stratified by the use of alternative therapies prior to index tofacitinib prescription dispensing, will be described and tabulated.

Logistic regression will be used to assess whether the distributions of these outcome variables are statistically significantly different across reporting periods.

9.7.2.4.3. Patients with cardiovascular risk factors

To describe changes in the utilisation of tofacitinib, this analysis will be stratified by the CV and malignancy reporting periods 1, 2 and 3. The proportion of patients with one or more CV risk factors, identified prior to tofacitinib initiation, will be described and tabulated overall and for each individual CV risk factor.

Logistic regression analyses will be used to calculate odds ratios along with their corresponding 95% confidence intervals and p values to formally compare the proportion of patients with CV risk factors across CV and malignancy reporting periods 1, 2 and 3.

To enhance statistical power in detecting changes, a composite score for the CV risk factors will also be generated by summing the individual CV risk factors. Linear regression analyses will be employed to compare the CV composite score across the CV and malignancy reporting periods. In addition to the summed composite score, the same analysis using a composite score weighting the risk factors may be performed in an exploratory fashion (weights will be developed and described in the SAP). Regression coefficients with their 95% confidence intervals and p values will be generated.

Proportions will be stratified by sex, age (≥65 years versus < 65 years) and prior use of alternative therapy (e.g., biologic), pending sufficient sample size.

The proportion of patients who discontinue or continue tofacitinib after developing one or more CV risk factors while taking tofacitinib will be described separately. The proportion will be further stratified by sex, age (≥65 years versus < 65 years) and prior use of alternative therapy (e.g., biologic), pending sufficient sample size.

9.7.2.4.4. Patients with malignancy risk factors

To describe changes in the utilisation of tofacitinib, this analysis will be stratified by the CV and malignancy reporting periods 1, 2 and 3. The proportion of patients with one or more malignancy risk factors, identified prior to tofacitinib initiation, will be described and tabulated overall and for each individual malignancy risk factor.

Logistic regression analyses will be used to calculate odds ratios along with their corresponding 95% confidence intervals and p values to formally compare the proportion of patients with malignancy risk factors across CV and malignancy reporting period 1, 2 and 3.

To enhance statistical power in detecting changes, a composite score for the malignancy risk factors will also be generated by summing the individual malignancy risk factors. Linear regression analyses will be employed to compare the malignancy composite score across the CV and malignancy reporting periods. In addition to the summed composite score, the same analysis using a composite score weighting the risk factors may be performed in an exploratory fashion (weights will be developed and described in the SAP). Regression coefficients with their 95% confidence intervals and p values will be generated.

Proportions may be stratified by age (≥65 years versus < 65 years) and prior use of alternative therapy (e.g., biologic), pending sufficient sample size.

The proportion of patients who discontinue or continue tofacitinib after developing one or more malignancy risk factors while taking tofacitinib will be described separately. Proportions will be stratified by age (≥65 years versus < 65 years) and prior use of alternative therapy (e.g., biologic), pending sufficient sample size.

9.7.2.5. Describe prescribing patterns over time: Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the JAKi 2022/2023 Article 20 referral

9.7.2.5.1. UC maintenance treatment dosage for patients with CV and malignancy risks, in addition to VTE risk factors

To describe changes in the utilisation of tofacitinib, this analysis will be stratified by the JAKi reporting periods 1, 2 and 3. The proportion of UC patients with CV or malignancy risk factors who have an ADD of > 10 mg in Weeks 17-24, Weeks 25-32, Weeks 33-40 and/or Weeks 41-48 of follow-up will be described and tabulated over each of the JAKi reporting periods.

A sensitivity analysis will be conducted with ADD ≥ 15 mg instead of ADD > 10 mg to capture patients receiving 10 mg BID during maintenance phase. Proportions may be stratified by prior use of alternative therapy (e.g., biologic), pending sufficient sample size.

The distribution of these outcomes will be compared across the JAKi reporting periods using logistic and/or linear regression analyses.

9.8. Quality control

Assessment of availability and completeness of variables, including missing data and implausible ranges, as described in previous sections, will be conducted. The study will conduct the analysis of secondary data and, as such, no source data verification is relevant. Certara will implement the study as an accredited partner with CNAM, the SNDS data owner representative. Data extraction delivered by the CNAM will be checked for plausibility and completeness by the statistical team. In addition, CNAM agreed to share SAS codes used for extraction, which will be reviewed by Certara programmer. The lead statistician will comply with Certara's quality control process for each programming code, which includes a check list to limit coding mistakes. All outputs will then be checked by the lead epidemiologist and

study director. All programmes will be reviewed by an independent statistician and the primary analysis will be recorded independently. The study will conduct the analysis of secondary data and, as such, no source data verification is relevant. In relation to any data cuts received and data outputs, Certara internal data security policy (System Level Security Policy [SLSP]) will apply. Certara will store the data cuts and outputs in a dedicated folder within the file server. The Asset Custodian will ask for user's accesses (for the team in charge of data analysis) and IT team will provide the requested accesses upon validation from the system owner (copy of Certara SLSP could be provided upon request).

9.9. Limitations of the research methods

9.9.1. Internal validity of study design

9.9.1.1. Measurement error(s)/misclassifications(s)

The French SNDS and linked datasets are extracted from claims and hospital practice databases, plus death registries. The possibility of misclassification and miscoded data exists. However, the SNDS and its linked datasets have been extensively used to assess utilization and post-authorisation safety of new interventions, including for drugs used to treat UC, RA or PsA.[13-19]

Tofacitinib exposure

Reimbursement data are used as a proxy for drug intake. Thus, the presence of a reimbursement for a drug does not indicate whether the medication was actually consumed or taken as prescribed. Given that tofacitinib is an expensive drug specifically prescribed by specialists, the likelihood of patients not taking the drug when dispensed is considered low. Furthermore, data from real-world studies have also demonstrated that adherence to tofacitinib treatment is typically very good among patients with UC, RA and PsA.[20-22]

Prescriptions reimbursed in outpatient settings are fully captured by the SNDS and linked datasets. Though not all medications administered during hospital stays are fully captured by the SNDS, it is estimated that tofacitinib is predominantly reimbursed in outpatient settings. As such, the likelihood of misclassification of index tofacitinib treatment due to missing inpatient medication data is considered negligible.

