NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz® (tofacitinib) in the European Union Using Secondary Data Sources
Protocol number	A3921321
Protocol version identifier	5.0
Date	11 February 2022
EU Post Authorisation Study (PAS) register number	To be registered prior to the start of data collection
Active substance	Tofacitinib ATC (Anatomical Therapeutic Chemical) code: L04AA29
Medicinal product	Tofacitinib (Xeljanz®)
Product reference	EU/1/17/1178/001-14
Procedure number	EMEA/H/C/004214
Marketing Authorisation Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	Is there evidence that prescribers in the European Union (EU) are compliant with the recommendations and limitations for use described in the tofacitinib additional risk minimisation measures (aRMM) materials? The primary objectives are to: 1. Describe the characteristics of patients treated with tofacitinib, stratified by study country (i.e., Sweden, Hungary, the Netherlands, and Germany) and

	indication (i.e., rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis; off-label indications), in terms of: • Demographics (e.g., age, sex); and • Comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically: • Compliance to the recommended posology per indication (average daily dose [ADD]) and duration of use; • Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and • Compliance to recommendations for limitations of use, including: • Use in patients with venous thromboembolism (VTE) risk factors; • Use in patients aged 65 years and older; • Use in patients with cardiovascular (CV) risk factors; • Use in patients with malignancy risk factors; • Contraindicated use; and • Use with concomitant medications not compatible with tofacitinib. The secondary objectives are to: 1. Describe prescribing patterns over time; and

	2. 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 VTE risk factors; • Use in the elderly (patients aged 65 years and older); • Use in patients with CV risk factors; and • Use in patients with malignancy risk factors.
Country(-ies) of study	Sweden, Hungary, the Netherlands, and Germany
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	Average daily dose
AIDS	Acquired immunodeficiency syndrome
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
aRMMs	Additional risk minimisation measures
ATC	Anatomical Therapeutic Chemical (classification)
BID	Bis in die (Latin: twice a day)
BIPS	Leibniz Institute for Prevention Research and Epidemiology—BIPS
BMI	Body mass index
CABG	Coronary artery bypass graft
CCMO	Centrale Commissie Mensgebonden Onderzoek
CDR	[Swedish] Cause of Death Register
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CV	Cardiovascular
CYP	Cytochrome P450 enzyme
DDD(s)	Defined daily dose(s)
csDMARD(s)	Conventional synthetic disease-modifying antirheumatic drug(s)
DALY	Disability adjusted life year
DHPC	Direct healthcare professional communications
DMARD	Disease-modifying antirheumatic drug
DMAID	Disease-modifying anti-inflammatory bowel disease drug
DRG	Diagnosis Related Group
DVT	Deep vein thromboembolism
EBM	Outpatient services (in Germany)
EBV	Epstein-Barr virus
EC	European Commission
EMA	European Medicines Agency
EMR	Electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	[The United States] Food and Drug Administration

Abbreviation	Definition
GePaRD	German Pharmacoepidemiological Research Database
GEP	Good Epidemiological Practice
GKV	Gesetzliche Krankenversicherung (German: public health insurance)
GP(s)	General practitioner(s)
GPP	Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIF	Health Insurance Fund
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
HZ	Herpes zoster
ICD	International Classification of Disease
ICD-10	International Classification of Disease, 10th Revision
ICD-10-GM	International Classification of Disease, 10th Revision, German Modification
ICH	International Conference on Harmonisation
ICPC	International Classification of Primary Care
ICPM	International Classification of Procedures in Medicine
IEA	International Epidemiological Association
IEC	Independent ethics committee
INN	International Non-proprietary Names
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KSHV	Kaposi sarcoma-associated herpesvirus
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular events
MAH	Marketing Authorisation Holder
MBR	[Swedish] Medical Birth Register
mg	Milligram
MI	Myocardial infarction
MTX	Methotrexate
N	Number

Abbreviation	Definition
N/A	Not applicable
NBHW	[Swedish] National Board of Health and Welfare
NHIF	National Health Insurance Fund
NHIFA	National Health Insurance Fund Administration of Hungary
NI	Non-interventional study
NMSC	Non-melanoma skin cancer
NCR	[Swedish] National Cancer Registry
NPR	[Swedish] National Patient Register
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PCI	Percutaneous coronary intervention
PDR	[Swedish] Prescribed Drug Register
PE	Pulmonary embolism
PHI	Private health insurance
PR	Prolonged-release
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic arthritis
Q	Quarter
QC	Quality Control
QD	Quaque die (Latin: once a day)
RA	Rheumatoid arthritis
RMP	Risk management plan
SAP	Statistical analysis plan
SC	Subcutaneous
SD(s)	Standard deviation(s)
SHI	(German) Statutory health insurance
SmPC	Summary of Product Characteristics
SOP(s)	Standard operating procedure(s)
SRQ	Swedish Rheumatology Quality register
TB	Tuberculosis
TG	Triglycerides
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
TNM	Tumour, nodes, metastases
UC	Ulcerative colitis
VTE	Venous thromboembolism
WHO	World Health Organization
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Sponsor

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Subcontractor acting as contracted principal investigator

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Title: A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz® (tofacitinib) in the European Union Using Secondary Data Sources

Version 4.0, 10 September 2021

Main author: Syd Phillips, MPH, IQVIA, Epidemiology & Drug Safety

Rationale and background: Tofacitinib citrate (Xeljanz®) is an oral Janus kinase inhibitor approved by the European Commission (EC) for the treatment of adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC). To minimise important potential and identified 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 there is evidence that prescribers are following 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, as well as the 2021 signal evaluation procedure, the MAH will evaluate healthcare professionals' compliance with the new Pharmacovigilance Risk Assessment Committee (PRAC) 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, and after the signal evaluation procedure to assess use in patients with cardiovascular (CV) risk factors and use in patients with malignancy risk factors.[a]

Research question and objectives: The research question is: Is there evidence that prescribers in the European Union (EU) are compliant with 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, stratified by study country (i.e., Sweden, Hungary, the Netherlands, and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of demographics (e.g., age, sex); and comorbidities and prior and current medication use.

[a] The 2021 signal evaluation procedure also required the evaluation of tofacitinib use in elderly patients aged ≥65 years, however, this assessment had already been added to the protocol following the findings from the 2019 Article 20 referral.

2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically:

    - Compliance to the recommended posology per indication (average daily dose [ADD]) and duration of use;
    - Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and
    - Compliance to recommendations for limitations of use, including:
        - Use in patients with VTE risk factors;
        - Use in patients aged 65 years and older;
        - Use in patients with CV risk factors;
        - Use in patients with malignancy risk factors;
        - Contraindicated use; and
        - Use with concomitant medications not compatible with tofacitinib.

The secondary objectives are to:

1. Describe prescribing patterns over time; and
2. 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 VTE risk factors; use in the elderly (patients aged 65 years and older); use in patients with CV risk factors; and use in patients with malignancy risk factors.

Note: In Gesetzliche Krankenversicherung (GKV) claims (Germany), outpatient diagnoses are reported quarterly, which could result in the misclassification of baseline clinical characteristics and select outcomes of interest, impacting all objectives except for primary objective 2.

In the PHARMO Database Network, the high-budget impact medication dataset contains only declared medication for approved indications. It might not be possible to determine off-label use in this dataset.

The objectives and sub-objectives that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), where tofacitinib use is captured, neither ADD nor the number of pills per prescription is captured.

The sub-objective that evaluates "prescribers' adherence to the tofacitinib aRMMs, specifically, compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment" will *not* be assessed in Sweden because the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, it may not be possible to differentiate an absolute lymphocyte count (ALC) laboratory test from an absolute neutrophil count (ANC) laboratory test, or an alanine aminotransferase (ALT) laboratory test from an aspartate aminotransferase (AST) laboratory test. In the PHARMO Database Network, tuberculosis (TB) screening and viral hepatitis B and C testing are not captured.

Study design: This will be a descriptive drug utilisation study using secondary data collected from databases in Sweden, Hungary, the Netherlands, and Germany. The study observation period will be 01 April 2016 through 31 December 2024. All results will be stratified by study country and approved indication (i.e., RA, PsA, and UC).

Population: Patients will be included in the study if they have ≥1 prescription dispensing of tofacitinib during the indexing period, 12 months of available medical history before and 12 months after the index tofacitinib dispensing, and 0 prescription dispensings of tofacitinib in the 12 months prior to the indexing period.

Variables: Demographic characteristics (age, sex), diagnoses (indication [including off-label indications], comorbidities, contraindicated use, VTE risk factors, CV risk factors, malignancy risk factors), patients 65 years and older with no alternative treatments prior to initiation of tofacitinib, prior and current medications, procedures (including screening and monitoring tests), ADD, and duration of tofacitinib therapy will be examined.

Data sources: This study will use the Swedish national health registers: National Patient Register (NPR), the Swedish Prescribed Drug Register (PDR), the Swedish Medical Birth Register (MBR), the Swedish National Cancer Registry (NCR), and the Swedish Cause of Death Register; in Hungary, the National Health Insurance Fund Administration (NHIFA), an administrative claims database; in the Netherlands, the PHARMO Database Network, a population-based network of electronic healthcare databases; and in Germany, GKV claims, an administrative claims database.

Data analysis: The primary analyses will be conducted per country and per indication (unless otherwise specified). Data will *not* be pooled across countries due to heterogeneity in: how the data are recorded in each database, local data protection laws, and prescribing and coding practices. Results will be provided as descriptive statistics; no comparative statistical analyses will be conducted. Reporting of the VTE-related outcomes, use among patients 65 years and older, CV-related outcomes, and malignancy-related outcomes will be stratified by time prior to and after the distribution of the revised aRMM materials consequential of the 2019 Article 20 procedure and subsequently, the 2021 signal procedure.

Milestones: Data collection (extraction) will begin 30 September 2022 and end 31 October 2026. The first interim study report will be submitted by 31 August 2023, and the second by 31 August 2025; the final study report will be submitted by 31 October 2027.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	04 September 2020	Cover page	• Updated protocol title and countries of study to include Hungary • Revised research question and objectives • Updated contact information for a protocol author; added one author and removed one author	• Pharmacovigilance Risk Assessment Committee (PRAC) request and clarifications • Change in contact information for a protocol author • Study staff transition for the Marketing Authorisation Holder's (MAH's) vendor
		2. List of Abbreviations	• Added abbreviations	• Abbreviations added to revised study protocol when incorporating PRAC's feedback
		4. Abstract	• Updated number of countries in protocol title to reflect that Hungary was added as a study country • Made clarifying edits throughout • Revised research question and objectives • Added Hungary as a study country • Revised submission date for final study report to occur 12 months after the end of data collection	• PRAC request and clarifications • Prior submission date for final study report was only 11 months after the end of data collection
		6. Milestones	• Revised submission date for final study report to occur 12 months after the end of data collection • Added footnote stating that if a given study country needed to extend Reporting Period 3 because the minimum target sample size had not been reached for all three indications, the study countries meeting the minimum target sample size for all three indications would submit a second interim report and the final study report for all study countries and all indications would be submitted no later than the planned date of 31 October 2025	• Prior submission date for final study report was only 11 months after the end of data collection • PRAC request and clarifications
		7. Rationale and Background	• Made clarifying edits throughout • Added Hungary as a study country to Table 2 • Added additional language related to the secondary objective (i.e., changes in the utilisation of tofacitinib among patients with venous thromboembolism [VTE] risk factors and among elderly patients following the updated	• PRAC request and clarifications

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			recommendations and limitations for use)	
		8. Research Question and Objectives	• Revised research question and objectives • Added Hungary as a study country	• PRAC request and clarifications
		9.1. Study design	• Added Hungary as a study country • Made clarifying edits throughout	• PRAC request and clarifications
		9.2. Setting	• Added Hungary as a study country • Revised length of Reporting Period 1 from '26-month period' to 'up-to-26-month period' • Revised Figure 1 to correct a typo • Made clarifying edits throughout • Added language related to revised study objectives	• PRAC request and clarification • Length of Reporting Period 1 revised to account for the different dates rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC) received full reimbursement in Sweden and Germany • Figure 1 contained a typo in 'start [date] of distribution and uptake of VTE-revised additional risk minimisation measures (aRMM) materials'
		9.3.1. Outcomes	• Revised and reorganized study outcomes to align with revised study objectives • Made clarifying edits throughout	• PRAC request and clarifications
		9.3.2. Variable definitions	• Revised and reorganized study variable definitions (Table 3) to align with revised study objectives • Added 'hepatic impairment' as a comorbidity of interest • Made clarifying edits throughout • Added a Hungary database-specific definition to the two pregnancy variables	• PRAC request and clarifications
		9.4. Data sources	• Added the Swedish National Cancer Registry (NCR) as another data source for Sweden • Added the National Health Insurance Fund Administration (NHIFA) of Hungary as a data source • Made clarifying edits throughout • Added NHIFA to Table 4 as a data source • Updated the expected number of tofacitinib patients by the end of 2021 in Sweden	• The NCR will be used in Sweden to assess malignancy (a comorbidity of interest) • PRAC request and clarifications
		9.5. Study size	• Made clarifying edits throughout • Added clarifying language regarding the minimum target sample size • Added Table 5, which shows the minimum number of patients required to achieve a	• PRAC request and clarifications

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			select confidence interval width • Added Section 9.5.1. Feasibility counts, which provides estimates for potential sample size across the three indications in each study country	
		9.7. Data analysis	• Revised and reorganized section to align with revised study objectives • Made clarifying edits throughout	• PRAC request and clarifications
		9.8. Quality control	• Added NHIFA as a data source	• PRAC request and clarifications
		9.9. Limitations of the research methods	• Added Hungary as a study country • Made clarifying edits throughout • Added the possible limitation of there not being robust capture of laboratory tests in some of the data sources (e.g., Sweden) • Added the limitation of not being able to distinguish new VTE from prior VTE if both occur during the same 12-month period in the Swedish national health registers • Added the limitation of assessing age in the German Pharmacoepidemiological Research Database (GePaRD), which only has year of birth and not date of birth and its impact on the objectives assessing tofacitinib use among patients aged 65 years and older • Added the limitation that Hungary will not have a Reporting Period 1 for any indication and also will not have a Reporting Period 2 for the PsA and UC indications. • Added the potential limitation of sample size in Hungary, given that PsA and UC are not currently fully reimbursed and are only available through the Named Patient Program	• PRAC request and clarifications
		10.1. Patient information	• Added relevant information for NHIFA of Hungary	• PRAC request and clarifications
		10.2. Patient consent	• Added relevant information for NHIFA of Hungary	• PRAC request and clarifications
		10.4. Institutional	• Added relevant information for NHIFA of Hungary	• PRAC request and clarifications

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		review board (IRB) / Independent ethics committee (IEC)		
		13. References	• Added references	• References added to revised study protocol when incorporating PRAC's feedback
		14. List of Tables	Added the following tables: • Table 5. Number of patients required to achieve select confidence interval widths; • Table 6. Tofacitinib patient counts through March 2020 in the NHIFA of Hungary; • Table 7. Annual tofacitinib patient counts in the Swedish Prescription Drug Register (2017-2019); and • Table 8. Summary of expected distribution of biologics across indications (RA, PsA, UC) in Sweden and Germany	• PRAC request and clarifications
		Annex 2. ENCePP Checklist for Study Protocols	• Updated number of countries in protocol title to reflect that Hungary was added as a study country • Added Section Number 9.5.1 to row 12.2 Does the protocol discuss study feasibility?	• Minor modifications to the checklist were required after incorporating the PRAC's feedback
2	15 December 2020	Cover page	• Updated protocol title to reflect that Germany was removed as a country of study and changed "Administrative Claims Databases and National Registries" to "Secondary Data Sources" • Removed Germany from the 'Research question and objectives' section • Removed Germany from the 'Country(ies) of study' section • Updated the title of one of the protocol authors	• The German Pharmacoepidemiological Research Database (GePaRD) was removed from the protocol due to the withdrawal of the Leibniz Institute for Prevention Research and Epidemiology—BIPS from the study. BIPS is the gatekeeper of GePaRD and the MAH cannot access GePaRD without their participation and collaboration. • Protocol title was edited to refer to "Secondary Data Sources" so that the MAH would not need to modify the protocol title in the future if different types of data sources (identified during the expanded data landscaping exercise) are added to the study
		2. List of abbreviations	• Removed some abbreviations specific to Germany	• Removal of GePaRD as a data source from the protocol
		4. Abstract	• Updated protocol title to reflect that Germany was removed as a country of study and changed "Administrative Claims Databases and National Registries" to "Secondary Data Sources"	• Removal of GePaRD as a data source from the protocol • Protocol title was edited to refer to "Secondary Data Sources" so that the MAH would not need to modify the protocol title in the future if different types of data sources (identified during the

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			• Removed Germany from the 'Research question and objectives' section • Noted that the Swedish national health registers do not capture the laboratory tests of interest • Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy • Removed Germany from the 'Study design' section and updated the study period dates accordingly • Removed GePaRD from the 'Data sources section'	expanded data landscaping exercise) are added to the study • PRAC request and clarifications
		5. Amendments and updates	• Minor editorial update	• Minor editorial update
		6. Milestones	• Updated the time periods that the interim and final study reports will cover	• Removal of GePaRD as a data source from the protocol
		7. Rationale and background	• Removed Germany as a country of study in Table 2	• Removal of GePaRD as a data source from the protocol
		8. Research question and objectives	• Removed Germany from the study objectives • Noted that the Swedish national health registers do not capture the laboratory tests of interest • Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• Removal of GePaRD as a data source from the protocol • PRAC request and clarifications
		9.1. Study design	• Removed Germany as a country of study	• Removal of GePaRD as a data source from the protocol
		9.2. Setting	• Removed Germany as a country of study • Updated the length and beginning of the study observation period to 80 months and 1 May 2016, respectively • Updated the length and beginning of the indexing period to 56 months and 1 May 2017, respectively • Updated the length and beginning of Reporting Period 1 to 'up to 25 months' and 1 May 2017, respectively • Made the above changes to Figures 1 and 2	• Removal of GePaRD as a data source from the protocol
		9.2.2. Exclusion criteria	• Removed Germany as a country of study • Removed the date of the earliest original aRMM	• Removal of GePaRD as a data source from the protocol

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			materials distribution for an indication for Germany (April 2017)	
		9.3.1. Outcomes	• Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy • Noted that the Swedish national health registers do not capture the laboratory tests of interest	• PRAC request and clarifications
		9.3.2. Variable definitions	• Removed references to EBM services codes (outpatient services in Germany) and the GePaRD pregnancy algorithm due to the removal of Germany as a country of study • Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy • Noted that the Swedish national health registers do not capture the laboratory tests of interest • Clarified that the abbreviation NHIFA referred to "the Hungarian administrative claims database"	• Removal of GePaRD as a data source from the protocol • PRAC request and clarifications • Editorial changes
		9.3.3. Duration of tofacitinib therapy	• Added the proxy that will be used for 'duration' in the Hungarian administrative claims database	• PRAC request and clarifications
		9.3.4. Average daily dose	• Replaced 'GePaRD' with 'Sweden' in the example operational definition provided for ADD • Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• Removal of GePaRD as a data source from the protocol • PRAC request and clarifications
		9.4. Data sources	• Removed GePaRD as a data source	• Removal of GePaRD as a data source from the protocol
		9.4.1. Germany: German Pharmacoepidemiological Research Database (GePaRD)	• Removed entire section describing GePaRD	• Removal of GePaRD as a data source from the protocol
		9.4.3. Summary of databases (previously 9.4.4. Summary of databases)	• Removed content specific to GePaRD in Table 4 (including table footnotes); re-ordered remaining table footnotes accordingly	• Removal of GePaRD as a data source from the protocol

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.5. Study size	• Removed Germany as a country of study and updated the total study size numbers accordingly	• Removal of GePaRD as a data source from the protocol
		9.5.1. Feasibility counts	• Removed Germany as a country of study • Removed in-text references to the time periods for the German studies included in Table 8; added the time period for the Swedish PsA study included in Table 8 • Removed content specific to Germany and/or GePaRD from Table 8	• Removal of GePaRD as a data source from the protocol
		9.7. Data analysis	• Updated the time periods that the interim and final study reports will cover	• Removal of GePaRD as a data source from the protocol
		9.7.1 Primary Analysis	• Removed the example provided for 'local data protection laws,' as it was specific to GePaRD	• Removal of GePaRD as a data source from the protocol
		9.7.1.2.1. Compliance to the recommended posology per indication and duration of use	• Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• PRAC request and clarifications
		9.7.1.2.2. Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment	• Noted that the Swedish national health registers do not capture the laboratory tests of interest	• PRAC request and clarifications
		9.7.1.2.2.1.1. Patients with VTE risk factors	• Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• PRAC request and clarifications
		9.7.1.3. Secondary Objectives 1 and 2: Describe prescribing patterns; and Describe changes in tofacitinib prescribing patterns (utilisation) following the updated	• Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• PRAC request and clarifications

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		recommendations and limitations for use implemented after the 2019 Article 20 referral		
		9.7.1.3.1. Use in patients with VTE risk factors	• Noted that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy	• PRAC request and clarifications
		9.8. Quality control	• Removed reference to BIPS due to the removal of GePaRD as a data source	• Removal of GePaRD as a data source from the protocol
		9.9 Limitations of the research methods	• Removed Germany as a country of study; removed GePaRD as a data source; and removed all limitations related to Germany and/or GePaRD • Added the limitation that the Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy • Added the limitation that the Swedish national health registers do not capture the laboratory tests of interest • Minor editorial updates	• Removal of GePaRD as a data source from the protocol • PRAC request and clarifications • Minor editorial updates
		10.1. Patient information	• Removed information about how patient data are anonymised in GePaRD	• Removal of GePaRD as a data source from the protocol
		10.2 Patient consent	• Removed information about the Code of Social Law, which regulates how statutory health insurance (SHI) data can be used for scientific research in Germany	• Removal of GePaRD as a data source from the protocol
		10.4. Institutional review board (IRB) / Independent ethics committee (IEC)	• Removed 'SHI board(s)' due to removal of Germany as a country of study	• Removal of GePaRD as a data source from the protocol
		13. References	• Removed references specific to Germany and/or GePaRD	• Removal of GePaRD as a data source from the protocol
		14. List of tables	• Removed Germany from the title of Table 8. Summary of expected distribution of biologics across indications (RA, PsA, UC) in Sweden	• Removal of GePaRD as a data source from the protocol
		Annex 2. ENCePP checklist for	• Updated protocol title to reflect that Germany was removed as a country of study and changed "Administrative Claims	• Removal of GePaRD as a data source from the protocol • Protocol title was edited to refer to "Secondary Data Sources" so

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		study protocols	Databases and National Registries" to "Secondary Data Sources"	that the MAH would not need to modify the protocol title in the future if different types of data sources (identified during the expanded data landscaping exercise) are added to the study
		Annex 4. List of diagnosis and procedure codes for interstitial lung disease	• Removed language specific to Germany, which noted that diagnosis codes for interstitial lung disease are available with 4 digits only in Germany	• Removal of GePaRD as a data source from the protocol
3	21 September 2021	Cover page	• Revised the EU Post Authorisation Study (PAS) register number information • Updated the primary and secondary objectives to include the new limitations of use in patients with CV risk factors and malignancy risk factors • Updated the objectives to include the Netherlands and Germany • Updated the study country(ies) to include the Netherlands and Germany • Changed title for Syd Phillips and addresses for Amanda Anderson and Laura Walsh; removed Susan Oliveria as an author	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings • Administrative update
		2. List of Abbreviations	• Updated abbreviations	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings • Replaced the Swedish Pregnancy Register with the Swedish MBR and added acronyms for the Swedish Cause of Death Register and the National Board of Health and Welfare (NBHW) • Removed acronyms used only in Annex 8, which has been removed from the protocol
		3. Responsible Parties	• Changed the subcontractor acting as contracted principal investigator from Susan Oliveria to Syd Phillips	• Administrative update
		4. Abstract	• Changed the main author from Susan Oliveria to Syd Phillips • Added background information about the 2021 signal evaluation procedure for the risk of CV events and malignancies excluding non-melanoma skin cancer (NMSC) • Updated the primary and secondary objectives, variables, and data analysis sections of the Abstract to include the new limitations of	• Administrative update • 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings • The Swedish Pregnancy Register was replaced with the Swedish MBR because the MBR is more closely aligned with the variables needed for the study. Additionally, the MBR is managed by the National Board of

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			use in patients with CV risk factors and malignancy risk factors • Updated objectives to include the Netherlands and Germany • Added limitations of the Dutch and German data sources • Editorial changes • Revised end of observation period • Replaced the Swedish Pregnancy Register with the Swedish Medical Birth Register (MBR) • Added the Swedish Cause of Death Register • Revised milestones to accommodate the extension of the observation period as a result of the study objectives added	Health and Welfare (NBHW), like the other proposed Swedish national health registers, making data access and linkage easier. • The Swedish Cause of Death Register was added to the protocol because it provides date of death
		6. Milestones	• Revised milestones to accommodate the extension of the observation period as a result of the study objectives added • Revised the EU Post Authorisation Study (PAS) register number information • Removed Final study report note	• 2021 signal evaluation procedure findings
		7. Rationale and Background	• Added background information about the 2021 signal evaluation procedure for the risk of CV events and malignancies excluding NMSC • Revised date of full reimbursement for PsA and UC in Hungary • Revised actual or anticipated start date of distribution of the 2021 signal evaluation procedure aRMM materials • Updated Table 2 to include the Netherlands and Germany • Added limitation of use in patients with CV risk factors and malignancy risk factors	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		8. Research Question and Objectives	• Added limitation of use in patients with CV risk factors and malignancy risk factors • Updated the objectives to include the Netherlands and Germany • Added limitations of the Dutch and German data sources • Added information regarding the 2021 signal evaluation procedure for the risk of CV events and malignancies excluding NMSC	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.1 Study Design	• Updated to include the Netherlands and Germany	• 2021 data landscaping and sourcing feasibility assessment findings
		9.2 Setting	• Revised end of observation period and indexing period to accommodate the new objectives added to the study • Revised date of full reimbursement for PsA and UC in Hungary • Added limitation of use in patients with CV risk factors and malignancy risk factors and the corresponding observation, indexing, and reporting periods • Indicated Reporting Periods 2 and 3 for the Netherlands will be adjusted accordingly in the SAP to reflect implementation of the 2021 signal evaluation procedure aRMMs in Q1 2022 • Revised Figure 1 and Figure 2 and added two additional figures	• 2021 signal evaluation procedure findings
		9.3.1 Outcomes	• Clarifying edits • Added limitation of use in patients with CV risk factors and malignancy risk factors • Added information regarding the 2021 signal evaluation procedure for the risk of CV events and malignancies excluding NMSC • Added that use in the elderly will also be assessed in the CV and Malignancy Reporting Periods 1, 2, and 3 • Added footnote that Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC • Added footnote that the study outcomes that contain a vaccination component will not be assessed in Sweden • Updated footnotes to include the limitations of the Dutch and German data sources • Updated abbreviation	• 2021 signal evaluation procedure findings • Additional information was obtained regarding the Swedish data sources • 2021 data landscaping and sourcing feasibility assessment findings
		9.3.2 Variable definitions	• Added footnote that the study outcomes that contain a vaccination component will not be assessed in Sweden • Added footnote that the study outcomes that contain an ADD component will not be assessed in Hungary • Made clarifying edits to the VTE-related variable definitions	• Additional information was obtained regarding the Swedish data sources • 2021 signal evaluation procedure findings • The Swedish Pregnancy Register was replaced with the Swedish MBR because the MBR is more closely aligned with the variables needed for the study. Additionally, the MBR is

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			• Added limitation of use in patients with CV risk factors and malignancy risk factors • Replaced the Swedish Pregnancy Register with the Swedish MBR • Revised footnotes • Added that use in the elderly will also be assessed in the CV and Malignancy Reporting Periods 1,2, and 3 • Updated footnotes to include the limitations of the Dutch and German data sources • Added abbreviations	managed by the NBHW, like the other proposed Swedish national health registers, making data access and linkage easier. • 2021 data landscaping and sourcing feasibility assessment findings
		9.3.4 Average Daily Dose	• Clarifying edits • Updated to include the limitations of the Dutch data source	• Clarification • 2021 data landscaping and sourcing feasibility assessment findings
		9.4 Data sources	• Replaced the Swedish Pregnancy Register with the Swedish MBR • Added the Swedish Cause of Death Register • Updated to include the PHARMO Database Network in the Netherlands and GKV claims in Germany	• The Swedish Pregnancy Register was replaced with the Swedish MBR because the MBR is more closely aligned with the variables needed for the study. Additionally, the MBR is managed by the NBHW, like the other proposed Swedish national health registers, making data access and linkage easier. • The Swedish Cause of Death Register was added to the protocol because it provides date of death • 2021 data landscaping and sourcing feasibility assessment findings
		9.4.1 Sweden: The National Patient Register, the Prescribed Drug Register, the Swedish Medical Birth Register, the National Cancer Registry, the Cause of Death Register	• Replaced the Swedish Pregnancy Register with the Swedish MBR • Revised the description of the NCR • Added the Swedish Cause of Death Register • Revised the data lag for Swedish registries • Revised abbreviation	• The Swedish Pregnancy Register was replaced with the Swedish MBR because the MBR is more closely aligned with the variables needed for the study. Additionally, the MBR is managed by NBHW, like the other proposed Swedish national health registers, making data access and linkage easier. • The Swedish Cause of Death Register was added to the protocol because it provides date of death • Additional information was obtained regarding the Swedish data sources
		9.4.3. The Netherlands: The PHARMO Database Network	• Added section for the PHARMO Database Network	• 2021 data landscaping and sourcing feasibility assessment findings
		9.4.4. Germany: Gesetzliche	• Added section for GKV claims	• 2021 data landscaping and sourcing feasibility assessment findings

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Krankenversicherung (GKV) claims (SHI Database)		
		9.4.5 Summary of Databases	• Replaced the Swedish Pregnancy Register with the Swedish MBR • Added the Swedish Cause of Death Register • Updated to include the PHARMO Database Network in the Netherlands and GKV claims in Germany • Revised country population for all countries • Added abbreviations and footnotes to Table 4 • Revised the data lag for Swedish registries	• The Swedish Pregnancy Register was replaced with the Swedish MBR because the MBR is more closely aligned with the variables needed for the study. Additionally, the MBR is managed by NBHW, like the other proposed Swedish national health registers, making data access and linkage easier. • The Swedish Cause of Death Register was added to the protocol because it provides date of death • 2021 data landscaping and sourcing feasibility assessment findings • Additional information was obtained regarding the Swedish data sources
		9.5 Study size	• Clarifying edits • Added justification of sample size • Revised minimum target sample size overall to 1200 patients	• 2021 signal evaluation procedure findings
		9.5.1 Feasibility Counts	• Clarifying edits • Revised the date of full reimbursement for PsA and UC in Hungary • Added Table 9 and Table 10 to include feasibility counts for the PHARMO Database Network and GKV claims	• 2021 signal evaluation procedure findings • The date of full reimbursement for PsA and UC in Hungary is now Q1 2023 • 2021 data landscaping and sourcing feasibility assessment findings
		9.7 Data analysis	• Revised the dates for the final study report • Added next steps if the minimum target sample size of 100 patients per indication is not attainable for a country	• 2021 signal evaluation procedure findings
		9.7.1.1. Primary Objective 1: Demographics, comorbidities, and prior and current medications	• Updated footnotes to include the limitations of the Dutch and German data sources	• 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.2.1 Compliance to the recommended posology per indication and	• Updated footnotes to include the limitations of the Dutch data source	• 2021 data landscaping and sourcing feasibility assessment findings

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		duration of use		
		9.7.1.2.2. Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment	• Updated footnotes to include the limitations of the Dutch and German data sources	• 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.2.2.1.1. Patients with VTE risk factors	• Updated footnotes to include the limitations of the German data source	• 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.2.2.1.3 Patients with CV Risk Factors	• Added limitation of use in patients with CV risk factors	• 2021 signal evaluation procedure findings
		9.7.1.2.2.1.4 Patients with Malignancy Risk Factors	• Added limitation of use in patients with malignancy risk factors	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.3 Secondary Objectives 1 and 2: Describe prescribing patterns; and Describe changes in tofacitinib prescribing patterns (utilisation) following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral	• Added information regarding 2021 signal evaluation procedure for the risk of CV events and malignancies excluding NMSC • Updated to include the limitations of the Dutch and German data sources	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.3.1 Use in patients with VTE risk factors	• Clarifying edits • Added footnote to include the limitations of the German data source	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		9.7.1.3.2 Use in the elderly (patients aged	• Clarifying edits • Added that use in the elderly will also be assessed in the CV	• 2021 signal evaluation procedure findings

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		65 years and older)	and Malignancy Reporting Periods 1,2, and 3	
		9.7.1.3.3 Use in patents with CV risk factors	• Added limitation of use in patients with CV risk factors • Added footnote that Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC	• 2021 signal evaluation procedure findings
		9.7.1.3.4 Use in patients with malignancy risk factors	• Added limitation of use in patients with malignancy risk factors • Added footnote to include the limitations of the German data source	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		9.8 Quality Control	• Updated to include the PHARMO Database Network and GKV claims	• 2021 data landscaping and sourcing feasibility assessment findings
		9.9 Limitations of Research Methods	• Clarifying edits • Added language related to reducing the increased risk of CV-related outcomes and malignancy-related outcomes • Added that Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC • Updated to include the limitations of the Dutch and German data sources	• 2021 signal evaluation procedure findings • 2021 data landscaping and sourcing feasibility assessment findings
		10.1 Patient information	• Clarified the information for the Swedish registries • Updated to include the Netherlands and Germany	• Additional information was obtained regarding the Swedish data sources • 2021 data landscaping and sourcing feasibility assessment findings
		10.2 Patient consent	• Clarified the information for the Swedish registries • Updated to include the Netherlands and Germany	• Additional information was obtained regarding the Swedish data sources • 2021 data landscaping and sourcing feasibility assessment findings
		10.4 Institutional review board (IRB) / Independent ethics committee (IEC)	• Updated to include the Netherlands and Germany	• 2021 data landscaping and sourcing feasibility assessment findings
		10.5 Ethical Conduct of the Study	• Added that the study protocol and information about the study will be sent to the Swedish Medical Products Agency	• Additional information was obtained regarding the procedure in Sweden
		14. List of Tables	• Added Table 9. Tofacitinib patient counts (through 2019)	• 2021 data landscaping and sourcing feasibility assessment findings