Indication for tofacitinib initiation

Reason for drug prescription is not documented in either inpatient or outpatient settings. Therefore, a proxy will be used to determine indication, adapted from published algorithms which use hospital discharge diagnoses codes and diagnostic reason for registration in the LTD database.[23] The development of these algorithms will be informed by literature review and input from subject-level experts in RA, UC or PsA and separately from SNDS database experts.

Inaccurate (or missing) indication(s) being assigned to the index tofacitinib dispensing is possible with the proposed algorithm. However, registrations into the LTD database have

high validity since they are specifically requested by the physician for full reimbursement of care linked to the condition.[24] Hospital discharge diagnoses are also expected to have high validity. Furthermore, misclassification of indications as an off-label indication when no diagnosis codes for RA, PsA or UC are identified during the time window will primarily impact sample size (and thus precision of estimates) of the RA, PsA or UC groups when evaluating the adherence of prescribers to aRMM materials, but are not expected to materially bias the results.

Duration of tofacitinib treatment and posology

Because automated health databases often do not record the intended duration of use of a dispensed prescription (i.e., days of supply), a proxy for days' supply is developed based on package size and time between reimbursed prescriptions and will be further detailed in the SAP. As such, calculated ADD would reflect the actual use of tofacitinib by patients if the patients did not take the drug as prescribed. Though this approach is commonly applied in the SNDS, to minimize potential misclassification of drug exposure, a series of checks will be undertaken, such as comparisons with recommended posology, the review of overlapping reimbursements and frequency of reimbursements over pre-specified time-periods.[25-27]

Adherence to the SmPC recommendation of "*if no suitable treatment alternatives are available*"

The alternative "*no prior use of an alternative therapy (i.e., biologic)*" is used as a proxy to measure adherence to the SmPC recommendation of "*if no suitable treatment alternatives are available*" due to constraints with the SNDS claims data source in which "suitability" of a treatment is not documented. A limitation associated with use of this proxy method is a possible overestimation of the non-adherence to the recommendations for limitations of use, which may lead to a conversative estimate of the effectiveness of aRMMs. For example, if a patient older than 65 years initiated tofacitinib because his/her prescriber thought all other therapies were unsuitable and did not prescribe other therapies prior to tofacitinib initiation, this event will be falsely counted as non-adherence to the recommendations for limitations of use (and thus undermining the effectiveness of aRMMs), because no prior use of an alternative therapy was identified from claims data.

9.9.1.2. Information bias

Diagnoses

There is the potential for misreporting of information in the existing health system from where the data are retrieved (medical records and national registry). However, for the variables that are to be collected for the present study, experience from previous research shows that the reporting to French SNDS database and linked dataset is reasonable.[28] Furthermore, chronic diagnoses as per the LTD database are approved by physicians of the health care insurance system, and choice of hospital diagnoses is guided by comprehensive coding instructions to enhance the homogeneity of data input. That the choice of diagnosis code is independent from the study team also facilitates the avoidance of information bias.

The identification of comorbidities in the SNDS does not rely on data from a single source, instead relying on validated algorithms using diagnoses, treatment and procedure data thereby decreasing risk of misclassification of these conditions.[24, 29] Specific algorithms are implemented to capture diagnosis performed outside of hospital as limited information on diagnosis (ICD-10 codes as per the registration in the LTD database only) is available in outpatient settings.[30] As such, the algorithms will utilise data on procedures, diagnosis codes as per the LTD database (where available) and reimbursed prescriptions, as relevant. Published, validated algorithms will be used where available.[6, 7]

Laboratory data

Although laboratory results are not reported in the datasets to be employed, adherence to the laboratory screening and monitoring can only be assessed at the level of whether a laboratory was done rather than the actual value. This limits the study's ability to evaluate whether a prescriber should properly continue or discontinue tofacitinib treatment according to laboratory results. As part of the development of the SAP, procedure codes for the screening and laboratory tests of interest will be identified and confirmed with the database owner/local clinicians. If procedure codes are not available for a given test, this will be noted in the SAP.

Other comorbidities (e.g., lifestyle risk factors)

Given that this is a claims database, certain lifestyle risk factors for VTE, MACE or malignancy are often underreported, such as smoking and alcohol consumption. Smoking variable defined in this analysis only represents the severe smoking behaviour that warrants medical attention but could still be susceptible to low sensitivity. There are conditions or illnesses or hospital claims that are associated with smoking and alcohol consumption that can be used as proxies, but they will not provide a full picture of all smokers or alcohol consumers. Similarly, other risk factors are likely to be underreported in the SNDS; these include immobilisation, obesity, family history of malignancy and family history of CV disease that were not included in this study due to the concern of a high level of missingness. Given that lifestyle risk factors are usually correlated with other risk factors (e.g., diabetes, cardiovascular diseases) that are captured by diagnosis codes, missingness of those lifestyle factors are not expected to undermine the study's ability to capture high risk population in which the utilisation of tofacitinib will be assessed.

9.9.2. Missing data and/or incomplete data

The French SNDS database and linked datasets are claims and hospital practice datasets where missing data are possible. Missing and/or incomplete data mainly applies to causes of death, which is not a variable of interest in this study. The use of multiple linked data sources (primary care, hospital, pharmacy data and central death registrations) has the potential to reduce missing and/or complete data and improve exposure and/or outcome ascertainment. Data on treatments administered over-the-counter or in hospital are not available (excluding for medications invoiced in addition to the hospital disease-related group) nor laboratory results, as described above.

To avoid missing or the input of inaccurate data, quality control processes are performed prior to the data being integrated in the SNDS.[31]

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymised structured format and contain no patient personal information.

The data for the study will be made available to the Certara France project team in a dedicated project area on the SNDS portal (subject to the favourable opinion of the relevant committees). Only authorised Certara France users will be able to access data extracted from the portal. Certara France is committed to strictly respecting the benchmark determining the criteria of confidentiality, expertise and independence for research laboratories and design offices provided for by the decree of 17 July 2017.

The data will be kept for the number of years authorised for the conduct of the study and the publication of the results, then they will be permanently deleted.

10.2. Patient consent

As this study involves anonymised structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer. Specifically, the study requires scientific opinion from external committee and ethical and legal authorisation from the independent national Data Protection Authority for France, National Commission on Informatics and Liberty (CNIL).