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			in the PHARMO Database Network of the Netherlands • Added Table 10. Tofacitinib patients counts (2017-2019) in GKV Claims of Germany	
		15. List of Figures	• Revised Figure 1 and Figure 2 and added two additional figures	• 2021 signal evaluation procedure findings
		Annex 8. aRMM Materials	• Annex 8, which included the aRMM materials, was removed	• The aRMM materials are subject to change throughout the course of the study
4	09 February 2022	Section 2 List of Abbreviations	• Addition of relevant abbreviations	• Minor editorial update
		9.3.2 Variable definitions	• Added CV and malignancy risk factors • Addition of abbreviations and spelling changes throughout Table 3, and the addition of table footnote 'x' in Section 9.3.2	• Additional CV and malignancy risk factors added as requested by the PRAC • Minor editorial updates
		9.7.1.2.2.1.3 Patients with CV risk factors	• Added current or past smoker, hypertension, hyperlipidaemia, chronic kidney disease, and stable angina pectoris as CV risk factors	• Additional CV risk factors added as requested by the PRAC
		9.7.1.2.2.1.4 Patients with malignancy risk factors	• Added current or past smoker as malignancy risk factors	• Additional malignancy risk factors added as requested by the PRAC
		9.7.1.3.3 Use in patients with CV risk factors	• Added current or past smoker, hypertension, hyperlipidaemia, chronic kidney disease, and stable angina pectoris as CV risk factors	• Additional CV risk factors added as requested by the PRAC
		9.7.1.3.4 Use in patients with malignancy risk factors	• Added current or past smoker as malignancy risk factors	• Additional malignancy risk factors added as requested by the PRAC
		9.9 Limitations of the research methods	• Removed smoking status as a variable that is under-captured in administrative databases and thus will not be reported due to the concern of a high level of missingness • Added limitations of the added CV and malignancy risk factors • Minor editorial changes	• Additional CV and malignancy risk factors added as requested by the PRAC • Minor editorial changes
		Annex 8. List of ATC codes for antihypertensives	• Added Annex 8 to provide the list of ATC codes for antihypertensives	• Additional CV risk factors added as requested by the PRAC

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Annex 9. List of ATC codes for antihyperlipidaemics	• Added Annex 9 to provide the list of ATC codes for antihyperlipidaemics	• Additional CV risk factors added as requested by the PRAC

6. MILESTONES

Milestone	Planned date
Start of data collection[a]	Estimated 30 September 2022
End of data collection[a]	Estimated 31 October 2026
Interim study report 1	Estimated 31 August 2023
Interim study report 2	Estimated 31 August 2025
Registration in the EU PAS register	To be registered prior to the start of data collection
Final study report	Estimated 31 October 2027[b]

Abbreviations: EU = European Union; MAH = Marketing Authorisation Holder; PAS = Post-authorisation studies.

a. Start and end of data collection refer to the start and end of data *extraction*, respectively, due to the approximate 2-year data lag associated with the databases. Interim study report 1 will cover data from 01 April 2016 through 31 December 2020. Interim study report 2 will cover data from 01 April 2016 through 31 December 2022. The final study report will cover data from 01 April 2016 through 31 December 2024.

b. If it is necessary to extend the study observation period for a country because the *minimum* number of tofacitinib patients (100 patients) per indication has not been met for all three indications by the end of the study observation period, the study observation period will be extended for those countries as the data are available and the MAH will submit the final study report later than 31 October 2027. For those countries that have met the *minimum* patient threshold of at least 100 tofacitinib patients per indication for all three indications at the end of the study observation period, a second interim study report will be submitted within 12 months after the planned end of data collection.

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 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 characterized 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 for the treatment of moderate-to-severe active RA is 5 mg BID or prolonged-release 11 mg QD, which should not be exceeded, in combination with MTX; it may also be given as monotherapy in the case of intolerance to MTX or when treatment with MTX is inappropriate.[4]

In June 2018, tofacitinib 5-mg tablet (immediate-release) 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%-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, which should not be exceeded.[4]

Finally, in July 2018, tofacitinib 5-mg tablet and 10-mg tablet (immediate release) were approved by the EC for the treatment of moderately-to-severely active ulcerative colitis (UC) in patients with an inadequate response, a loss of response, or an intolerance to conventional therapy or a biologic agent. UC is a bowel disease characterized 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.

The following table summarizes the date tofacitinib was approved by the EC and the approved dose for each of the 3 approved indications as of June 2021.

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
UC	July 2018	5 mg or 10 mg immediate-release tablets BID

Abbreviations: EC = European Commission; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

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 and mortality arising in an ongoing Pfizer-sponsored Phase 3b/4 safety study (A3921133) 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, based on a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC), that patients treated with tofacitinib are at increased risk of venous thromboembolism (VTE) events, both for deep venous thrombosis as well as pulmonary embolism, 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 treatment 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 tumour necrosis factor [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 treatment is available. These conclusions and revisions to the SmPC were approved by the EC on 31 January 2020.

Subsequently, in June 2021, as a result of a signal evaluation procedure (EPITT number 19382) to assess the increased incidence rate of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients treated with tofacitinib for RA, the European Medicines Agency (EMA) concluded that myocardial infarction (MI), lung cancer, and lymphoma were important identified risks. To minimise these risks, and the important 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.

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 program designed to increase awareness of the risks of tofacitinib in each member state of the European Union (EU). This program consists of routine (i.e., SmPC and patient package insert) and additional risk minimisation measures (aRMMs; i.e., 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., minimizing the risk of VTE events among patients treated with tofacitinib), with distribution of these "Article 20-VTE-revised aRMM materials" to the member states beginning in February 2020 (Table 2; termed "2019 Article 20 referral aRMM materials" hereafter). 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 malignancies excluding NMSC among patients treated with tofacitinib), with distribution of these "CV and Malignancy-revised aRMM materials" to the member states anticipated to begin in Q4 2021 (Table 2; termed "2021 signal evaluation procedure aRMM materials" hereafter).

Table 2. Dates for full reimbursement of tofacitinib and full distribution of the original, 2019 Article 20 referral, and 2021 signal evaluation procedure aRMM materials

Country	Indication	Date of full reimbursement	Date of full distribution of the original aRMM materials	Actual or anticipated start date of distribution of the 2019 Article 20 referral or 2021 signal evaluation procedure aRMM materials	
				2019 Article 20 referral	2021 signal evaluation procedure
Sweden	RA	April 2017	May 2017	March 2020	Q4 2021
	PsA	October 2018	July 2018		
	UC	October 2018	September 2018		
Hungary	RA	May 2019	December 2018	September 2020	Q4 2021
	PsA	Anticipated Q1 2023[a]	N/A		
	UC	Anticipated Q1 2023[a]	N/A		
The Netherlands	RA	May 2017	May 2017	May 2020	Q1 2022
	PsA	August 2018	September 2018		
	UC	September 2018	September 2018		
Germany	RA	May 2017	April 2017	March 2020	Q4 2021
	PsA	June 2018	July 2018		
	UC	July 2018	September 2018		

Abbreviations: aRMM = additional risk minimisation measures; N/A = not applicable; PsA = psoriatic arthritis; Q = quarter; RA = rheumatoid arthritis; UC = ulcerative colitis.

a. Currently available via the Named Patient Program.

A comprehensive plan was proposed to assess the effectiveness of the aRMM program, 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 realise these 2 components, the MAH proposed 2 post-authorisation safety studies with the aim of evaluating the effectiveness of the aRMM program:

1. A survey of tofacitinib prescribers; and

2. A drug utilisation study to assess prescribing patterns of tofacitinib and whether there is evidence that prescribers are compliant with 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.

As a result of the Article 20 benefit-risk reassessment, the MAH will additionally evaluate HCPs' compliance with 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' compliance with 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.[b] The MAH will also examine tofacitinib prescribing patterns over time in the context of the 2021 signal evaluation procedure outcome.

This protocol describes the drug utilisation study (i.e., component 2 described above). Data from this study, together with the findings from the tofacitinib prescriber survey (A3921334), will be used to assess whether the aRMM materials are effective. This non-interventional (NI) study is designated as a Post-Authorisation Safety Study (PASS) and is conducted by the MAH as a Category 3 commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is: Is there evidence that prescribers in the EU are compliant with 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, stratified by study country (i.e., Sweden, Hungary, the Netherlands, and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of:

    - Demographics (e.g., age, sex); and
    - Comorbidities and prior and current medication use.

[b] The 2021 signal evaluation procedure also required the evaluation of tofacitinib use in elderly patients aged ≥65 years, however, this assessment had already been added to the protocol following the findings from the 2019 Article 20 referral.

2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically:

    - Compliance to the recommended posology per indication (average daily dose [ADD]) and duration of use;
    - Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and
    - Compliance to recommendations for limitations of use, including:
        - Use in patients with VTE risk factors;
        - Use in patients aged 65 years and older;
        - Use in patients with CV risk factors;
        - Use in patients with malignancy risk factors;
        - Contraindicated use; and
        - Use with concomitant medications not compatible with tofacitinib.

The secondary objectives are to:

1. Describe prescribing patterns over time; and
2. 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 VTE risk factors;
    - Use in the elderly (patients aged 65 years and older);
    - Use in patients with CV risk factors; and
    - Use in patients with malignancy risk factors.

Note: In Gesetzliche Krankenversicherung (GKV) claims (Germany), outpatient diagnoses are reported quarterly, which could result in the misclassification of baseline clinical characteristics and select outcomes of interest, impacting all objectives except for primary objective 2.

In the PHARMO Database Network, the high-budget impact medication dataset contains only declared medication for approved indications. It might not be possible to determine off-label use in this dataset.

The objectives and sub-objectives that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), where tofacitinib use is captured, neither ADD nor the number of pills per prescription is captured.

The sub-objective that evaluates "prescribers' adherence to the tofacitinib aRMMs, specifically, compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment" will *not* be assessed in Sweden because the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, it may not be possible to differentiate an absolute lymphocyte count (ALC) laboratory test from an absolute neutrophil count (ANC) laboratory test, or an alanine aminotransferase (ALT) laboratory test from an aspartate aminotransferase (AST) laboratory test. In the PHARMO Database Network, tuberculosis (TB) screening and viral hepatitis B and C testing are not captured.

9. RESEARCH METHODS

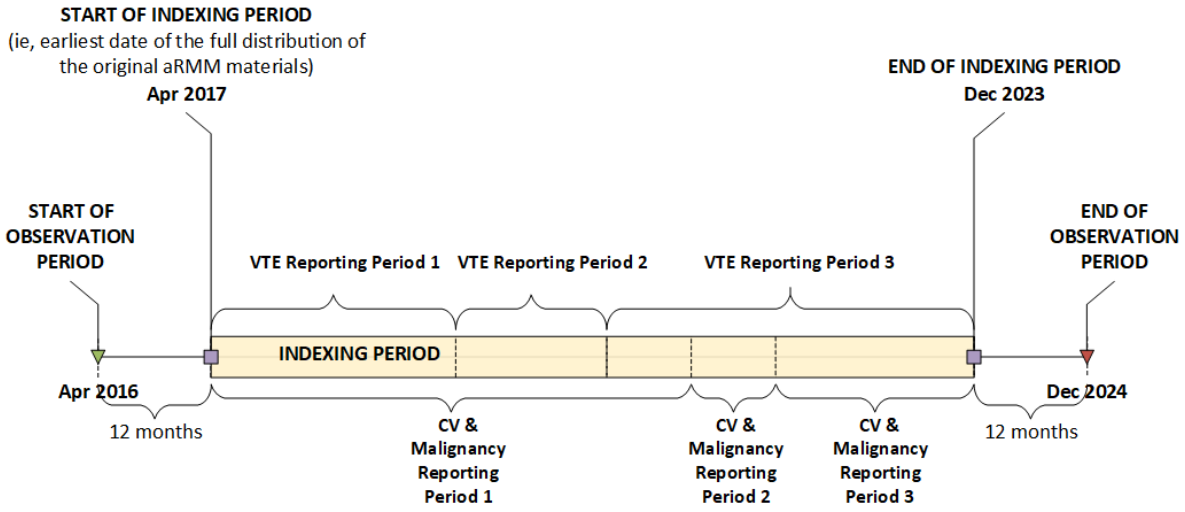
9.1. Study design

This will be a descriptive drug utilisation study using secondary data collected from databases in Sweden, Hungary, the Netherlands, and Germany. These databases will be used to identify patients who are tofacitinib users and obtain data on patient demographics, diagnoses, prescription medication dispensings, procedures, and administered screening and monitoring tests. All results will be stratified by country and approved indication (i.e., RA, PsA, and UC), unless otherwise specified. Additionally, the proportion of patients treated with tofacitinib without evidence of an approved indication will be described and tabulated, stratified by study country.

9.2. Setting

See Figure 1 for an overview of the study observation period, including the indexing period, the VTE Reporting Periods 1-3, and the CV and Malignancy Reporting Periods 1-3.

Figure 1. Overview of the study observation period



9.2.1. VTE Reporting Periods

A 105-month **observation period** will begin 01 April 2016 and end 31 December 2024. An 81-month **indexing period** will begin 01 April 2017 (i.e., the earliest date of the full distribution of the original aRMM materials for a country and indication [Sweden, RA]), end 31 December 2023, and be used to identify patients with ≥1 tofacitinib prescription dispensing. Additionally, for some analyses, the indexing period will be split into the following 3 periods:

- **Reporting Period 1**, which will cover the up-to-26-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 April 2017 through 31 May 2019, to allow for dissemination of DHPC letters following announcement of the provisional measures);

  Note: Hungary will not have a **Reporting Period 1** because it received full reimbursement for RA in May 2019 and has yet to receive full reimbursement for PsA and UC (anticipated Q1 2023).

- **Reporting Period 2**, which will cover the 16-month period of and 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 (1 June 2019 through 30 September 2020); and

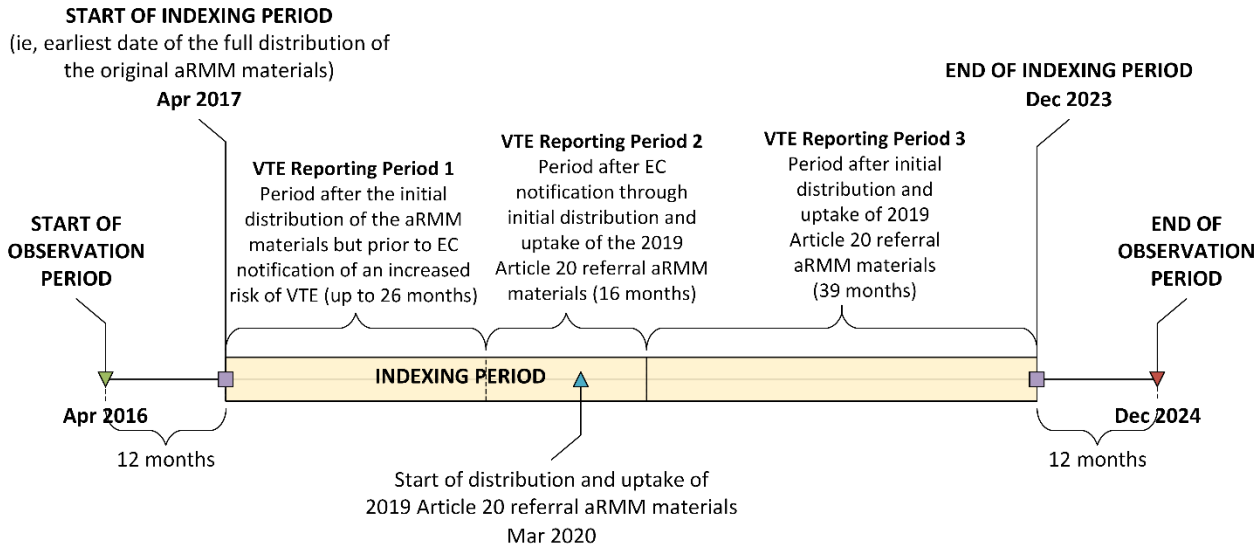
  Note: Hungary will not have a **Reporting Period 2** for PsA and UC because the September 2020 distribution date for the 2019 Article 20 referral aRMM materials in Hungary occurred prior to PsA and UC receiving full reimbursement (anticipated Q1 2023). Additionally, **Reporting Period 2** for RA in Hungary will only allow for <1 month of uptake of the 2019 Article 20 referral aRMM materials (which were distributed starting September 2020), in comparison to the approximate 6-7 month uptake of the

2019 Article 20 referral aRMM materials allowed for Sweden (which were distributed starting March 2020).

- **Reporting Period 3,** which will cover the 39-month period *after* the period of initial distribution and uptake of the 2019 Article 20 referral aRMM materials (1 October 2020 through 31 December 2023).

  See Figure 2 for an overview of the VTE Reporting Periods 1-3.

Figure 2. Overview of the VTE Reporting Periods



9.2.2. CV and Malignancy Reporting Periods

A 105-month **observation period** will begin 01 April 2016 and end 31 December 2024. An 81-month **indexing period** will begin 01 April 2017 (i.e., the earliest date of the full distribution of the original aRMM materials for a country and indication [Sweden, RA]), end 31 December 2023, and be used to identify patients with ≥1 tofacitinib prescription dispensing. Additionally, for some analyses, the indexing period will be split into the following 3 periods:

- **Reporting Period 1**, which will cover the up-to-51-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 April 2017 through 30 June 2021, to allow for dissemination of DHPC letters);

  Note: Hungary will not have a **Reporting Period 1** for PsA and UC because it has yet to receive full reimbursement for PsA and UC (anticipated Q1 2023).