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigour and follow generally accepted research practices described Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)[32], and the European Medicines Agency, ENCePP Guide on Methodological Standards in Pharmacoepidemiology.[33].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE; i.e., identifiable patient, identifiable reporter, a suspect product and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

The study will be registered in the EU post-authorisation study (PAS) register by the MAH.

The interim and final study reports describing the study results will be disseminated to the tofacitinib clinical programme teams and to the EMA. Data may be used in regulatory communications external to the EMA for contextualisation purposes. Conference abstracts and/or manuscripts based on specific endpoints of interest may be developed for external publication purposes.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Not applicable	31 October 2019	List of opportunistic infections diagnosis codes
2	Not applicable	31 October 2019	List of serious infections diagnosis codes

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz® (tofacitinib) Using an Administrative Healthcare Database in France

EU PAS Register® number: Pending
Study reference number (if applicable):
Protocol #: A3921403

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	n/a
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan and an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	n/a
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	n/a

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in case of secondary use of data, the date from which data extraction starts.

[3] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional and other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk and prevalence)	☒	☐	☐	9.3.1
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference and number needed to harm [NNH])	☐	☐	☒	n/a
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☐	☐	☒	n/a

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1, 9.2 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☐	☐	☒	n/a
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☐	☐	☒	n/a
	4.2.5 Duration of	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2 9.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure and measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy and use of validation sub-study)	☐	☐	☒	n/a
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.2

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.4 Is intensity of exposure addressed? (e.g., dose and duration)	☒	☐	☐	9.3.2 9.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	n/a
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	n/a

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value and use of validation sub-study)	☐	☐	☒	n/a
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, healthcare services utilisation, burden of disease or treatment, compliance and disease management)	☐	☐	☒	n/a

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	n/a
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☐	☐	☒	n/a
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes and time-related bias)	☒	☐	☐	9.9.1.2

Comments:

Given the descriptive nature of the study and a lack of control groups, the study is not concerned with the impact of confounding or selection bias.

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses and anticipated direction of effect)	☐	☐	☒	n/a

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report and face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires and vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage and prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event and severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications and lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g., WHO Drug Dictionary and Anatomical Therapeutic Chemical [ATC] Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g., International Classification of Diseases [ICD] and Medical Dictionary for Regulatory Activities [MedDRA])	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☒	☐	☐	9.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	n/a
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	9.1.1.1

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1,9.9.2
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

There are no measures of association in this study.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and antifraud protection and archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	n/a

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	n/a
12.1.2 Information bias?	☒	☐	☐	9.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data and analytical methods).	☐	☐	☒	n/a
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment and precision of the estimates)	☒	☐	☐	9.2.3, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3, 10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	n/a
13.3 Have data protection requirements been described?	☒	☐	☐	10.1, 10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Juan (Joanne) Wu

Date: 03/11/2022

Signature: Juan Wu

ANNEX 3. LIST OF DIAGNOSIS CODES FOR SELECT INFECTIONS OF INTEREST

All codes will be reviewed and updated prior to study initiation. For a list of codes, see the following files:

- Final_A3921321_Xeljanz-EU DUS opportunistic infections Dx codes_v1.2.pdf
- Final_A3921321_Xeljanz-EU DUS serious infections DX codes_v1.2.pdf

ANNEX 4. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST

All codes will be reviewed and updated prior to study initiation.

Class of drug	Drug	ATC code
Corticosteroids	Aldosterone	H02AA01
	Fludrocortisone	H02AA02
	Desoxycortone	H02AA03
	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Fluocortolone	H02AB03
	Methylprednisolone	H02AB04
	Paramethasone	H02AB05
	Prednisolone	H02AB06
	Prednisone	H02AB07
	Triamcinolone	H02AB08
	Hydrocortisone	H02AB09 (D07XA01 topical use)
	Cortisone	H02AB10
	Prednylidene	H02AB11
	Rimexolone	H02AB12
	Deflazacort	H02AB13
	Cloprednol	H02AB14
	Meprednisone	H02AB15
	Cortivazol	H02AB17
	Methylprednisolone, combinations	H02BX01
	Trilostane	H02CA01
	Phenylbutazone and corticosteroids	M01BA01
	Dipyrocetyl and corticosteroids	M01BA02
	Acetylsalicylic acid and corticosteroids	M01BA03
Methotrexate	Methotrexate	L04AX03
Statins	Atorvastatin	C10AA05
	Atorvastatin and acetylsalicylic acid	C10BX08
	Atorvastatin and amlodipine	C10BX03
	Atorvastatin and ezetimibe	C10BA05
	Atorvastatin and perindopril	C10BX15
	Atorvastatin, acetylsalicylic acid and perindopril	C10BX12
	Atorvastatin, acetylsalicylic acid and ramipril	C10BX06
	Atorvastatin, amlodipine and perindopril	C10BX11
	Cerivastatin	C10AA06
	Fluvastatin	C10AA04
	Gemigliptin and rosuvastatin	A10BH52
	Imipenem and cilastatin	J01DH51
	Lovastatin	C10AA02
	Lovastatin and nicotinic acid	C10BA01
	Nystatin	A07AA02, D01AA01, G01AA01
	Nystatin, combinations	G01AA51
	Pentostatin	L01XX08
	Pitavastatin	C10AA08
	Pravastatin	C10AA03
	Pravastatin and acetylsalicylic acid	C10BX02

Class of drug	Drug	ATC code
	Pravastatin and fenofibrate	C10BA03
	Rosuvastatin	C10AA07
	Rosuvastatin and acetylsalicylic acid	C10BX05
	Rosuvastatin and amlodipine	C10BX09
	Rosuvastatin and ezetimibe	C10BA06
	Rosuvastatin and valsartan	C10BX10
	Rosuvastatin, amlodipine and lisinopril	C10BX07
	Rosuvastatin, amlodipine and perindopril	C10BX14
	Rosuvastatin, perindopril and indapamide	C10BX13
	Simvastatin	C10AA01
	Simvastatin and acetylsalicylic acid	C10BX01
	Simvastatin and ezetimibe	C10BA02
	Simvastatin and fenofibrate	C10BA04
	Simvastatin, acetylsalicylic acid and ramipril	C10BX04
	Sitagliptin and simvastatin	A10BH51
Vaccinations	Anthrax antigen	J07AC01
	Brucella antigen	J07AD01
	Cholera, inactivated, whole cell	J07AE01
	Cholera, live attenuated	J07AE02
	Cholera, combinations with typhoid vaccine, inactivated, whole cell	J07AE51
	Diphtheria toxoid	J07AF01
	Haemophilus influenzae B, purified antigen conjugated	J07AG01
	Haemophilus influenzae B, combinations with toxoids	J07AG51
	Haemophilus influenzae B, combinations with pertussis and toxoids	J07AG52
	Haemophilus influenzae B, combinations with meningococcus C, conjugated	J07AG53
	Meningococcus A, purified polysaccharides antigen	J07AH01
	Other meningococcal monovalent purified polysaccharides antigen	J07AH02
	Meningococcus A,C, bivalent purified polysaccharides antigen	J07AH03
	Meningococcus A,C,Y,W-135, tetravalent purified polysaccharides antigen	J07AH04
	Other meningococcal polyvalent purified polysaccharides antigen	J07AH05
	Meningococcus B, outer membrane vesicle vaccine	J07AH06
	Meningococcus C, purified polysaccharides antigen conjugated	J07AH07
	Meningococcus A,C,Y,W-135, tetravalent purified polysaccharides antigen conjugated	J07AH08
	Meningococcus B, multicomponent vaccine	J07AH09
	Meningococcus A, purified polysaccharides antigen conjugated	J07AH10
	Pertussis, inactivated, whole cell	J07AJ01
	Pertussis, purified antigen	J07AJ02

Class of drug	Drug	ATC code
	Pertussis, inactivated, whole cell, combinations with toxoids	J07AJ51
	Pertussis, purified antigen, combinations with toxoids	J07AJ52
	Plague, inactivated, whole cell	J07AK01
	Pneumococcus, purified polysaccharides antigen	J07AL01
	Pneumococcus, purified polysaccharides antigen conjugated	J07AL02
	Pneumococcus purified polysaccharides antigen and haemophilus influenzae, conjugated	J07AL52
	Tetanus toxoid	J07AM01
	Tetanus toxoid, combinations with diphtheria toxoid	J07AM51
	Tetanus toxoid, combinations with tetanus immunoglobulin	J07AM52
	Tuberculosis, live attenuated	J07AN01
	Typhoid, oral, live attenuated	J07AP01
	Typhoid, inactivated, whole cell	J07AP02
	Typhoid, purified polysaccharide antigen	J07AP03
	Typhoid, combinations with paratyphi types	J07AP10
	Typhus exanthematicus, inactivated, whole cell	J07AR01
	Encephalitis, tick borne, inactivated, whole virus	J07BA01
	Encephalitis, Japanese, inactivated, whole virus	J07BA02
	Encephalitis, Japanese, live attenuated	J07BA03
	Influenza, inactivated, whole virus	J07BB01
	Influenza, inactivated, split virus or surface antigen	J07BB02
	Influenza, live attenuated	J07BB03
	Hepatitis B, purified antigen	J07BC01
	Hepatitis A, inactivated, whole virus	J07BC02
	Combinations	J07BC20
	Measles, live attenuated	J07BD01
	Measles, combinations with mumps, live attenuated	J07BD51
	Measles, combinations with mumps and rubella, live attenuated	J07BD52
	Measles, combinations with rubella, live attenuated	J07BD53
	Measles, combinations with mumps, rubella and varicella, live attenuated	J07BD54
	Mumps, live attenuated	J07BE01
	Poliomyelitis oral, monovalent, live attenuated	J07BF01
	Poliomyelitis oral, trivalent, live attenuated	J07BF02
	Poliomyelitis, trivalent, inactivated, whole virus	J07BF03
	Poliomyelitis oral, bivalent, live attenuated	J07BF04
	Rabies, inactivated, whole virus	J07BG01
	Rota virus, live attenuated	J07BH01
	Rota virus, pentavalent, live, reassorted	J07BH02
	Rubella, live attenuated	J07BJ01
	Rubella, combinations with mumps, live attenuated	J07BJ51
	Varicella, live attenuated	J07BK01
	Zoster, live attenuated	J07BK02
	Zoster, purified antigen	J07BK03
	Yellow fever, live attenuated	J07BL01
	Papillomavirus (human types 6, 11, 16 and 18)	J07BM01

Class of drug	Drug	ATC code
	Papillomavirus (human types 16 and 18)	J07BM02
	Papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52 and 58)	J07BM03
	Smallpox, live attenuated	J07BX01
	Diphtheria-poliomyelitis-tetanus	J07CA01
	Diphtheria-pertussis-poliomyelitis-tetanus	J07CA02
	Diphtheria-rubella-tetanus	J07CA03
	Haemophilus influenzae B and poliomyelitis	J07CA04
	Diphtheria-hepatitis B-pertussis-tetanus	J07CA05
	Diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus	J07CA06
	Diphtheria-hepatitis B-tetanus	J07CA07
	Haemophilus influenzae B and hepatitis B	J07CA08
	Diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	J07CA09
	Typhoid-hepatitis A	J07CA10
	Diphtheria-haemophilus influenzae B-pertussis-tetanus-hepatitis B	J07CA11
	Diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B	J07CA12
	Diphtheria-haemophilus influenzae B-pertussis-tetanus-hepatitis B-meningococcus A + C	J07CA13

Abbreviations: ATC = Anatomical Therapeutic Chemical.

ANNEX 5. LIST OF DIAGNOSIS CODES FOR SELECT IMMUNODEFICIENCIES OF INTEREST

All codes will be reviewed and updated prior to study initiation.

Immunodeficiency diagnosis description	ICD-10 diagnosis code
Immunodeficiency with predominantly antibody defects	D80.x
Combined immunodeficiencies	D81.x
Immunodeficiency associated with other major defects	D82.x
Common variable immunodeficiency	D83.x
Other immunodeficiencies	D84.x
Sarcoidosis	D86.x
Other disorders involving the immune mechanism, not elsewhere classified	D89.x

ANNEX 6. LIST OF DIAGNOSIS AND PROCEDURE CODES FOR INTERSTITIAL LUNG DISEASE

A majority of the following codes were derived from Curtis et al. (2015).[34] All codes will be reviewed and updated prior to study initiation.