The anticipated start date of distribution of the 2021 signal evaluation procedure aRMM materials for most countries is some time in Q4 2021. Therefore, ranges have been included

for the start and end dates of the CV and Malignancy Reporting Periods 2 and 3 assuming that the 2021 signal evaluation procedure aRMM materials are distributed at the beginning of Q4 (01 Oct 2021) and at the end of Q4 (31 Dec 2021). Thus, the CV and Malignancy Reporting Period 2 will start 01 July 2021 and end either as early as 31 March 2022 (lasting 9 months) or as late as 30 June 2022 (lasting 12 months). Accordingly, the CV and Malignancy Reporting Period 3 will start either as early as 01 April 2022 or as late as 01 July 2022 and end 31 December 2023, lasting either 21 months or 18 months, respectively.

- **Reporting Period 2**, which will cover the 9-12 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 Q1/Q2 2022);

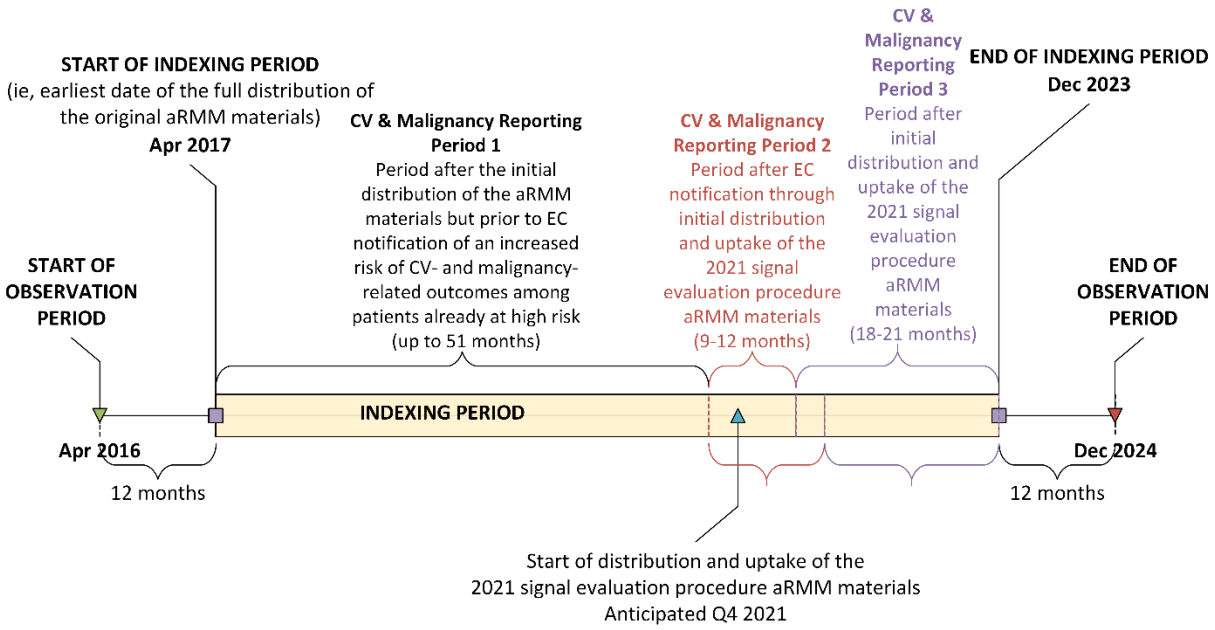
  Note: Hungary will not have a **Reporting Period 2** for PsA and UC because the anticipated distribution date for the 2021 signal evaluation procedure aRMM materials (Q4 2021) will occur prior to PsA and UC receiving full reimbursement (anticipated Q1 2023). Additionally, **Reporting Period 2** for the Netherlands will be adjusted in the statistical analysis plan (SAP) to reflect distribution and uptake of the 2021 signal evaluation procedure aRMM materials in Q1 2022.

- **Reporting Period 3,** which will cover the 18-21-month period *after* the period of initial distribution and uptake of the 2021 signal evaluation procedure aRMM materials (Q2/Q3 2022 through 31 December 2023).

  Note: Reporting Period 3 for the Netherlands will be adjusted in the SAP to reflect distribution and uptake of the 2021 signal evaluation procedure aRMM materials in Q1 2022.

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

Figure 3. Overview of the CV and Malignancy Reporting Periods

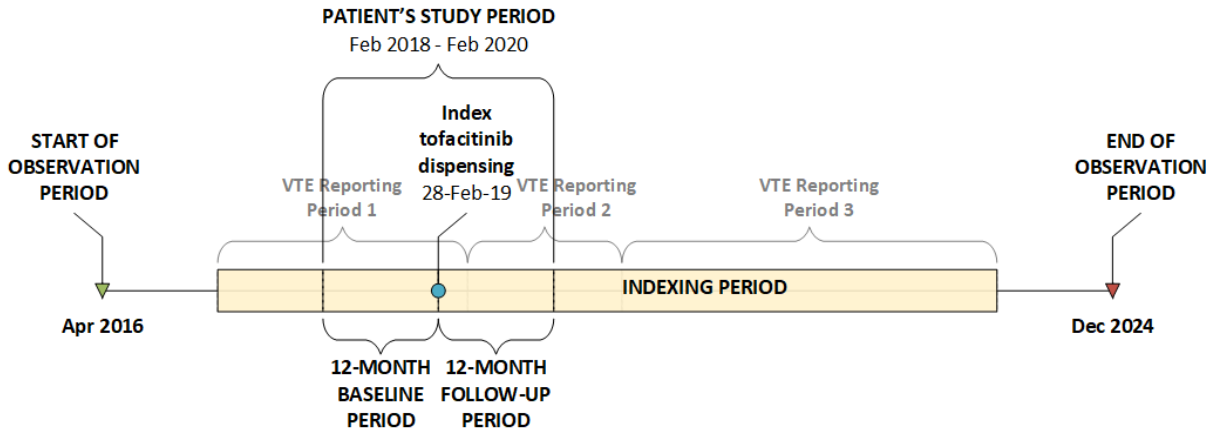


Note: If, at the end of CV and Malignancy Reporting Period 3, a minimum of 100 tofacitinib patients have not been accrued for a specific approved indication-country combination (e.g., UC in Sweden), then CV and Malignancy Reporting Period 3 will be extended as the data are available. For example, if market uptake is slower than expected, then CV and Malignancy Reporting Period 3 will be extended by 12 months or longer if necessary.

9.2.3. Patient-specific study period

Patients will be included in the study analyses if they have ≥1 tofacitinib prescription dispensing during the indexing period and meet the study inclusion and exclusion criteria (described in Section 9.2.4 [Inclusion criteria] and 9.2.5 [Exclusion criteria], respectively). The date of a patient's first tofacitinib prescription dispensing during the indexing period will be considered the patient's **index date**. Each patient will have their own unique **study period** (based on their index date), consisting of a 12-month **baseline period** and a 12-month **follow-up period** (Figure 4).

Figure 4. Example index tofacitinib dispensing and patient-specific study period against the VTE Reporting Periods



The 12-month **baseline period** will immediately precede the patient's index date and will be used to ascertain indication (including off-label indications), comorbidities, prior and current medications, potential contraindicated use of tofacitinib, VTE risk factors, use in patients aged 65 years and older, CV risk factors, malignancy risk factors, 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 and will be used to ascertain comorbidities, comedications, compliance to the recommended posology per indication (ADD) and duration of tofacitinib treatment, potential contraindicated use of tofacitinib, VTE risk factors, CV risk factors, 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. Inclusion criteria

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

1. Have ≥1 prescription dispensing of tofacitinib (Anatomical Therapeutic Chemical [ATC] code L04AA29) in the selected databases during the indexing period;

2. Have 12 months of available medical history *prior to* the index tofacitinib dispensing; and

3. Have 12 months of available medical history *after* the index tofacitinib dispensing.

9.2.5. Exclusion criteria

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

- ≥1 prescription dispensing of tofacitinib in the selected databases in the 12 months *prior to* the indexing period; and/or

- Patients with an index tofacitinib prescription dispensing for an indication for which the original aRMM materials for that indication were not yet distributed[c].

  For example, if a patient indexes with a tofacitinib prescription dispensing for UC in Sweden prior to September 2018 (the date of full distribution of the original aRMM materials), they will be excluded from the study. For a patient that has another (unapproved) or unknown indication, the date of the earliest original aRMM materials distribution for an indication, specific to the patient's country (i.e., May 2017 in Sweden, December 2018 in Hungary, May 2017 in the Netherlands, and April 2017 in Germany), will be used to evaluate this criterion.

9.3. Variables

9.3.1. Outcomes

The primary outcomes of interest will be (see Table 3 for operational definitions):

- The demographics, comorbidities, and prior and current medications (including prior use of biologics) of tofacitinib patients;[d,e]

- Prescribers' adherence to the tofacitinib aRMMs, specifically:

  - Compliance to the recommended posology per indication and duration of use, as measured by:[f]

    - ADD of tofacitinib therapy, calculated in 8-week intervals from Week 0 through Week 47, and reported in the following categories:

      - Up to 5 mg ADD;

      - >5 to 11 mg ADD;

[c] This exclusion criterion will primarily apply to those patients who received their index tofacitinib prescription for an indication within the first 3 months after approval of that indication.

[d] The data sources are unable to reliably ascertain severity of hepatic impairment and renal impairment.

[e] In GKV claims, outpatient diagnoses are reported quarterly.

[f] The study outcomes that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), neither ADD nor the number of pills per prescription is captured.

- >11 to 15 mg ADD;
- >15 to 20 mg ADD; and
- >20 mg ADD;

Note that within these reporting intervals and categories, ADD will also be reported by approved indication or by the indication groups: "PsA or RA" and "UC", presence of ≥1 VTE risk factor prior to tofacitinib initiation, and prior use of an alternative therapy (i.e., biologic) in the 12 months prior to tofacitinib initiation; depending on the objective, outcomes will be stratified by reporting period;[e,g]

- The proportion of patients with an ADD of >11 mg during any of the 8-week follow-up intervals and no evidence of a diagnosis for UC; and
- The proportion of patients with an ADD of ≥15 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and/or Weeks 40-47 of follow-up with evidence of a diagnosis for UC but no use of an alternative therapy (i.e., biologic) *prior to* tofacitinib initiation;

- Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment, as measured by:[h]
  - The proportion of patients with evidence of having received the following recommended screenings *prior to* initiation of tofacitinib:
    - Creatinine (serum or urine) laboratory testing;
    - TB screening;
    - Viral hepatitis B and C screening;
    - ALC laboratory testing;
    - ANC laboratory testing;
    - Haemoglobin laboratory testing; and

[g] Hungary will not have a VTE Reporting Period 1. Hungary will also not have a VTE Reporting Period 2 for PsA and UC.

[h] This outcome (and all sub-outcomes) will *not* be assessed in Sweden because the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, it may not be possible to differentiate an ALC laboratory test from an ANC laboratory test, or an ALT laboratory test from an AST laboratory test. In the PHARMO Database Network, TB screening and viral hepatitis B and C testing are not captured.

- ALT and/or AST laboratory testing (i.e., liver function testing);

- For patients with 6 and 12 months of tofacitinib therapy, the proportion of patients with evidence of having received the following recommended monitoring *after* initiation of tofacitinib in the respective periods:

  - TB screening;

  - Viral hepatitis B and C screening;

  - ALC laboratory testing;

  - ANC laboratory testing;

  - Haemoglobin laboratory testing;

  - ALT and/or AST laboratory testing; and

  - Lipid panel (i.e., total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides [TG]) laboratory testing;

- Compliance to recommendations to limitations for use, including

  - Use in patients with VTE risk factors, as measured by:[e]

    - The proportion of patients with evidence of ≥1 VTE risk factors *prior to* initiation of tofacitinib, reported overall and by approved indication;

    - The number of VTE risk factors identified *prior to* initiation of tofacitinib, reported overall and by approved indication;

    - The proportion of patients with UC who have: ≥1 VTE risk factor identified *prior to* tofacitinib initiation; no use of an alternative therapy (i.e., biologic) *prior to* tofacitinib initiation; and an ADD >10 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39; and Weeks 40-47 of follow-up;[f]

    - The proportion of patients who discontinue tofacitinib after developing ≥1 VTE risk factor while taking tofacitinib; and

    - The proportion of patients who continue taking tofacitinib after developing ≥1 VTE risk factor while taking tofacitinib;

  - Use in patients aged 65 years and older, as measured by:

    - The proportion of patients 65 years and older with no alternative treatments *prior to* initiation of tofacitinib, reported overall and by approved indication;

- The proportion of patients aged 65 years, receiving tofacitinib, who have 0 prescription dispensings of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period, reported overall and by approved indication;

- The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and no history of alternative treatments *prior to* that tofacitinib prescription dispensing, reported overall and by approved indication; and

- The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and a history of alternative treatments *prior to* that tofacitinib prescription dispensing, reported overall and by approved indication;

- Use in patients with CV risk factors, as measured by:[e]

  - The proportion of patients with evidence of ≥1 CV risk factors *prior to* initiation of tofacitinib, reported overall and by approved indication;

  - The proportion of patients with evidence of ≥1 CV risk factors *prior to* initiation of tofacitinib and no prior use of an alternative therapy (i.e., biologic), reported overall and by approved indication;

  - The proportion of patients who discontinue tofacitinib after developing ≥1 CV risk factor while taking tofacitinib; and

  - The proportion of patients who continue taking tofacitinib after developing ≥1 CV risk factor while taking tofacitinib;

- Use in patients with malignancy risk factors, as measured by:[e]

  - The proportion of patients with evidence of ≥1 malignancy risk factors *prior to* initiation of tofacitinib, reported overall and by approved indication;

  - The proportion of patients with evidence of ≥1 malignancy risk factors *prior to* initiation of tofacitinib and no prior use of an alternative therapy (i.e., biologic), reported overall and by approved indication;

  - The proportion of patients who discontinue tofacitinib after developing ≥1 malignancy risk factor while taking tofacitinib; and

  - The proportion of patients who continue taking tofacitinib after developing ≥1 malignancy risk factor while taking tofacitinib;

- Contraindicated use, as measured by:[e]
  - A patient *initiating* tofacitinib therapy if they have severe hepatic impairment;[i]
  - A woman *initiating* tofacitinib therapy if she is pregnant;
  - 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;
- Use with concomitant medications not compatible with tofacitinib, as 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;[j]

The secondary outcomes of interest will be:

- Tofacitinib prescribing patterns over time;[e,f] and
- Changes in the prescribing patterns (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 VTE risk factors, as measured by:[e,f]
    - The proportion of patients with evidence of ≥1 VTE risk factors *prior to* initiation of tofacitinib, reported overall and by approved indication and stratified by VTE Reporting Period[k]

[i] The data sources are unable to reliably ascertain severity of hepatic impairment; thus, this sub-outcome may be overestimated.

[j] This sub-outcome will not be assessed in Sweden because most vaccinations are not done in specialist care and therefore are not captured in the National Patient Register (NPR), nor are vaccines prescribed and purchased by the patients in the pharmacies and therefore are not be captured in the Prescribed Drug Register (PDR). Vaccination data are also unavailable in the PHARMO Database Network. In GKV claims, it is not possible to differentiate between live and non-live vaccines.

[k] Hungary will not have a VTE Reporting Period 1. Hungary will also not have a VTE Reporting Period 2 for PsA and UC.

- The number of VTE risk factors identified *prior to* initiation of tofacitinib, reported overall and by approved indication and stratified by VTE Reporting Period[k]

- The proportion of patients with UC who have: ≥1 VTE risk factor identified *prior to* tofacitinib initiation; no use of an alternative therapy (i.e., biologic) *prior to* tofacitinib initiation; and an ADD >10 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39; and Weeks 40-47 of follow-up, stratified by VTE Reporting Period[f,k]

- The proportion of patients who discontinue tofacitinib after developing ≥1 VTE risk factor while taking tofacitinib, reported overall and by approved indication and stratified by VTE Reporting Period[k]

- The proportion of patients who continue taking tofacitinib after developing ≥1 VTE risk factor while taking tofacitinib, reported overall and by approved indication and stratified by VTE Reporting Period[k]

- Use in the elderly (patients 65 years and older), as measured by:

  - The proportion of patients 65 years and older with no alternative treatments *prior to* initiation of tofacitinib, reported overall and by approved indication and stratified by VTE Reporting Period[k] and CV and Malignancy Reporting Period[l]

  - The proportion of patients aged 65 years, receiving tofacitinib, who have 0 prescription dispensings of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period, reported overall and by approved indication and stratified by VTE Reporting Period[k] and CV and Malignancy Reporting Period[l]

  - The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and no history of alternative treatments *prior to* that tofacitinib prescription dispensing, reported overall and by approved indication and stratified by VTE Reporting Period[k] and CV and Malignancy Reporting Period[l]

  - The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and a history of alternative treatments *prior to* that tofacitinib prescription dispensing, reported overall and by approved indication and stratified by VTE Reporting Period[k] and CV and Malignancy Reporting Period[l]

[l] Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC.