ILD diagnosis description	ICD-10 diagnosis code
Codes in the standard, specific definition of ILD	
Pulmonary fibrosis, unspecified	J841
Other specified interstitial pulmonary diseases	J848
Acute interstitial pheumonitis	J841
Alveolar proteinosis	J840
Interstitial pulmonary disease, unspecified	J849
Rheumatoid lung disease with rheumatoid arthritis of unspecified site	M0510

ILD procedure description (codes to be provided in the SAP)
Computed tomography of the thorax
Computerised axial tomography of thorax
Other tomography of thorax
Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial or endobronchial biopsy(s), single or multiple sites
Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transbronchial lung biopsy(s), single lobe
Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transbronchial needle aspiration biopsy(s), trachea, main stem and/or lobar bronchus
Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transbronchial lung biopsy(s), each additional lobe
Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transbronchial needle aspiration biopsy(s), each additional
Thoracotomy, limited, for biopsy of lung or pleura
Thoracotomy, with diagnostic biopsy of lung infiltrate(s) (e.g., wedge and incisional), unilateral
Thoracotomy, with diagnostic biopsy of lung nodule/mass (e.g., wedge and incisional), unilateral
Thoracotomy, with biopsy(ies) of pleura
Biopsy, pleura; percutaneous needle
Biopsy, lung or mediastinum, percutaneous needle
Thoracoscopy, diagnostic (separate procedure); pericardial sac, with biopsy
Thoracoscopy, diagnostic (separate procedure); mediastinal space, with biopsy
Thoracoscopy; with diagnostic biopsy of lung infiltrate (e.g., wedge and incisional), unilateral
Thoracoscopy; with diagnostic biopsy of lung nodule/mass (e.g., wedge and incisional), unilateral
Thoracoscopy; with biopsy(ies) of pleura

ANNEX 7. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB

All codes will be verified and updated prior to study initiation.

Class of drug	Drug	ATC code
Biologics	Abatacept	L04AA24
	Adalimumab	L04AB04
	Anakinra	L04AC03
	Certolizumab	L04AB05
	Etanercept	L04AB01
	Golimumab	L04AB06
	Infliximab	L04AB02
	Ixekizumab	L04AC13
	Rituximab	L01XC02
	Secukinumab	L04AC10
	Sarilumab	L04AC14
	Tocilizumab	L04AC07
	Ustekinumab	L04AC05
	Vedolizumab	L04AA33
Conventional synthetic DMARDS (csDMARD)	Gold preparation (sodium aurothiomalate)	M01CB01
	Gold preparation (sodium aurotiosulfate)	M01CB02
	Gold preparation (auranofin)	M01CB03
	Gold preparation (aurothioglucose)	M01CB04
	Gold preparation (aurotioprol)	M01CB05
	Hydroxychloroquine	P01BA02
	Leflunomide	L04AA13
	Olsalazine	A07EC03
	Penicillamine	M01CC01
	Sulfasalazine	A07EC01
Targeted synthetic DMARDS	Apremilast	L04AA32
	Baricitinib	L04AA37
	Upadacitinib	L04AA44
	Filgotinib	L04AA45
Other DMARDS	Balsalazide	A07EC04
	Olsalazine	A07EC03
	Sulfasalazinea[a]	A07EC01
Selected potent immunosuppressant	6-Mercaptopurine	L01BB02
	Azathioprinea[a]	L04AX01
	Cyclosporinea[a]	L04AD01
	Tacrolimus	L04AD02

a Denotes that the medicine may also be classified as a csDMARD.
csDMARD = conventional synthetic DMARDS

ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES

All codes will be reviewed and updated prior to study initiation.

Class of drug	Drug	ATC code
Antiadrenergic agents, centrally acting	Rescinnamine	C02AA01
	Reserpine	C02AA02
	Combinations of rauwolfia alkaloids	C02AA03
	Rauwolfia alkaloids, whole root	C02AA04
	Deserpidine	C02AA05
	Methoserpidine	C02AA06
	Bietaserpine	C02AA07
	Reserpine, combinations	C02AA52
	Combinations of rauwolfia alkoloids, combinations	C02AA53
	Bietaserpine, combinations	C02AA57
	Rescinnamine	C02AA01
	Methyldopa (levorotatory)	C02AB01
	Methyldopa (racemic)	C02AB02
	Clonidine	C02AC01
	Guanfacine	C02AC02
	Tolonidine	C02AC04
	Moxonidine	C02AC05
	Rilmenidine	C02AC06
Antiadrenergic agents, ganglion-blocking	Trimetaphan	C02BA01
	Mecamylamine	C02BB01
Antiadrenergic agents, peripherally acting	Prazosin	C02CA01
	Indoramin	C02CA02
	Trimazosin	C02CA03
	Doxazosin	C02CA04
	Urapidil	C02CA06
	Betanidine	C02CC01
	Guanethidine	C02CC02
	Guanoxan	C02CC03
	Debrisoquine	C02CC04
	Guanoclor	C02CC05
	Guanazodine	C02CC06
	Guanoxabenz	C02CC07
Arteriolar smooth muscle, agents acting on	Diazoxide	C02DA01
	Dihydralazine	C02DB01
	Hydralazine	C02DB02
	Endralazine	C02DB03
	Cadralazine	C02DB04
	Minoxidil	C02DC01
	Nitroprusside	C02DD01
	Pinacidil	C02DG01
Other antihypertensives	Veratrum	C02KA01
	Metirosine	C02KB01
	Pargyline	C02KC01
	Ketanserin	C02KD01
	Bosentan	C02KX01

Class of drug	Drug	ATC code
	Ambrisentan	C02KX02
	Sitaxentan	C02KX03
	Macitentan	C02KX04
	Riociguat	C02KX05
	Ambrisentan and tadalafil	C02KX52

ANNEX 9. LIST OF ATC CODES FOR ANTIHYPERLIPIDAEMICS

All codes will be reviewed and updated prior to study initiation.

Class of drug	Drug	ATC code
Lipid modifying agents, plain	Simvastatin	C10AA01
	Lovastatin	C10AA02
	Pravastatin	C10AA03
	Fluvastatin	C10AA04
	Atorvastatin	C10AA05
	Cerivastatin	C10AA06
	Rosuvastatin	C10AA07
	Pitavastatin	C10AA08
	Clofibrate	C10AB01
	Bezafibrate	C10AB02
	Aluminium clofibrate	C10AB03
	Gemfibrozil	C10AB04
	Fenofibrate	C10AB05
	Simfibrate	C10AB06
	Ronifibrate	C10AB07
	Ciprofibrate	C10AB08
	Etofibrate	C10AB09
	Clofibride	C10AB10
	Choline fenofibrate	C10AB11
	Clofibrate	C10AB01
	Colestyramine	C10AC01
	Colestipol	C10AC02
	Colextran	C10AC03
	Colesevelam	C10AC04
	Niceritrol	C10AD01
	Nicotinic acid	C10AD02
	Nicofuranose	C10AD03
	Aluminium nicotinate	C10AD04
	Nicotinyl alcohol (pyridylcarbinol)	C10AD05
	Acipimox	C10AD06
	Nicotinic acid, combinations	C10AD52
	Dextrothyroxine	C10AX01
	Probucol	C10AX02
	Tiadenol	C10AX03
	Meglutol	C10AX05
	Omega-3-triglycerides incl. other esters and acids	C10AX06
	Magnesium pyridoxal 5-phosphate glutamate	C10AX07
	Policosanol	C10AX08
	Ezetimibe	C10AX09
	Alipogene tiparvovec	C10AX10
	Mipomersen	C10AX11
	Lomitapide	C10AX12
	Evolocumab	C10AX13
	Alirocumab	C10AX14
	Bempedoic acid	C10AX15

Class of drug	Drug	ATC code
	Inclisiran	C10AX16
	Evinacumab	C10AX17
	Volanesorsen	C10AX18

ANNEX 10. LIST OF LABORATORY TEST CODES

Laboratory test	Label (French)	Biology code
Creatinine (serum or urine)	CLAIRANCE (RENALE) DE LA CREATININE	0407
	PROFIL ENZ PANCREATIQUE (AMYLASEMIE+AMYLASURIE+EVENT CREATININEMIE)	1531
	SANG : CREATININE	0592
	SANG : UREE ET CREATININE	0593
	UR. : CREATININE (CREATININURIE)	0627
TB screening	MYCOBACTERIES : IDENTIF. BIOCH AUTRE QUE MYCOBACTERIUM TUBERCULOSIS	0244
	MYCOBACTERIES : IDENTIFICATION BIOCHIMIQUE DE MYCOBACTERIUM TUBERCULOSIS	0243
Viral hepatitis B and C screening	HEPATITE B (VHB) : SD : AC ANTIHBC IGM PAR EIA	0352
	HEPATITE B (VHB) : SD : AC ANTIHBC TOTAUX PAR EIA	0351
	HEPATITE B (VHB) : SD : AC ANTIHBE PAR EIA	0354
	HEPATITE B (VHB) : SD : AC ANTIHBS (IGG OU IG TOTALES) PAR EIA	0323
	HEPATITE B (VHB) : SD : AG HBE PAR EIA	0353
	HEPATITE B (VHB) : SD : AG HBS PAR EIA	0322
	HEPATITE B (VHB): CONTROLE DE GUERISON	4712
	HEPATITE B (VHB): DEPISTAGE ET/OU DIAGNOSTIC	4500
	HEPATITE B (VHB): DEPISTAGE ET/OU DIAGNOSTIC IGM ANTI HBC	4501
	HEPATITE B (VHB): GENOME (ADN) (VHB): HYBRIDATION MOLECULAIRE	4120
	HEPATITE B (VHB): STATUT IMMUNITAIRE DANS LE CADRE D'UNE VACCINATION.	4714
	HEPATITE B (VHB): SUIVI D'UNE HEPATITE B CHRONIQUE	4711
	HEPATITE B (VHB): SURVEILLANCE DE LA GROSSESSE	4715
	HEPATITE B (VHB):SD CONTROLE AVANT VACCINATION:AC ANTI HBS+AC ANTI HBC EIA	4713
	HEPATITE B (VHB):SD INFECTION RECENTE:AG HBS+AC ANTI-HBC IGM PAR EIA	4710
	GENOME (ARN) VIRUS DE L'HEPATITE C (VHC) : HYBRID MOLEC : DETECTION QUALITATIVE	4121
	GENOME (ARN) VIRUS DE L'HEPATITE C (VHC) : HYBRID MOLEC : DETECTION QUALITATIVE	4123
	HEPATITE C (VHC) : DETECTION QUANTITATIVE GENOME (ARN)	4124
	HEPATITE C (VHC) : GENOTYPAGE DU VHC PAR BIOLOGIE MOLECULAIRE	4125
	HEPATITE C (VHC) : SD DE CONTROLE	3785
	HEPATITE C (VHC) : SD DE DEPISTAGE : AC ANTI-VHC	3784
Haemoglobin laboratory testing	ELECTROPHORESE DE L'HEMOGLOBINE (CITRATE AGAR)	1114
	ELECTROPHORESE DE L'HEMOGLOBINE (GEL POLYACRYLAMIDE)	1113
	HEMOGRAMME Y COMPRIS PLAQUETTES (NFS , NFP)	1104
	HEMATOCRITE (HTE)	2108

Laboratory test	Label (French)	Biology code
Alanine aminotransferase and/or aspartate aminotransferase laboratory testing (i.e., liver function testing)	ALANINE AMINOTRANSFERASE (ALAT,TGP) (SANG)	0516
	ASPARTATE AMINOTRANSFERASE (ASAT,TGO)(SANG)	0517
	TRANSAMINASES (ALAT ET ASAT, TGP ET TGO)(SANG)	0522
Lipid panel (i.e., total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides [TG]) laboratory testing	SANG : CHOLESTEROL TOTAL (CHOL)	0580
	SANG : CHOLESTEROL-LDL (C-LDL)	2001
	SANG : TRIGLYCERIDES (TG)	0590