- Use in patients with CV risk factors, as measured by:[e]
    - The proportion of patients with evidence of ≥1 CV risk factors *prior to* initiation of tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients with evidence of ≥1 CV risk factors *prior to* initiation of tofacitinib and no prior use of an alternative therapy (i.e., biologic), reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients who discontinue tofacitinib after developing ≥1 CV risk factor while taking tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients who continue taking tofacitinib after developing ≥1 CV risk factor while taking tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
- Use in patients with malignancy risk factors, as measured by:[e]
    - The proportion of patients with evidence of ≥1 malignancy risk factors prior to initiation of tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients with evidence of ≥1 malignancy risk factors prior to initiation of tofacitinib and no prior use of an alternative therapy (i.e., biologic), reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients who discontinue tofacitinib after developing ≥1 malignancy risk factor while taking tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]
    - The proportion of patients who continue taking tofacitinib after developing ≥1 malignancy risk factor while taking tofacitinib, reported overall and by approved indication and stratified by CV and Malignancy Reporting Period[l]

9.3.2. Variable definitions

Table 3 summarises and defines the study variables to be collected and analysed in the selected databases. 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 (validated against a gold standard measure, where possible) and/or other code lists to identify study variables. All code-based algorithms and code lists will be reviewed and/or approved by the study sponsor

prior to study initiation. Preliminary algorithms and/or codes are proposed in the following table (see also ANNEX 3 through ANNEX 7). Final algorithms and/or code lists will be refined as part of the SAP development.

Where possible, operational definitions for the variables listed in Table 3 will be similar across the databases. Only ICD-10 diagnosis codes and procedure codes are referenced in Table 3; the specific coding systems used in each data source will be further described in the SAP. See Section 9.4 (Data sources) for a description of the selected databases and Section 9.9 (Limitations of the research methods) for a summary of the limitations associated with these databases.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Indication[m]		
Indication[n]	Indication (including potential off-label indications)	Reported in the following categories: RA, PsA, UC, and Other / unknown (i.e., potential off-label indications). Defined as ≥1 International Classification of Disease, 10th Revision (ICD-10) diagnosis code for RA, PsA, or UC in the 12 months prior to and including the day of tofacitinib initiation. If there is no ICD-10 diagnosis code in the patient's data for RA, PsA, or UC during this time period, then the indication will be reported as Other / unknown. If a patient has multiple codes for any combination of indications (e.g., RA and PsA), the ICD-10 diagnosis code closest to the index tofacitinib prescription dispensing will be used to determine indication.
Primary Objective 1: Demographics, comorbidities, and prior and current medications[m]		
Age at tofacitinib initiation	Demographic	Calculated as the date of tofacitinib initiation minus the patient's year of birth and reported in the following categories: <18 years, 18-29 years, 30-39 years; 40-49 years; 50-59 years; 60-69 years; 70-79 years; and ≥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.

[m] In GKV claims, outpatient diagnoses are reported quarterly.

[n] In the PHARMO Database Network, the high-budget impact medication dataset contains only declared medication for approved indications. It might not be possible to determine off-label use in this dataset.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Hepatic impairment	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for hepatic impairment.
Hepatic impairment, mild or moderate[o]	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for mild or moderate hepatic impairment.
Hepatic impairment, severe[o]	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for severe hepatic impairment.
Renal impairment	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for renal impairment or a combination of ICD-10 diagnosis codes and/or ICD-10 procedure codes.
Renal impairment, mild[o]	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for mild renal impairment or a combination of ICD-10 diagnosis codes and/or ICD-10 procedure codes.
Renal impairment, moderate[o]	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for moderate renal impairment or a combination of ICD-10 diagnosis codes and/or ICD-10 procedure codes.
Renal impairment, severe[o]	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for severe renal impairment or a combination of ICD-10 diagnosis codes and/or ICD-10 procedure codes.
Herpes zoster (HZ)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for HZ.
Human immunodeficiency virus (HIV)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for HIV.
Tuberculosis (TB), including both active and latent TB[p]	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.

[o] The data sources are unable to reliably ascertain severity of hepatic impairment and renal impairment.

[p] The data sources may not be able to differentiate between active and latent TB.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Malignancy (non-metastatic and metastatic, excluding non-melanoma skin cancer)	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for a malignancy (excluding non-melanoma skin cancer).
Non-melanoma skin cancer	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for non-melanoma skin cancer.
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 4. LIST OF DIAGNOSIS AND PROCEDURE CODES FOR INTERSTITIAL LUNG DISEASE.
Diabetes	Comorbidity	Defined as ≥1 ICD-10 diagnosis code for diabetes.
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 7. 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 7. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Prior use of any biologic[q]	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 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Prior use of conventional synthetic DMARDs (csDMARDs)	Medication history	Defined as ≥1 prescription dispensing of a csDMARD (as identified by ATC code[s]) in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Prior use of methotrexate (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[r]	Medication history	Defined as ≥1 procedure code and/or ≥1 prescription dispensing (as identified by ATC code[s]) for a vaccination, overall and stratified by live and non-live vaccinations in the 12 months prior to the index tofacitinib dispensing. Complete list in ANNEX 7. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.

[q] Biologics that are dispensed or administered primarily through hospital channels may not captured (completely) in the data sources.

[r] This variable will not be assessed in Sweden because most vaccinations are not done in specialist care and therefore are not captured in the NPR, nor are vaccines prescribed and purchased by the patients in the pharmacies and therefore are not be captured in the PDR. Vaccination data are also unavailable in the PHARMO Database Network. In GKV claims, it is not possible to differentiate between live and non-live vaccines.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Concomitant use of a contraindicated immunomodulator csDMARD	Comedication	Defined as ≥1 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for a contraindicated immunomodulator csDMARD (as identified by ATC code[s]) during the follow-up period. **Note:** Concomitancy with a contraindicated csDMARD can occur even if the contraindicated medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. Duration of tofacitinib therapy defined in Section 9.3.3.
Concomitant use of MTX	Comedication	Defined as ≥1 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for MTX (as identified by ATC code L04AX03) during the follow-up period. **Note:** Concomitancy with MTX can occur even if the medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. Duration of tofacitinib therapy defined in Section 9.3.3.
Concomitant use of a corticosteroid	Comedication	Defined as ≥1 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. **Note:** Concomitancy with a corticosteroid can occur even if the medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. Duration of tofacitinib therapy defined in Section 9.3.3.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Concomitant use of anti-TB therapy	Comedication	Defined as ≥1 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. **Note:** Concomitancy with anti-TB therapy can occur even if the medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. Duration of tofacitinib therapy defined in Section 9.3.3.
Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs[s]		
Compliance to the recommended posology per indication and duration of use[t]		
Duration of tofacitinib therapy	Utilisation	Defined in Section 9.3.3. Assessed during the follow-up period.
Average daily dose (ADD)[t]	Outcome: Compliance to recommended posology	Defined in Section 9.3.4. Assessed during the follow-up period.
A patient with an ADD of >11 mg during any of the 8-week follow-up intervals and no evidence of a diagnosis for UC[t]	Outcome: Compliance to recommended posology	Defined as 0 ICD-10 diagnosis codes for UC prior to and including the date of the first tofacitinib prescription dispensing in an 8-week follow-up interval that has an ADD of >11 mg (ADD defined in Section 9.3.4).

[s] In GKV claims, outpatient diagnoses are reported quarterly.

[t] The study outcomes that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network, neither ADD nor the number of pills per prescription is captured.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
A patient with an ADD of ≥15 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and/or Weeks 40-47 of follow-up with evidence of a diagnosis for UC but no use of an alternative therapy (i.e., biologic) *prior to* tofacitinib initiation[t]	Outcome: Compliance to recommended posology	Defined as ≥1 ICD-10 diagnosis codes for UC and ≥1 prescription dispensing for a biologic (as identified by ATC codes) prior to and including the date of the index tofacitinib prescription with an ADD ≥15 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and/or Weeks 40-47 of follow-up (ADD defined in Section 9.3.4). Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB. **Note:** This definition will miss those who have 1 10-mg BID prescription and the remaining prescriptions are 5-mg BID.
Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment[u]		
The following recommended screenings and monitoring will be assessed in the following timeframes: • In the 30 days prior to and including the day of tofacitinib initiation; • In the 31 to 60 days prior to tofacitinib initiation; • In the 61 to 90 days prior to tofacitinib initiation; • In the 91 to 180 days prior to tofacitinib initiation; For patients with 6 months of tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.3): • In the 60 days after and including 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 9.3.3): • 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. Timeframes for the baseline period are mutually exclusive. For patients with multiple procedure and/or diagnosis codes during the baseline period, the procedure or diagnosis code occurring closest to the index tofacitinib prescription dispensing will be selected.		

[u] This outcome (and all sub-outcomes) will *not* be assessed in Sweden because the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, it may not be possible to differentiate an ALC laboratory test from an ANC laboratory test, or an ALT laboratory test from an AST laboratory test. In the PHARMO Database Network, TB screening and viral hepatitis B and C testing are not captured.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
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.
Lipid panel (i.e., total cholesterol, HDL, LDL, and TG) laboratory testing	Outcome: Monitoring	Defined as ≥1 procedure code or ≥1 ICD-10 diagnosis code for lipid panel laboratory testing. **Note:** The patient must have evidence of receiving *all* 4 laboratory tests that comprise a lipid panel.
Compliance to recommendations for limitations of use in patients with VTE risk factors[v]		
Assessment of VTE risk factors prior to initiation of tofacitinib		
Prior VTE	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for VTE in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of surgery, major	Outcome: VTE risk factor	Defined as ≥1 procedure code for a major surgery in the 12 months prior to or on the day of the index tofacitinib dispensing.
Prior recent myocardial infarction (MI)	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for an MI in the 3 months prior to or on the day of the index tofacitinib dispensing.

[v] In GKV claims, outpatient diagnoses are reported quarterly.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
History of heart failure	Outcome: VTE risk factor	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.
History of combined hormonal contraceptives or hormonal replacement therapy use	Outcome: VTE risk factor	Defined as ≥1 prescription dispensing of a combined hormonal contraceptives and/or hormonal replacement therapy (as identified by ATC codes) in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of inherited coagulation disorder	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for inherited coagulation disorder in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of malignancy (non-metastatic and metastatic; excluding non-melanoma skin cancer)	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding non-melanoma skin cancer) in the 12 months prior to or on the day of the index tofacitinib dispensing.
Age >50 years at tofacitinib initiation	Outcome: VTE risk factor	Defined as age at tofacitinib initiation >50 years.
History of diabetes	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for diabetes in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of hypertension	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for hypertension in the 12 months prior to or on the day of the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 VTE risk factor	Outcome: VTE risk factor	Defined as ≥1 VTE risk factor (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing (unless otherwise specified).
Number of VTE risk factors identified prior to tofacitinib initiation	Outcome: VTE risk factor	Calculated as the sum of the number of VTE risk factors (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing (unless otherwise specified).

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Number of UC patients with: ≥1 VTE risk factor; no prior alternative therapy (i.e., biologic); and an ADD >10 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and Weeks 40-47 of follow-up[t]	Outcome: VTE risk factor	Defined as a patient meeting all of the following criteria: ≥1 ICD-10 diagnosis code for UC; ≥1 VTE risk factor (as listed and defined above); 0 prescription medication dispensings for a biologic (as identified by ATC codes) in the 12 months prior to and including the date of the index tofacitinib prescription dispensing; and an ADD of >10 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and Weeks 40-47 of follow-up, respectively (ADD defined in Section 9.3.4). Complete list of biologics in ANNEX 6. 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 9.3.3)		
VTE	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for VTE while receiving tofacitinib therapy.
Surgery, major	Outcome: VTE risk factor	Defined as ≥1 procedure code for a major surgery while receiving tofacitinib therapy.
MI	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for an MI while receiving tofacitinib therapy.
Heart failure	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for heart failure while receiving tofacitinib therapy.
Use of combined hormonal contraceptives or hormonal replacement therapy	Outcome: VTE risk factor	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: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for inherited coagulation disorder while receiving tofacitinib therapy.
Malignancy (non-metastatic and metastatic; excluding non-melanoma skin cancer)	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for malignancy (excluding non-melanoma skin cancer) while receiving tofacitinib therapy.
Diabetes	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for diabetes while receiving tofacitinib therapy.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Hypertension	Outcome: VTE risk factor	Defined as ≥1 ICD-10 diagnosis code for hypertension while receiving tofacitinib therapy.
Discontinuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: VTE risk factor	Defined as ≥1 VTE risk factor while receiving tofacitinib therapy (as listed and defined above) PLUS 0 prescription dispensings for tofacitinib within a specific time window *after* the code for the VTE risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the VTE risk factor acquired while receiving tofacitinib therapy and will be operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.
Continuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: VTE risk factor	Defined as ≥1 VTE 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 VTE risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the VTE risk factor acquired while receiving tofacitinib therapy and will be operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.
Compliance to recommendations for limitations of use in patients aged 65 years and older		
Initiating tofacitinib with no prior use of an alternative therapy (i.e., biologic) among patients 65 years of age and older	Outcome: Age 65 years and older	Defined as patients who are 65 years and older on the date of the index tofacitinib dispensing with 0 prescription dispensings for a biologic (as identified by ATC codes) in the 12 months prior. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Discontinuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Age 65 years and older	Defined as patients aged 65 years, receiving tofacitinib, who have 0 prescription dispensings of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period. **Note:** Patients have 6 months to discontinue tofacitinib to allow them time to be seen by their healthcare provider. Duration of tofacitinib therapy defined in Section 9.3.3.
Inappropriate continuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Age 65 years and older	Defined as patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and 0 prescription dispensings for a biologic (as identified by ATC codes) *prior to* that tofacitinib prescription dispensing. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB. **Note:** Patients have 6 months to discontinue tofacitinib to allow them time to be seen by their healthcare provider. Duration of tofacitinib therapy defined in Section 9.3.3.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Appropriate continuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Age 65 years and older	Defined as patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period PLUS ≥1 prescription dispensing for a biologic (as identified by ATC codes) *prior to* that tofacitinib prescription dispensing. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB. **Note:** Patients have 6 months to discontinue tofacitinib to allow them time to be seen by their healthcare provider. Duration of tofacitinib therapy defined in Section 9.3.3.
Analysis of CV risk factors in patients using tofacitinib[w]		
Assessment of CV risk factors prior to initiation of tofacitinib (will be stratified by sex as outlined in Section 9.7.1.2.2.1.3 [Patients with CV risk factors])		
Elderly at tofacitinib initiation (patients 65 years and older)	Outcome: CV risk factor	Calculated as the date of tofacitinib initiation minus the patient's year of birth and reported in the following categories: <65 years and ≥65 years.
Current or past smoker[x]	Outcome: CV 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 in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of diabetes	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for diabetes in the 12 months prior to or on the day of the index tofacitinib dispensing.

[w] In GKV claims, outpatient diagnoses are reported quarterly.

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

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
History of hypertension	Outcome: CV risk factor	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 or on the day of the index tofacitinib dispensing. Complete list in ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES.
History of hyperlipidaemia	Outcome: CV risk factor	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 or on the day of the index tofacitinib dispensing. Complete list in ANNEX 9. LIST OF ATC CODES FOR ANTIHYPERLIPIDAEMICS.
History of coronary artery disease (defined as MI, stroke, CABG [coronary artery bypass graft], or PCI [percutaneous coronary intervention])	Outcome: CV risk factor	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 or on the day of the index tofacitinib dispensing.
History of chronic kidney disease	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for chronic kidney disease in the 12 months prior to or on the day of the index tofacitinib dispensing.
History of stable angina pectoris	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for stable angina pectoris in the 12 months prior to or on the day of the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 CV risk factor	Outcome: CV risk factor	Defined as ≥1 CV risk factor (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Initiating tofacitinib with ≥1 CV risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: CV risk factor	Defined as ≥1 CV risk factor (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing—AND—0 prescription medication dispensings for a biologic (as identified by ATC code) in the 12 months prior to and including the date of the index tofacitinib prescription dispensing. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.
Assessment of CV risk factors while receiving tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.3) (will be stratified by sex as outlined in Section 9.7.1.2.2.1.3 [Patients with CV risk factors])		
Elderly (patients 65 years and older)	Outcome: CV risk factor	Defined as patients aged 65 years or older while receiving tofacitinib.
Current smoker[x]	Outcome: CV 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.
Diabetes	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for diabetes while receiving tofacitinib therapy.
Hypertension	Outcome: CV risk factor	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.
Hyperlipidaemia	Outcome: CV risk factor	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.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Coronary artery disease (defined as MI, stroke, CABG [coronary artery bypass graft], or PCI [percutaneous coronary intervention])	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for MI or stroke or ≥1 procedure code for CABG or PCI while receiving tofacitinib therapy.
Chronic kidney disease	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for chronic kidney disease while receiving tofacitinib.
Stable angina pectoris	Outcome: CV risk factor	Defined as ≥1 ICD-10 diagnosis code for stable angina pectoris while receiving tofacitinib.
Discontinuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: CV risk factor	Defined as ≥1 CV risk factor while receiving tofacitinib therapy (as listed and defined above) PLUS 0 prescription dispensings for tofacitinib within a specific time window *after* the code for the CV risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the CV risk factor acquired while receiving tofacitinib therapy and will be operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.
Continuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: CV risk factor	Defined as ≥1 CV 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 CV risk factor. **Note:** The time window for when to look for a tofacitinib prescription dispensing will be specific to the CV risk factor acquired while receiving tofacitinib therapy and will be operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Analysis of malignancy risk factors in patients using tofacitinib[y]		
Assessment of malignancy risk factors prior to initiation of tofacitinib		
Elderly at tofacitinib initiation (patients 65 years and older)	Outcome: Malignancy risk factor	Calculated as the date of tofacitinib initiation minus the patient's year of birth and reported in the following categories: <65 years and ≥65 years.
History of malignancy (non-metastatic and metastatic, excluding non-melanoma skin cancer)	Outcome: Malignancy risk factor	Defined as ≥1 ICD-10 diagnosis code for a malignancy (excluding non-melanoma skin cancer) in the 12 months prior to or on the day of the index tofacitinib dispensing.
Current or past smoker[x]	Outcome: 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 in the 12 months prior to or on the day of the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 malignancy risk factor	Outcome: Malignancy risk factor	Defined as ≥1 malignancy risk factor (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing.
Initiating tofacitinib with ≥1 malignancy risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: Malignancy risk factor	Defined as ≥1 malignancy risk factor (as listed and defined above) identified in the 12 months prior to or on the day of the index tofacitinib dispensing—AND— 0 prescription medication dispensings for a biologic (as identified by ATC code) in the 12 months prior to and including the date of the index tofacitinib prescription dispensing. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB
Assessment of malignancy risk factors while receiving tofacitinib therapy (duration of tofacitinib therapy defined in Section 9.3.3)		
Elderly (patients 65 years and older)	Outcome: Malignancy risk factor	Defined as patients aged 65 years or older while receiving tofacitinib.