ANNEX 11. LIST OF CODES FOR COMORBIDITIES

Comorbidity	Definition	Codes (ICD-10 codes, ATC codes, CCAM procedure codes)
Hepatic impairment	Defined as ≥1 ICD-10 diagnosis code for hepatic impairment.	K71 and K72
Renal impairment	Defined as ≥1 ICD-10 diagnosis code for renal impairment or a combination of EBM service codes, ICD-10 diagnosis codes and/or ICD-10 procedure codes.	Stage III, IV or V (end stage) Chronic kidney disease **ICD-10 diagnosis:** Specific diagnoses of CKD Stage 3: N183 Stage 4: N184 Stage 5: N185 Other chronic renal disease: N188 and N189 Diagnoses linked to CKD stage 5 Hypertensive cardionephropathy, with renal failure: I131 and I132 Extra-corporeal dialysis: Z491 Preparatory care for dialysis: Z490 Failure and rejection of a kidney transplant: T861 Dependence to kidney dialysis: Z992+1 **CCAM codes for medical procedures due to kidney failure (stage 5):** JVJF002, JVJF004, JVJF003, JVJF005, JVJF006, JVJF007, JVJF008, JVRP004, JVRP007, JVRP008 and YYYY007 [TBC IN LAST VERSION]
Diabetes	Defined as ≥1 ICD-10 diagnosis code for diabetes or at least 3 reimbursements (or at least 2 in case of large pack sizes) of oral antidiabetes agents and/or insulin.	ICD-10 diagnosis: E10-E14 ATC code medications: A10*
Herpes zoster	Defined as ≥1 ICD-10 diagnosis code for herpes zoster.	B02*
Human immunodeficiency virus	Defined as ≥1 ICD-10 diagnosis code for human immunodeficiency virus.	B20-B24 and Z21
Tuberculosis, including both active and latent TB	Defined as ≥1 ICD-10 diagnosis code for tuberculosis.	
Viral hepatitis B or C	Defined as ≥1 ICD-10 diagnosis code for viral hepatitis B or C.	B180, B181 and B182

Comorbidity	Definition	Codes (ICD-10 codes, ATC codes, CCAM procedure codes)
Diverticulitis	Defined as ≥1 ICD-10 diagnosis code for diverticulitis.	Q396, Q696, K225, K382, N323, Q430, K314, N361 and C173
Malignancy (non-metastatic and metastatic, excluding non-melanoma skin cancer)	Defined as ≥1 ICD-10 diagnosis code for a malignancy (excluding non-melanoma skin cancer).	See table below
Non-melanoma skin cancer	Defined as ≥1 ICD-10 diagnosis code for non-melanoma skin cancer.	C44 other malignant tumour of the skin
Gastrointestinal perforation	Defined as ≥1 ICD-10 diagnosis code for gastrointestinal perforation.	K285
Hypertension	Defined as ≥1 ICD-10 diagnosis code for hypertension or at least 3 reimbursements (or at least 2 in case of large pack sizes) of antihypertensive in the 12 months prior to or on the day of the index tofacitinib dispensing.	I10-I15
Prior myocardial infarction	Defined as ≥1 ICD-10 diagnosis code for a myocardial infarction in the 3 months prior to or on the day of the index tofacitinib dispensing.	I20-I25
Heart failure	Defined as ≥1 ICD-10 diagnosis code for heart failure in the 12 months prior to or on the day of the index tofacitinib dispensing.	I50, I110, I130 and I132
Inherited coagulation disorder	Defined as ≥1 ICD-10 diagnosis code for inherited coagulation disorder while receiving tofacitinib therapy.	D680, D681, D682, D66, D67, D689 and D686
Coronary heart disease	Defined as ≥1 ICD-10 diagnosis code for coronary heart disease.	I20-I25, I77 and Z95
Stable angina pectoris	Defined as ≥1 ICD-10 diagnosis code for stable angina pectoris.	I208 and I209
Hypercholesterolemia or dyslipidaemia or atherosclerosis	Defined as ≥1 ICD-10 diagnosis code for hypercholesterolemia or dyslipidaemia or atherosclerosis and ATC codes LLTs (statins, fibrates etc).	ICD-10: E780, E782, E783, E784, E785, E788, E789, Z863 and I70 ATC codes Statins : C10BA05, C10AA04 C10AA02, C10AA08, C10AA03, C10AA07 and C10AA01 ATC codes Fibrates : C10AB
Epstein-Barr virus (EBV)	Defined as ≥1 ICD-10 diagnosis code for Epstein-Barr virus.	D823, B348, B270, P358 and Z228
Hepatitis B virus (HBV)	Defined as ≥1 ICD-10 diagnosis code for Hepatitis B virus.	B181
Human papillomavirus (HPV)	Defined as ≥1 ICD-10 diagnosis code for HPV.	A630

Comorbidity	Definition	Codes (ICD-10 codes, ATC codes, CCAM procedure codes)
Human T-cell lymphotropic virus (HTLV)	Defined as ≥1 ICD-10 diagnosis code for human T-cell lymphotropic virus.	Z226, L303, B333 and B973
Hepatitis C virus (HCV)	Defined as ≥1 ICD-10 diagnosis code for hepatitis C virus.	B182 and B171
Coronary artery procedures*	Replacement of the ascending thoracic aorta and horizontal aorta with aortic valve replacement, with reimplantation of the coronary arteries, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA014
	Ascending thoracic aorta replacement without aortic valve replacement, with coronary artery reimplantation, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA003
	Replacement of the ascending thoracic aorta and horizontal aorta without aortic valve replacement, without reimplantation of the coronary arteries, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA001
	Ascending thoracic aorta replacement with aortic valve replacement, with coronary artery reimplantation, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA015
	Ascending thoracic aorta replacement with aortic valve replacement, without coronary artery reimplantation, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA011
	Ascending thoracic aorta replacement without aortic valve replacement, without coronary artery reimplantation, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA025
	Replacement of the ascending thoracic aorta and horizontal aorta without aortic valve replacement, with reimplantation of the coronary arteries, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA026

Comorbidity	Definition	Codes (ICD-10 codes, ATC codes, CCAM procedure codes)
	Replacement of the ascending thoracic aorta and horizontal aorta with aortic valve replacement, without coronary artery re-implantation, by thoracotomy with extracorporeal circulation	CCAM procedure code: DGKA018
	Coronary revascularisation with 2 arterial and 3 venous grafts with 3 distal anastomoses, by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA005
	Coronary revascularisation using 3 arterial grafts with 3 distal anastomoses, by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA003
	Coronary revascularisation using 2 arterial grafts with 3 distal anastomoses, by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA006
	Coronary revascularisation using 2 arterial grafts with 4 or more distal anastomoses, by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA008
	Coronary revascularization with 3 arterial and 4 or more distal venous grafts by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA012
	Coronary revascularisation by arterial and venous graft with 2 distal anastomoses, by thoracotomy with extracorporeal circulation	CCAM procedure code: DDMA011

* Revascularisation procedures are part of the definition of coronary artery disease. Final list of procedures will be fine-tuned based on medical advice and data distribution.