[y] In GKV claims, outpatient diagnoses are reported quarterly.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Malignancy (non-metastatic and metastatic, excluding non-melanoma skin cancer)	Outcome: Malignancy risk factor	Defined as ≥1 ICD-10 diagnosis code for a malignancy (excluding non-melanoma skin cancer) while receiving tofacitinib.
Current smoker[x]	Outcome: 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.
Discontinuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: Malignancy risk factor	Defined as ≥1 malignancy risk factor while receiving tofacitinib therapy (as listed and defined above) PLUS 0 prescription dispensings for tofacitinib within a specific time window *after* the code for the 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 operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.
Continuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: 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 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 operationalized during SAP development. Duration of tofacitinib therapy defined in Section 9.3.3.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Compliance to recommendations for limitations of contraindicated use[z]		
Initiating tofacitinib with severe hepatic impairment[aa]	Outcome: Contraindicated use	Defined as ≥1 ICD-10 diagnosis code for severe hepatic impairment in the 12 months prior to and including the day of 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, as identified in the Swedish MBR and in the Perinatal Registry of the PHARMO Database Network (Netherlands) ; or as estimated using a combination of pregnancy-related diagnosis and/or procedure codes in the Swedish NPR, in NHIFA, the Hungarian administrative claims database, and in GKV claims (Germany).
Receiving tofacitinib while pregnant	Outcome: Contraindicated use	Defined as evidence of a pregnancy while receiving tofacitinib therapy in the follow-up period, as identified in the Swedish MBR and in the Perinatal Registry of the PHARMO Database Network (Netherlands); or as estimated using a combination of pregnancy-related diagnosis and/or procedure codes in the Swedish NPR, in NHIFA, the Hungarian administrative claims database, and in GKV claims (Germany). Duration of tofacitinib therapy defined in Section 9.3.3.
Initiating tofacitinib while having TB (active or latent)[bb]	Outcome: Contraindicated use	Defined as ≥1 ICD-10 diagnosis code for TB in the 60 days prior to and including the day of tofacitinib initiation.
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 and including the day of tofacitinib initiation. Complete list of serious and/or opportunistic infections in ANNEX 3. LIST OF DIAGNOSIS CODES FOR SELECT INFECTIONS OF INTEREST.

[z] In GKV claims, outpatient diagnoses are reported quarterly.

[aa] The data sources are unable to reliably ascertain severity of hepatic impairment and renal impairment.

[bb] The data sources may not be able to differentiate between active and latent TB.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Compliance to recommendations for limitations of use with concomitant medications not compatible with tofacitinib		
Use of biologics approved to treat RA, PsA, or UC while taking tofacitinib[cc]	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥1 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. **Note:** Concomitancy with a biologic can occur even if the contraindicated medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. **Note:** This variable will be presented overall and by patients with and without ≥2 tofacitinib prescription dispensings[dd] during the follow-up period (where the second prescription is dispensed within 15 days of the last day of the days' supply [or the equivalent] of the first prescription). Duration of tofacitinib therapy defined in Section 9.3.3. Complete list of biologics in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.

[cc] Biologics that are dispensed or administered primarily through hospital channels may not captured (completely) in the data sources.

[dd] Patients with ≥2 dispensings of tofacitinib are more likely to have taken tofacitinib for the full days' supply of the prescription as opposed to patients with only 1 dispensing of tofacitinib.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Use of selected potent immunosuppressants while taking tofacitinib	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥1 overlapping days' supply of a tofacitinib prescription dispensing and a prescription dispensing for the selected potent immunosuppressants azathioprine, 6-mercaptopurine, cyclosporine, or tacrolimus (as identified by ATC code[s]) during the follow-up period. **Note:** Concomitancy with a selected potent immunosuppressant can occur even if the contraindicated medication is *dispensed* prior to the index tofacitinib dispensing, provided that there is ≥1 overlapping days' supply with a tofacitinib prescription dispensing during the follow-up period. **Note:** This variable will be presented overall and by patients with and without ≥2 tofacitinib prescription dispensings[dd] during the follow-up period (where the second prescription is dispensed within 15 days of the last day of the days' supply [or the equivalent] of the first prescription). Duration of tofacitinib therapy defined in Section 9.3.3. Complete list of selected potent immunosuppressants in ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Receipt of a live vaccination while taking tofacitinib[ee]	Outcome: Concomitant medications not compatible with tofacitinib	Defined as ≥1 procedure code and/or ≥1 prescription dispensing (as identified by ATC code[s]) for a live vaccination (as available) while receiving tofacitinib therapy in the follow-up period. **Note:** This variable will be presented overall and by patients with and without ≥2 tofacitinib prescription dispensings[dd] during the follow-up period (where the second prescription is dispensed within 15 days of the last day of the days' supply [or the equivalent] of the first prescription) Duration of tofacitinib therapy defined in Section 9.3.3. Complete list of vaccinations in ANNEX 7. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST.
Secondary Objectives 1 and 2: Describe prescribing patterns over time; and Describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use after the 2019 Article 20 referral and the 2021 signal evaluation procedure[ff,gg]		
In patients with VTE risk factors (will be assessed separately in VTE Reporting Periods 1, 2, and 3[hh])		
Initiating tofacitinib with ≥1 VTE risk factor	Outcome: Changes in the utilisation of tofacitinib—VTE risk factors	See '***Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs – Compliance to recommendations to limitations for use in patients with VTE risk factors***' for operational definitions.
Number of VTE risk factors identified prior to tofacitinib initiation	Outcome: Changes in the utilisation of tofacitinib —VTE risk factors	

[ee] This study sub-outcome will not be assessed in Sweden because most vaccinations are not done in specialist care and therefore are not captured in the NPR, nor are vaccines prescribed and purchased by the patients in the pharmacies and therefore are not be captured in the PDR. Vaccination data are also unavailable in the PHARMO Database Network. In GKV claims, it is not possible to differentiate between live and non-live vaccines.

[ff] The study outcomes that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network, neither ADD nor the number of pills per prescription is captured.

[gg] In GKV claims, outpatient diagnoses are reported quarterly.

[hh] Hungary will not have a VTE Reporting Period 1. Hungary will also not have a VTE Reporting Period 2 for PsA and UC.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
Number of UC patients with: ≥1 VTE risk factor; no prior alternative therapy (i.e., biologic); and an ADD >10 mg in Weeks 16-23, Weeks 24-31, Weeks 32-39, and Weeks 40-47 of follow-up[t]	Outcome: Changes in the utilisation of tofacitinib —VTE risk factors	
Discontinuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib —VTE risk factors	
Continuation of tofacitinib after developing ≥1 VTE risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib —VTE risk factors	
Use in the elderly (patients 65 years and older) (will be assessed separately in VTE Reporting Periods 1, 2, and 3,[hh] and CV and Malignancy Reporting Periods 1, 2, and 3[ii])		
Initiating tofacitinib with no prior use of an alternative therapy (i.e., biologic) among patients 65 years of age and older	Outcome: Changes in prescribing patterns—Age 65 years and older	See '***Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs – Compliance to recommendations to limitations for use in patients aged 65 years and older***' for operational definitions.
Discontinuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Changes in prescribing patterns—Age 65 years and older	
Failure to discontinue tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Changes in prescribing patterns—Age 65 years and older	
Appropriate continuation of tofacitinib for patients who turn 65 years old while receiving tofacitinib	Outcome: Changes in prescribing patterns—Age 65 years and older	

[ii] Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC.

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition
In patients with CV risk factors (will be assessed separately in CV and Malignancy Reporting Periods 1, 2, and 3[ii] and stratified by sex as outlined in Section 9.7.1.3.3 [Use in patients with CV risk factors])		
Initiating tofacitinib with ≥1 CV risk factor	Outcome: Changes in the utilisation of tofacitinib —CV risk factors	See '***Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs – Compliance to recommendations to limitations for use in patients with CV risk factors***' for operational definitions.
Initiating tofacitinib with ≥1 CV risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: Changes in the utilisation of tofacitinib —CV risk factors	
Discontinuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib —CV risk factors	
Continuation of tofacitinib after developing ≥1 CV risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib —CV risk factors	
In patients with malignancy risk factors (will be assessed separately in CV and Malignancy Reporting Periods 1, 2, and 3[ii])		
Initiating tofacitinib with ≥1 malignancy risk factor	Outcome: Changes in the utilisation of tofacitinib — Malignancy risk factors	See '***Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs – Compliance to recommendations to limitations for use in patients with malignancy risk factors***' for operational definitions.
Initiating tofacitinib with ≥1 malignancy risk factor and no prior use of an alternative therapy (i.e., biologic)	Outcome: Changes in the utilisation of tofacitinib — Malignancy risk factors	
Discontinuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib — Malignancy risk factors	
Continuation of tofacitinib after developing ≥1 malignancy risk factors while taking tofacitinib	Outcome: Changes in the utilisation of tofacitinib — Malignancy risk factors	

Table 3. Operational definitions of study variables in the selected databases

Variable	Role	Operational definition

Abbreviations: AIDS = acquired immunodeficiency syndrome; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aRMM = additional risk minimisation measures; AST = aspartate aminotransferase; ATC = Anatomical Therapeutic Chemical; CABG = coronary artery bypass graft; cs = conventional synthetic; CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; EBV = Epstein-Barr virus; HDL = high-density lipoprotein; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HPV = human papillomavirus; HZ = herpes zoster; ICD-10 = International Classification of Disease, 10th Revision; KSHV = Kaposi sarcoma-associated herpesvirus; LDL = low-density lipoprotein; MBR = (Swedish) Medical Birth Register; MI = myocardial infarction; MTX = methotrexate; NHIFA = National Health Insurance Fund Administration (of Hungary); NPR = (Swedish) National Patient Register; PCI = percutaneous coronary intervention; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SAP = statistical analysis plan; TB = tuberculosis; TG = triglycerides; UC = ulcerative colitis; VTE=venous thromboembolism.

9.3.3. 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 and made specific to each database. For example, for NHIFA, the Hungarian administrative claims database, the following proxy will be used to estimate duration: time between two prescription dispensings 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.

9.3.4. Average daily dose

Average daily dose (ADD) will be calculated in milligrams per day, starting from the index date and according to the variables available in the database, for the following pre-specified time intervals[jj]:

- Week 0 through Week 7 (from Day 1 to Day 56);
- Week 8 through Week 15 (from Day 57 to Day 112);
- Week 16 through Week 23 (from Day 113 to Day 168);
- Week 24 through Week 31 (from Day 169 to Day 224);
- Week 32 through Week 39 (from Day 225 to Day 280); and

[jj] The intervals will provide estimates for ADD over time. Some patients, for example those diagnosed with UC and prescribed an induction dose of 10 mg BID, may see a dose decrease over time showing the change from induction to maintenance therapy. However, given that patients may begin maintenance either at Week 8 or 16 and that patients may start and stop their medication anytime throughout follow-up, the periods are not labeled as induction or maintenance.

- Week 40 through Week 47 (from Day 281 to Day 336[kk]).

For each of these pre-specified time intervals, ADD will reported as a continuous and categorical variable:

- 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 will be further stratified by:

- Approved indication, or by the indication groups: "PsA or RA" and "UC";
- Presence of ≥1 VTE risk factor 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 and made specific to each database. For example, in Sweden, daily dose will be estimated by the defined daily doses (DDDs) or the strength of a single unit. Days' supply will be estimated by the number of DDDs in the respective dispensation.

Note: The objectives and sub-objectives that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), neither ADD nor the number of pills per prescription is captured.

9.4. Data sources

This study will use the following European databases, which were selected based on anticipated sample size, data availability and completeness, and/or geographic location to increase the generalisability of the study results to the EU:

[kk] The last 29 days of a 365-day year will not be captured in an 8-week interval.

- Sweden: National health registers: The National Patient Register (NPR); the Prescribed Drug Register (PDR); the Swedish Medical Birth Register (MBR); the National Cancer Registry (NCR); and the Swedish Cause of Death Register (CDR);

- Hungary: National Health Insurance Fund Administration (NHIFA), an administrative claims database;

- The Netherlands: PHARMO Database Network; and

- Germany: GKV claims, an administrative claims database.

9.4.1. Sweden: The National Patient Register, the Prescribed Drug Register, the Swedish Medical Birth Register, the National Cancer Registry, the Cause of Death Register

Health care in Sweden is primarily government-funded and managed at the national, regional, and local level. Only a small proportion of the population (6%) also have some type of supplementary private health insurance.[6] In most regions, there is no formal gatekeeping and patients may contact specialists directly.[6] In Sweden, patients with inflammatory rheumatic diseases like RA and UC are typically treated by hospital-based specialists as opposed to general practitioners (GPs).[7-9] The current study will utilize four large Swedish registers linked via patients' personal identifications numbers: the NPR, the PDR, the Swedish Pregnancy Register, and the NCR.

The NPR includes information regarding inpatient and outpatient non-primary (i.e., specialist) encounters across Sweden; outpatient GP encounters are not captured in the NPR. Beginning in 1987, coverage for inpatient admissions became nationwide and is near 100%.[7] Coverage for outpatient non-primary care began nationwide in 2001 and is around 87% (although it may be higher for somatic care such as rheumatology).[8] Key variables include diagnosis, surgery, external causes of injury (E-codes), age, sex, hometown, hospital, specialty, and information related to hospital admissions and discharges (e.g., dates, main and contributory diagnoses, mode of discharge). Information on patient anthropometric data (e.g., height, weight, body mass index) is not available nor are laboratory test results (e.g., ALC, blood lipid levels) or clinical measurements (e.g., blood pressure). A number of diagnoses, including RA, have been reported to have high positive predictive values in the inpatient register;[10] in recent studies, the reported positive predictive value in the NPR was 91% for RA[8] and 79% for UC.[11] The NPR is updated annually.

The PDR, maintained by the National Board of Health and Welfare, contains all prescribed and dispensed medication for patients in Sweden. Coverage of prescriptions is close to 100%, however, inpatient administrations are not captured and there is only partial capture of drugs administered in hospital outpatient visits. Information included in the PDR include basic demographic characteristics such as age, sex, and residency, as well as medication-specific information such as the prescribed / dispensed drug (e.g., ATC code, International Non-proprietary Names [INN]), prescription dispensing date, pack size, dispensed amount, formulation, dosage, prescribing healthcare practitioner, and costs. The PDR is updated monthly.

The Swedish MBR was established in 1973 and is managed by the National Board of Health and Welfare (NBHW). The register covers 100% of births and stillbirths of at least 22 gestational weeks since July 2008 (and of at least 28 gestational weeks before July 2008) in Sweden thereby facilitating the identification of tofacitinib exposure during pregnancy. There are no data on elective terminations or spontaneous abortions in the register. The register covers information such as gestational duration, self-reported smoking status during pregnancy, diagnoses during pregnancy, date of birth, delivery complications, diagnoses of the mother and the child, Apgar score, low birthweight, head circumference and survival. The data for the previous calendar year are usually available in December of the following year. Access to the register data for scientific research is decided by the NBHW through a standard application procedure and is assessed on a case-by-case basis.

The NCR was started in 1958 and is managed by the NBHW. The registry records all newly diagnosed tumours and blood cancers diagnosed by clinical, morphological, or other laboratory examinations, as well as cases diagnosed at autopsy. Since the mid-1980s, there are six regional registries associated with the oncological centres in each medical region of Sweden where the registration, coding, and major check-up and correction work is performed. The register includes information on patient characteristics, tumour characteristics, diagnosis, and date and cause of death. Data are updated on an annual basis with a lag time of approximately 13 months. Applications for data access are sent to the National Board of Health and Welfare and processed by a pre-defined data permit process.

The Cause of Death Register (CDR) is managed by the NBHW. It contains data from 1961 and is updated annually. There is also a historical register of causes of death for the years 1952–1960. The register includes all deaths that have occurred in Sweden, including deaths of non-Swedish citizens. Key variables include age, sex, country of birth and residency, date of death, cause of death (ICD-9/10 codes have been used since 1988), and intent (in cases of injury or poisoning), medical procedures (if death occurred within 4 months after surgery), and autopsy. Stillbirths are not included in the register. The register is updated annually for the cause of death variables with a preliminary update in March and a second update in August. Dates of death are available in the register earlier. Access to the register data for scientific research is decided by the NBHW through a standard application procedure and is assessed on a case-by-case basis.

Most of the Swedish registries are updated yearly, and it can take 6-9 months to receive a data extraction. As a result, there is a lag in data availability of approximately 14-21 months.

9.4.2. Hungary: National Health Insurance Fund Administration (NHIFA)

Hungary has a single-payer healthcare system with a purchaser-provider split model and output-based payment system.[12] The budget of the Health Insurance Fund (HIF), managed by the National Health Insurance Fund Administration (NHIFA), consists of health insurance contributions, health care taxes, government transfers, and other incomes.[13] Participation in health insurance is mandatory. Coverage is theoretically universal, as patients cannot be penalized for missed contributions. Family doctors are intended to be gatekeepers, however, certain specialties are accessible without referral (dermatology; ear, nose and throat diseases; obstetrics and gynaecology; general surgery; traumatology; ophthalmology; oncology;

urology; and psychiatry).[12] The NHIFA database contains information on healthcare covered by the state and has national coverage for reimbursed services (medicine, out- and inpatient services), but non-reimbursed services (including over the counter medications) are not included. Data are available for retrospective analyses from 01 January 2004.[14]

There are four NHIFA registers: Demography, Drugs, Inpatient, and Outpatient. The Demography register includes sex, age, and date of death. The Drugs register captures brand information, date, ATC7 codes, volume, ICD codes, and territory. Further, information is collected regarding EU number, invented name, strength, pharmaceutical form, route of administration, packaging, and content. The Inpatient register comprises date (admission, discharge, and length of stay), location, ICD codes, Diagnosis Related Groups (DRG), and International Classification of Procedures in Medicine (ICPM) codes. The Outpatient register captures labs and diagnostic services and specialist visits, including date, location, ICD codes, and ICPM codes.[14]

9.4.3. The Netherlands: The PHARMO Database Network

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. The databases are linked on an annual basis, meaning that the average lag time of the data is approximately 1 year (the updated databases are available in the second half of the year). The PHARMO Database Network is broadly representative of the Dutch population and covers both primary and secondary (inpatient and outpatient) settings of care, as well as pharmacy (community and in-patient) dispensed treatments through its different databases.

The different databases in the network include:

- The General Practitioner Database captures electronic medical record (EMR) data from registered GPs (covering approximately 20% of the Dutch population). Key variables include diagnoses (coded via the International Classification of Primary Care [ICPC]), symptoms, laboratory tests and test results, referrals to specialists, and drug prescription information including type of product (ATC codes), prescription date, strength, dosage, regimen, quantity, and route of administration. Height, weight, tobacco use, and alcohol abuse information are also available.

- The Out-patient Pharmacy Database (covering approximately 25% of the Dutch population) includes data on all GP or specialist prescribed products, as well as hospital pharmacies. -The Outpatient Pharmacy Database captures drug dispensings from outpatient pharmacies. Key variables include product (ATC codes), dispensing date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs.

- The In-patient Pharmacy Database captures inpatient medication administrations and drug dispensings from hospital pharmacies (covering approximately 10% of the Dutch

population). Key variables include drug type (ATC codes), start and end date of use, strength, dosage regimen, and route of administration.

- The Clinical Laboratory Database captures the results of laboratory tests requested by GPs and medical specialists (covering approximately 5% of the Dutch population). Key variables include date and time of testing, test result, unit of measurement, and type of clinical specimen.

- The Hospital Database, including the high-budget impact medication database (where tofacitinib will be captured), captures hospital admission data for admissions of more than 24 hours or admissions of less than 24 hours that require a bed(covering approximately 80% of the Dutch population). Key variables include information on discharge diagnoses (coded according to the WHO International Classification of Disease and ICD-10), procedures (coded via the Dutch Hospital Data Foundation registration system), and hospital admission and discharge dates.

- The Cancer Registry Database captures cases of newly diagnosed cancer (with national coverage). Key variables include cancer diagnosis, tumour staging (according to tumour, nodes, metastases [TNM] staging), tumor site (topography), morphology (histology; coded via the ICD-O-3), comorbidity at diagnosis, and treatment received directly after diagnosis.

- The Netherlands Perinatal Registry is maintained by Perined and comprises data on pregnancies, births, and neonatal outcomes of births in the Netherlands, voluntarily collected by perinatal caregivers, mainly for benchmarking. For research purposes the data are linked with the PHARMO Database Network via a trusted third party, resulting in the PHARMO Perinatal Research Network (PPRN20). Records include information on mothers (e.g., maternal age, obstetric history, parity), pregnancy (e.g., mode of conception, mode of delivery), and children (e.g., birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists.

These data sources are linked on a patient level through probabilistic linkage[15] based on validated algorithms. The number of analysable patients for a given outcome will be limited by the availability of patient data in the databases required to be linked for that outcome. The longitudinal and ongoing nature of the PHARMO Database Network system enables follow-up of more than 10 million residents of the Netherlands for an average of 12 years.

9.4.4. Germany: Gesetzliche Krankenversicherung (GKV) claims (SHI Database)

Germany has a multi-payer healthcare system consisting of a combination of statutory health insurance (SHI)—i.e., the Gesetzliche Krankenversicherung (GKV)—and private health insurance (PHI). GKV claims collects German healthcare data based on insurance claims from approximately 8-10 different SHI providers. Since an SHI is a requirement for individuals with a permanent place of residence in Germany, even for short-term stays, the general population coverage in the SHI is considered nationwide. The SHIs also allow insurance coverage for children and spouses within a family insurance policy. The population size available through this claims database is approximately 5 million individuals which

represents an estimated 6.9% of the SHI-insured population in Germany and is nationally representative. Available data history reaches back to January 2011. In the database all individuals have a de-identified ID; therefore, longitudinal follow-up is possible. The database includes information on patient demographics and inpatient and outpatient care, as well as outpatient medical prescriptions. Available demographic information includes sex, age, insurance status, time insured, and region of residence. Inpatient and outpatient diagnoses are coded via International Classification of Disease, 10th Revision, German Modification (ICD-10-GM) codes and procedures are available. For outpatient diagnoses, only the quarter of the diagnosis is reported (i.e., the actual date is unavailable). Outpatient physician specialty information and inpatient medical department of care can be accessed. Medical prescriptions from retail pharmacies are coded using the ATC hierarchy and the date of the prescription dispensing is available. Information on patient anthropometric data (e.g., height, weight, body mass index [BMI]) is not available nor are result outcomes for laboratory tests (e.g., ALC, blood lipid levels) or clinical measurements (e.g., blood pressure).

Data for the previous year are updated in the 3rd quarter of the following year, implying a 9--12-month lag for data availability. Furthermore, IQVIA cannot access the data directly and must secure access through a partner, which can take an additional 4-5 months.

9.4.5. Summary of databases

A summary of the selected databases is provided below in Table 4.

Table 4. Summary of selected databases

Characteristics	**Sweden** ***NPR, PDR, MBR, NCR, and CDR***	**Hungary** ***NHIFA***	**The Netherlands** ***PHARMO Database Network***	**Germany** ***GKV claims***
Database type	Administrative records	Claims	EMRs	Claims
Country population	10.4 million (as of 2020)	9.8 million (as of 2020)	17.4 million (as of 2020)	83.2 million (as of 2020)
Overall representativeness	National coverage	National coverage	National coverage	National coverage
Physician population	NPR: All except GPs PDR: Almost complete coverage	All	All	All
Expected number of tofacitinib patients by the end of 2021	~3400[a]	450[b, c]	280[d]	1111[e]
Lag in data availability	14-21 months	6 months	Approximately 12 months	At least 12 months

Table 4. Summary of selected databases

Characteristics	Sweden *NPR, PDR, MBR, NCR, and CDR*	Hungary *NHIFA*	The Netherlands *PHARMO Database Network*	Germany *GKV claims*

Abbreviations: CDR = [Swedish] Cause of Death Register; EMR = electronic medical record; GKV = Gesetzliche Krankenversicherung; GP(s) = general practitioner(s); MAH = Marketing Authorisation Holder; NHIFA = National Health Insurance Fund Administration; MBR = [Swedish] Medical Birth Register; NCR = [Swedish] National Cancer Registry; NPR = [Swedish] National Patient Register; PDR = [Swedish] Prescribed Drug Register.

a. Based on tofacitinib data for 2017-2019 that was obtained using the publicly available tools for querying the Swedish national health registers (available at https://sdb.socialstyrelsen.se/if_lak/val.aspx).

b. Patient counts provided by the MAH.

c. Patient counts are through 2022 given the shorter data lag (6 months) associated with NHIFA.

d. Patient counts as of 2019. This number will decrease when the GP database and the Clinical Laboratory Database are required, because only 30% and 40% of patients observed in the High Budget Impact Medication Dataset are also observed in the GP database (covering approximately 20% of the Dutch population) and the Clinical Laboratory Database (covering approximately 5% of the Dutch population), respectively.

e. Patient counts 2017-2019.

9.5. Study size

The sample size was based on achieving a desired precision of the estimation for the binary endpoints. The following formula, based on the normal approximation to the binomial proportion, was used to calculate the minimum sample size for significance level α for each indication per country:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

where P is the expected proportion of patients with the outcome of interest; e is the margin of error, or half the desired width of the confidence interval (CI); and $Z_{1-\alpha/2}$ is the standard normal Z-score corresponding to a cumulative probability of 1–α/2.

The outcomes of interest are described in Section 9.3.1 (Outcomes) and Table 3. As the proportion of patients with each of the outcomes of interest (*p)* is not known in advance, it will be set to 50%, which yields the most conservative (i.e., the largest) sample size for a specified margin of error.

Therefore, to obtain 95% CIs with a desired total width of 20% for each outcome of interest (per indication per country), the study will require a sample size of *at least* 97 patients, which is rounded up to a *minimum* target sample size of at least 100 patients per indication per country. Note that the sample size will be smaller for some of the outcomes measured (e.g.,

use of tofacitinib while pregnant [women only] and all outcomes that require patients to have six months of tofacitinib therapy) and thus precision will vary by outcome.

$$n = \frac{0.50 \cdot 0.50 \cdot 1.96^2}{0.10^2} = 96.04$$

As such, the *minimum* target sample size per country (across all three indications) will be 300 patients and the *minimum* target sample size overall (across all countries and all three indications) will be 1200 patients.

Note that the target sample size of 100 patients per indication per country represents a *minimum*—i.e., enrolment will not stop at 100 patients but will rather include *all* patients identified during the indexing period who meet the study inclusion/exclusion criteria. Some indication-country combinations (e.g., RA in Sweden) are likely to have enough patients to have a higher precision (e.g., a confidence interval width closer to 10%) than other indication-country combinations (e.g., UC in Hungary), because tofacitinib has been approved for longer for that indication in that country. The MAH will include all eligible patients within each indication-country combination to maximize the precision of the estimates reported.

If the *minimum* target sample size of 100 patients per indication is not attainable for a country at the end of the study observation period, then the CV and Malignancy Reporting Period 3 will be extended for that country as the data are available.

Table 5 presents the number of patients required for a given indication in each country to achieve select confidence interval widths ranging from 10-20%.

Table 5. Number of patients required to achieve select confidence interval widths

Number of patients	Confidence interval width (%)
385	10
267	12
196	14
151	16
119	18
97	20

9.5.1. Feasibility counts

The expected distribution of patients across indications (RA, PsA, UC) for the databases in Hungary, Sweden, the Netherlands, and Germany is described below. Where limited information is available, the methods used to predict uptake of tofacitinib are discussed.

High-level feasibility counts for NHIFA of Hungary are available and provided in Table 6. As of June 2021, only the RA indication has received full reimbursement in Hungary, with the PsA and UC indications available via the Named Patient Program. Thus, there may be smaller patient numbers for these two indications relative to the RA indication in Hungary.

Table 6. Tofacitinib patient counts through March 2020 in NHIFA of Hungary

Condition (ICD-10 code)	Date approved by the EC	Date of full reimbursement	Number of patients
RA (M05)	Mar 2017 (5-mg) Dec 2019 (11-mg PR)	May 2019	156
PsA (L40)	Jun 2018 (5-mg)	Anticipated Q1 2023[a]	10
UC (K51)	Jul 2018 (5-, 10-mg)	Anticipated Q1 2023[a]	46
Total			**218**

Abbreviations: EC = European Commission; ICD-10: International Classification of Diseases, Tenth Revision; mg = milligram; NHIFA = National Health Insurance Fund Administration (of Hungary); PR = prolonged-release; PsA = psoriatic arthritis; Q = quarter; RA = rheumatoid arthritis; UC = ulcerative colitis.

a. As of June 2021, only available via the Named Patient Program.

Based on publicly available tools for querying the Swedish national health registries,[ll] the annual number of tofacitinib patients are reported in Table 7 (overall, but not stratified by indication).

Table 7. Annual tofacitinib patient counts in the Swedish Prescription Drug Register (2017-2019)

	2017	2018	2019
Number of tofacitinib patients[a]	336	889	1912

In Sweden, tofacitinib received full reimbursement for RA in April 2017 and full reimbursement for PsA and UC in October 2018.

Abbreviations: PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

a. Counts were obtained using the publicly available tools for querying the Swedish national health registers (available at https://sdb.socialstyrelsen.se/if_lak/val.aspx). Note that only data on the annual number of tofacitinib patients (overall) are available.

Counts for the number of patients with RA, PsA, and UC in Sweden with moderate-to-severe disease (defined as treated with a biologic) are reported in Table 8, as this patient population represents those patients who are most likely to be eligible to receive tofacitinib and thus potentially be prescribed tofacitinib during the study observation period. The time periods for the studies listed in the table below varied by indication and ranged from 2006 (PsA) to 2019 (UC).

Table 8. Summary of expected distribution of biologics across indications (RA, PsA, UC) in Sweden

Country	Indication	N	Details
Sweden	RA[16]	13274	2010-2016

[ll] Available at https://sdb.socialstyrelsen.se/if_lak/val.aspx.

Table 8. Summary of expected distribution of biologics across indications (RA, PsA, UC) in Sweden

Country	Indication	N	Details
			Swedish Rheumatology Quality register (SRQ) linked with the Swedish national health registers (PDR, NPR, NCR) Incident and prevalent biologic users
	PsA[17]	898 (first line) 146 (second line)	May 2010 to Dec 2012 PDR SC-TNFi
	PsA[18]	5357	2006 to 2017 SRQ Incident and prevalent biologic users
	UC[a]	2005 (TNFi) <63[b] (tofacitinib)	1 July 2019 and 31 Dec 2019 Swedish Quality Register for Inflammatory Bowel Disease TNFi; tofacitinib

Abbreviations: MAH = Marketing Authorisation Holder; N = number; NCR = (Swedish) National Cancer Registry; NPR = (Swedish) National Patient Register; PDR = (Swedish) National Prescription Register; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SC = subcutaneous; SRQ = Swedish Rheumatology Quality register; TNFi = tumour necrosis factor inhibitor; UC = ulcerative colitis.

a. Data provided by the MAH.
b. An exact number cannot be reported due to the masking of small cell counts to comply with privacy regulations.

High-level feasibility counts for PHARMO Database Network of the Netherlands are available and provided in Table 9.

Table 9. Tofacitinib patients counts (through 2019) in the PHARMO Database Network of the Netherlands

Condition	Date approved by the EC	Date of full reimbursement	Number of patients[a]
RA	Mar 2017 (5-mg) Dec 2019 (11-mg PR)	May 2017	180
PsA	Jun 2018 (5-mg)	August 2018	40
UC	Jul 2018 (5-, 10-mg)	September 2018	65
Total			**280**

Abbreviations: EC = European Commission; mg = milligram; PR = prolonged-release; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

a. This number will decrease when the GP database and the Clinical Laboratory Database are required, as only 30% and 40% of patients observed in the High Budget Impact Medication Dataset are also observed in the GP database (covering approximately 20% of the Dutch population) and the Clinical Laboratory Database (covering approximately 5% of the Dutch population), respectively. Notably, the patient numbers outlined are from 2019, and these are expected to increase with tofacitinib uptake at the initial study execution in September 2022.

High-level feasibility counts for GKV claims of Germany are available and provided in Table 10.

Table 10. Tofacitinib patients counts (2017-2019) in GKV Claims of Germany

Condition (ICD-10 code)	Date approved by the EC	Date of full reimbursement	Number of patients
RA (M05)	Mar 2017 (5-mg) Dec 2019 (11-mg PR)	May 2017	843
PsA (L40)	Jun 2018 (5-mg)	June 2018	169
UC (K51)	Jul 2018 (5-, 10-mg)	July 2018	190
Total			**1111**

Abbreviations: EC = European Commission; ICD-10: International Classification of Diseases, Tenth Revision; mg = milligram; GKV = Gesetzliche Krankenversicherung; PR = prolonged-release; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

Market uptake of tofacitinib for the three indications in the proposed study countries (Hungary, Sweden, the Netherlands, and Germany) cannot be determined *a priori*. Additionally, as this is a multi-year study, changes in the treatment landscape (e.g., approval of new medications for RA, PsA, and UC treatment) may limit the number of patients prescribed tofacitinib. As such, it may be difficult to achieve the minimum target sample size of 100 patients per indication for certain indication-country combinations during the proposed study observation period, depending on overall tofacitinib uptake and when a particular indication received full reimbursement. This could be especially true for the UC (and PsA) indication, which received or will receive full reimbursement after RA (sometimes much later). Thus, if the *minimum* of 100 tofacitinib patients have not been accrued for a specific indication-country combination (e.g., UC in Sweden), then the CV and Malignancy Reporting Period 3 will be extended for that country as the data are available.