Pregnancy, ICD-10 codes

Pregnancy cessation	ICD-10
Spontaneous abortion	O03
Medical abortion	O04
Other abortion	O05
Unspecified abortion	O06
Preterm labour and delivery	O60
Single delivery by forceps and vacuum extractor	O81
Single delivery by caesarean section	O82

Pregnancy cessation	ICD-10
Other assisted single delivery	O83
Multiple delivery	O84
Ectopic pregnancy	O00
Hydatidiform mole	O01
Other abnormal products of conception	O02
Failed attempted abortion	O07
Complications following abortion and ectopic and molar pregnancy	O08
Pre-existing hypertension complicating pregnancy, childbirth and the puerperium	O10
Pre-existing hypertensive disorder with superimposed proteinuria	O11
Gestational [pregnancy-induced] oedema and proteinuria without hypertension	O12
Gestational [pregnancy-induced] hypertension without significant proteinuria	O13
Gestational [pregnancy-induced] hypertension with significant proteinuria	O14
Eclampsia	O15
Unspecified maternal hypertension	O16
Haemorrhage in early pregnancy	O20
Excessive vomiting in pregnancy	O21
Venous complications in pregnancy	O22
Infections of genitourinary tract in pregnancy	O23
Diabetes mellitus in pregnancy	O24
Malnutrition in pregnancy	O25
Maternal care for other conditions predominantly related to pregnancy	O26
Abnormal findings on antenatal screening of mother	O28
Complications of anaesthesia during pregnancy	O29

Malignant cancer (except skin cancer)

ICD-10	Description
C00	Malignant neoplasm of lip
C01	Malignant neoplasm of base of tongue
C02	Malignant neoplasm of other and unspecified parts
C03	Malignant neoplasm of gum
C04	Malignant neoplasm of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of other and unspecified parts
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of other and unspecified major salivary glands
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of pyriform sinus

ICD-10	Description
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15	Malignant neoplasm of oesophagus
C16	Malignant neoplasm of stomach
C17	Malignant neoplasm of small intestine
C18	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21	Malignant neoplasm of anus and anal canal
C22	Malignant neoplasm of liver and intrahepatic bile
C23	Malignant neoplasm of gallbladder
C24	Malignant neoplasm of other and unspecified parts of biliary tract
C25	Malignant neoplasm of pancreas
C26	Malignant neoplasm of other and ill-defined digest
C30	Malignant neoplasm of nasal cavity and middle ear
C31	Malignant neoplasm of accessory sinuses
C32	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38	Malignant neoplasm of heart, mediastinum and pleura
C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40	Malignant neoplasm of bone and articular cartilage
C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C45	Mesothelioma
C46	Kaposi’s sarcoma
C47	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48	Malignant neoplasm of retroperitoneum and peritoneum
C49	Malignant neoplasm of other connective and soft tissue
C50	Malignant neoplasm of breast
C51	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53	Malignant neoplasm of cervix uteri
C54	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56	Malignant neoplasm of ovary
C57	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta

ICD-10	Description
C60	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C62	Malignant neoplasm of testis
C63	Malignant neoplasm of other and unspecified male genital organs
C64	Malignant neoplasm of kidney, except renal pelvis
C65	Malignant neoplasm of renal pelvis
C66	Malignant neoplasm of ureter
C67	Malignant neoplasm of bladder
C68	Malignant neoplasm of other and unspecified urinary organs
C69	Malignant neoplasm of eye and adnexa
C70	Malignant neoplasm of meninges
C71	Malignant neoplasm of brain
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73	Malignant neoplasm of thyroid gland
C74	Malignant neoplasm of adrenal gland
C75	Malignant neoplasm of other endocrine glands and related structures
C76	Malignant neoplasm of other and ill-defined sites
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
C80	Malignant neoplasm without specification of site
C81	Hodgkin’s disease
C82	Follicular [nodular] non-Hodgkin’s lymphoma
C83	Diffuse non-Hodgkin’s lymphoma
C84	Peripheral and cutaneous T-cell lymphomas
C85	Other and unspecified types of non-Hodgkin’s lymph
C86	Other specified types of T/NK-cell lymphoma
C88	Malignant immunoproliferative diseases
C90	Multiple myeloma and malignant plasma cell neoplasm
C91	Lymphoid leukaemia
C92	Myeloid leukaemia
C93	Monocytic leukaemia
C94	Other leukaemias of specified cell type
C95	Leukaemia of unspecified cell type
C96	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue
C97	Malignant neoplasms of independent (primary), multiple

ANNEX 12. LIST OF DIAGNOSIS CODES FOR VTE

VTE will be identified with the following ICD-10 codes:

Description	ICD-10 codes
Deep vein thrombosis (DVT)	
Phlebitis and thrombophlebitis of femoral vein	I80.1
Phlebitis and thrombophlebitis of other deep vessels of lower extremities	I80.2
Phlebitis and thrombophlebitis of lower extremities, unspecified	I80.3
Deep phlebothrombosis in pregnancy	O22.3
Pulmonary embolism (PE)	
PE with mention of acute cor pulmonale	I26.0
PE without mention of acute cor pulmonale	I26.9

ANNEX 13. LIST OF DIAGNOSIS CODES FOR INDICATIONS

Approved Indication	ICD10 Code	Code Description
Ulcerative colitis	K51	Ulcerative colitis
Rheumatoid arthritis	M05 M06	Rheumatoid arthritis with rheumatoid factor Other rheumatoid arthritis
Psoriatic arthritis	L40.5 L40* (for LTD only) M07.0 M07.1 M07.2 M07.3 M07* (for LTD only)	Arthropathic psoriasis Psoriasis Distal interphalangeal psoriatic arthropathy Arthritis mutilans Psoriatic spondylitis Other psoriatic arthropathies Psoriatic and enteropathic arthropathies

LTD stands for long-term disease registration database

Document Approval Record

Document Name:	A3921403_PROTOCOL- FRANCE DUS_V4.0_26FEB2024
Document Title:	A3921403_PROTOCOL- FRANCE DUS_V4.0_26FEB2024

Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	29-Feb-2024 17:52:13	Final Approval
De Bernardi, Barbara	03-Mar-2024 17:58:00	EUQPPV Approval