9.6. Data management

The processes for database management differ by country. Generally, the data are stored at the database level and analysed locally. SAS® software (SAS Institute Inc., Cary, North Carolina, United States) or other appropriate analytical software will be used to access the raw data, manage the analytic datasets, and conduct data analyses. If the study is conducted by a third-party, the datasets and analytic programs will be stored according to the third-party's procedures. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH) 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., pregnancy diagnosis for a male patient).

9.7. Data analysis

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.

Interim study report 1 will cover data from 01 April 2016 through 31 December 2020. Interim study report 2 will cover data from 01 April 2016 through 31 December 2022. The final study report will cover data from 01 April 2016 through 31 December 2024. If it is necessary to extend the study observation period for a country because the *minimum* number of tofacitinib patients (100 patients) per indication has not been met for all three indications by the end of the study observation period, the study observation period will be extended for those countries as the data are available.

9.7.1. Primary analysis

The primary analyses will be conducted per approved indication per country, unless otherwise specified. Data will *not* be pooled across countries due to heterogeneity in: how the data are recorded in each database, local data protection laws, and prescribing and coding practices.

Results will be provided as descriptive statistics; no comparative statistical analyses will be conducted. 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.

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

9.7.1.1. Primary Objective 1: Demographics, comorbidities, and prior and current medications[mm,nn]

The proportion of patients treated with tofacitinib without evidence of an approved indication will be described and tabulated.

The demographic variables listed in Table 3 will be described and tabulated.

The comorbidity and medication variables listed in Table 3 will be described and tabulated for each patient's overall study period and stratified by whether they occurred prior to and/or after the index tofacitinib dispensing (as applicable) and by age (e.g., <65 and 65 years and older). They may also be additionally stratified by sex.

[mm] In GKV claims, outpatient diagnoses are reported quarterly.

[nn] The data sources are unable to reliably ascertain severity of hepatic impairment and renal impairment.

9.7.1.2. Primary Objective 2: Prescribers' adherence to the tofacitinib aRMMs[oo,pp]

9.7.1.2.1. Compliance to the recommended posology per indication and duration of use

Average daily dose, as listed in Table 3 and defined in Section 9.3.4, will be reported for each of the pre-specified time intervals as a continuous and categorical variable and stratified by approved indication group ("RA and PsA" or "UC"), age (e.g., <65 and ≥65 years), presence of ≥1 VTE risk factor in the 12 months prior to tofacitinib initiation, prior use of an alternative therapy (i.e., biologic) in the 12 months prior to tofacitinib initiation; and reporting period;[qq] it may additionally be stratified by sex.

Duration of tofacitinib therapy, as listed in Table 3 and defined in Section 9.3.3, will also be described, tabulated, and stratified by age (e.g., <65 and ≥65 years); it may additionally be stratified by sex.

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

9.7.1.2.2. Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment[rr]

The screening and monitoring variables listed in Table 3 will be described and tabulated.

9.7.1.2.2.1. Compliance to recommendations for limitations of use

9.7.1.2.2.1.1. Patients with VTE risk factors

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, recent MI). Proportions will be stratified by "RA or PsA" and "UC."

The total number of VTE risk factors identified prior to tofacitinib initiation will also be described continuously and stratified by "RA or PsA" and "UC."

The proportion of patients diagnosed with UC, one or more VTE risk factors identified prior to tofacitinib initiation, and no use of an alternative therapy (i.e., biologic) prior to tofacitinib

[oo] The study outcomes that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), neither ADD nor the number of pills per prescription is captured.

[pp] In GKV claims, outpatient diagnoses are reported quarterly.

[qq] Hungary will not have a VTE Reporting Period 1. Hungary will also not have a VTE Reporting Period 2 for PsA and UC.

[rr] This outcome (and all sub-outcomes) will not be assessed in Sweden because the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, it may not be possible to differentiate an ALC laboratory test from an ANC laboratory test, or an ALT laboratory test from an AST laboratory test. In the PHARMO Database Network, TB screening and viral hepatitis B and C testing are not captured.

initiation whose ADD in Week 16 through Week 23, Week 24 through Week 31, Week 32 through Week 39, and Week 40 through Week 47 was >10 mg will be described and tabulated.

The proportion of patients who discontinue tofacitinib after developing one or more VTE risk factors while taking tofacitinib will be described and tabulated overall and by individual VTE risk factor (e.g., VTE, MI). Proportions will be stratified by "RA or PsA" and "UC."

The proportion of patients who continue tofacitinib after developing one or more VTE risk factors while taking tofacitinib will be described and tabulated overall and by individual VTE risk factor (e.g., VTE, MI). Proportions will be stratified by "RA or PsA" and "UC."

9.7.1.2.2.1.2. Patients aged 65 years and older

The proportion of patients initiating tofacitinib aged 65 years and older at the index date without prior alternative therapy (defined as ≥1 biologic in the 12 months prior to index date), will be described and tabulated. Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have 0 prescription dispensings of tofacitinib from the time they turn 65.5 years old through the end of the follow-up period, will be described and tabulated. Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through the end of the follow-up period and no history of alternative treatments *prior to* that tofacitinib prescription dispensing, will be described and tabulated. Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through the end of the follow-up period and a history of alternative treatments *prior to* that tofacitinib prescription dispensing, will be described and tabulated. Proportions will be presented overall and stratified by approved indication.

9.7.1.2.2.1.3. Patients with CV risk factors

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 (i.e., elderly, current or past smoker[x], history of diabetes, history of hypertension, history of hyperlipidaemia, history of coronary artery disease, history of chronic kidney disease, history of stable angina pectoris). Proportions will be stratified by approved indication and sex.

The proportion of patients with one or more CV risk factors, identified prior to tofacitinib initiation and no prior use of an alternative therapy (i.e., biologic), will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current or past smoker[x],**Error! Bookmark not defined.** history of diabetes, history of hypertension, history

of hyperlipidaemia, history of coronary artery disease, history of chronic kidney disease, history of stable angina pectoris). Proportions will be stratified by approved indication and sex.

The proportion of patients who discontinue tofacitinib after developing one or more CV risk factors while taking tofacitinib, will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current smoker[x], diabetes, hypertension, hyperlipidaemia, coronary artery disease, chronic kidney disease, stable angina pectoris). Proportions will be stratified by "RA or PsA" and "UC" and sex.

The proportion of patients who continue tofacitinib after developing one or more CV risk factors while taking tofacitinib, will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current smoker[x], diabetes, hypertension, hyperlipidaemia, coronary artery disease, chronic kidney disease, stable angina pectoris). Proportions will be stratified by "RA or PsA" and "UC" and sex.

9.7.1.2.2.1.4. Patients with malignancy risk factors

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 (i.e., elderly, history of malignancy, current or past smoker[x]). Proportions will be stratified by approved indication.

The proportion of patients with one or more malignancy risk factors, identified prior to tofacitinib initiation and no prior use of an alternative therapy (i.e., biologic), will be described and tabulated overall and for individual malignancy risk factor (i.e., elderly, history of malignancy, current or past smoker[x]). Proportions will be stratified by approved indication.

The proportion of patients who discontinue tofacitinib after developing one or more malignancy risk factors while taking tofacitinib will be described and tabulated overall and by individual malignancy risk factor (i.e., elderly, history of malignancy, current smoker[x]). Proportions will be stratified by "RA or PsA" and "UC."

The proportion of patients who continue tofacitinib after developing one or more malignancy risk factors while taking tofacitinib will be described and tabulated overall and by individual malignancy risk factor (i.e., elderly, history of malignancy, current smoker[x]). Proportions will be stratified by "RA or PsA" and "UC."

9.7.1.2.2.1.5. Potential contraindicated use of tofacitinib

The proportion of patients treated with tofacitinib with potential contraindicated use will be described and tabulated overall and reported by type of contraindicated use (e.g., patients with severe hepatic impairment, pregnant patients, etc.). Note that patients may be captured in more than one type of contraindicated use category.

9.7.1.2.2.1.6. Use with concomitant 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 dispensings.[ss] Additionally, the number of overlapping days' supply of the biologic or selected potent immunosuppressant with the tofacitinib prescription dispensing will be described continuously and categorically (e.g., 1-7 days, 8-14 days, 15-21 days, 22-30 days, ≥31 days; final cut-offs to be determined after examining the distribution of the data).

9.7.1.3. Secondary Objectives 1 and 2: Describe prescribing patterns; and Describe changes in tofacitinib prescribing patterns (utilisation) following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure[tt,uu,vv,ww]

9.7.1.3.1. Use in patients with VTE risk factors

The proportion of patients with one or more risk factors for VTE, identified prior to tofacitinib initiation, will be described and tabulated overall and for each individual VTE risk factor (e.g., prior VTE, recent MI) for VTE Reporting Period 1, VTE Reporting Period 2, and VTE Reporting Period 3.[vv] Proportions will be stratified by "RA or PsA" and "UC."

The total number of VTE risk factors identified prior to tofacitinib initiation will also be described continuously for VTE Reporting Period 1, VTE Reporting Period 2, and VTE Reporting Period 3[vv] and stratified by "RA or PsA" and "UC."

The proportion of patients diagnosed with UC, one or more VTE risk factors identified prior to tofacitinib initiation, and no use of an alternative therapy (i.e., biologic) prior to tofacitinib initiation whose ADD in Week 16 through Week 23, Week 24 through Week 31, Week 32 through Week 39, and Week 40 through Week 47 was >10 mg will be described and tabulated for VTE Reporting Period 1, VTE Reporting Period 2, and VTE Reporting Period 3.[vv]

The proportion of patients who discontinue tofacitinib after developing one or more VTE risk factors while taking tofacitinib will be described and tabulated overall and for each individual VTE risk factor (e.g., VTE, MI) for VTE Reporting Period 1, VTE Reporting

[ss] Patients with ≥2 dispensings of tofacitinib are more likely to have taken tofacitinib for the full days' supply of the prescription as opposed to patients with only 1 dispensing of tofacitinib.

[tt] The study outcomes that contain an ADD component will *not* be assessed in Hungary or the Netherlands. The Hungarian administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. In the high-budget impact medication dataset of the PHARMO Database Network (Netherlands), neither ADD nor the number of pills per prescription is captured.

[uu] In GKV claims, outpatient diagnoses are reported quarterly.

[vv] Hungary will not have a VTE Reporting Period 1. Hungary will also not have a VTE Reporting Period 2 for PsA and UC.

[ww] Hungary will not have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for PsA and UC.

Period 2, and VTE Reporting Period 3.[vv] Proportions will be stratified by "RA or PsA" and "UC."

The proportion of patients who continue tofacitinib after developing one or more VTE risk factors while taking tofacitinib will be described and tabulated overall and for each individual VTE risk factor (e.g., VTE, MI) for VTE Reporting Period 1, VTE Reporting Period 2, and VTE Reporting Period 3.[vv] Proportions will be stratified by "RA or PsA" and "UC."

9.7.1.3.2. Use in the elderly (patients aged 65 years and older)

The proportion of patients initiating tofacitinib aged 65 years and older at the index date without prior alternative therapy (defined as ≥1 biologic in the 12 months prior to index date) will be described and tabulated for VTE Reporting Period 1, VTE Reporting Period 2, VTE Reporting Period 3,[vv] CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have 0 prescription dispensings of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period, will be described and tabulated for VTE Reporting Period 1, VTE Reporting Period 2, VTE Reporting Period 3,[vv] CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and no history of alternative treatments *prior to* that tofacitinib prescription dispensing, will be described and tabulated for VTE Reporting Period 1, VTE Reporting Period 2, VTE Reporting Period 3,[vv] CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be presented overall and stratified by approved indication.

The proportion of patients aged 65 years, receiving tofacitinib, who have ≥1 prescription dispensing of tofacitinib from the time they turn 65.5 years old through to the end of the follow-up period and a history of alternative treatments *prior to* that tofacitinib prescription dispensing, will be described and tabulated for VTE Reporting Period 1, VTE Reporting Period 2, VTE Reporting Period 3,[vv] CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be presented overall and stratified by approved indication.

9.7.1.3.3. Use in patients with CV risk factors

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 (i.e., elderly, current or past smoker[x], history of diabetes, history of hypertension, history of hyperlipidaemia, history of coronary artery disease, history of chronic kidney disease, history of stable angina pectoris) for CV and Malignancy Reporting Period 1, CV and Malignancy

Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication and sex.

The proportion of patients with one or more CV risk factors, identified prior to tofacitinib initiation and no prior use of an alternative therapy (i.e., biologic), will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current or past smoker[x], history of diabetes, history of hypertension, history of hyperlipidaemia, history of coronary artery disease, history of chronic kidney disease, history of stable angina pectoris) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication and sex.

The proportion of patients who discontinue tofacitinib after developing one or more CV risk factors while taking tofacitinib will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current smoker[x], diabetes, hypertension, hyperlipidaemia, coronary artery disease, chronic kidney disease, stable angina pectoris) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication and sex.

The proportion of patients who continue tofacitinib after developing one or more CV risk factors while taking tofacitinib will be described and tabulated overall and for each individual CV risk factor (i.e., elderly, current smoker[x], diabetes, hypertension, hyperlipidaemia, coronary artery disease, chronic kidney disease, stable angina pectoris) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication and sex.

9.7.1.3.4. Use in patients with malignancy risk factors

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 (i.e., elderly, history of malignancy, current or past smoker[x]) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication.

The proportion of patients with one or more malignancy risk factors, identified prior to tofacitinib initiation and no prior use of an alternative therapy (i.e., biologic), will be described and tabulated overall and for each individual malignancy risk factor (i.e., elderly, history of malignancy, current or past smoker[x]) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication.

The proportion of patients who discontinue tofacitinib after developing one or more malignancy risk factors while taking tofacitinib will be described and tabulated overall and for each individual VTE risk factor (i.e., elderly, history of malignancy, current smoker[x]) for

CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication.

The proportion of patients who continue tofacitinib after developing one or more malignancy risk factors while taking tofacitinib will be described and tabulated overall and for each individual malignancy risk factor (i.e., elderly, history of malignancy, current smoker[x]) for CV and Malignancy Reporting Period 1, CV and Malignancy Reporting Period 2, and CV and Malignancy Reporting Period 3.[ww] Proportions will be stratified by approved indication.

9.8. Quality control

The study will be conducted according to the standard operating procedures (SOPs) of IQVIA, Pfizer, the NBHW (Swedish national health registers) NHIF (NHIFA), the PHARMO Institute (the PHARMO Database Network), and Team Gesundheit (GKV claims).

At IQVIA, at the study level, all aspects of the study, from protocol development to the reporting of the results, will be conducted within the framework of the IQVIA Quality Management System. A quality control (QC) plan for the study will be developed and executed, which will include QC on the study methodology, SAP, programming, data management and analysis, study results, conclusions, and interim and final study reports. Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps;
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks;
- The result of the execution of the individual steps of the QC plan will be documented and will include the required corrective actions, if any. The execution of any required corrective action will be documented (if necessary);
- The QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study;
- Datasets and analytic programs will be stored according to IQVIA procedures with access restricted to study personnel; and
- IQVIA confidentiality agreements are signed by all employees and include data protection and strict prohibitions on reidentification attempts.

9.9. Limitations of the research methods

This study uses large real-world data sources in Sweden, Hungary, the Netherlands, and Germany to describe utilisation of tofacitinib and prescriber adherence to related screening and monitoring guidelines. These data sources are large and representative of patient and physician populations in their respective countries. Given the late introduction of the 2019

Article 20 referral and 2021 signal evaluation procedure aRMM materials, the study is uniquely positioned to describe use patterns before and after the revised guidelines were instituted.

The use of automated health databases for research has limitations, particularly regarding potential misclassification of the treatment and outcome variables. For example, the Swedish national health registers have minimal capture of inpatient hospital medication administrations and prescription dispensings, and partial capture of outpatient hospital medication administrations (i.e., medications administered in outpatient clinics located in hospitals) and prescription dispensings; thus, biologics that are dispensed or administered primarily through hospital channels will be missed. The major limitation for GKV claims (Germany) is that diagnoses recorded in the outpatient setting are reported quarterly and the same date is assigned to all visits in the quarter. Thus, it might not be possible to determine the exact date of RA/PsA/UC diagnosis or the exact date of diagnosis for comorbidities and outcomes that are managed in the outpatient setting. In the PHARMO Database Network, the high-budget impact medication dataset contains only declared medication for approved indications. It might not be possible to determine off-label use in this dataset. Additionally, in Sweden, vaccinations are typically administered by a GP or at a vaccination clinic and thus are not likely to be captured in the national health registers. In the PHARMO Database Network (Netherlands), the Out-patient Pharmacy Database does not capture vaccinations. The number of analysable patients for a given outcome will be limited by the availability of patient data in the databases required to be linked for that outcome. In GKV claims, differentiating between live and non-live vaccines is not possible. Furthermore, while these databases provide detailed information on dispensed medications, actual use cannot be determined. Thus, it is possible that patients who have never used tofacitinib may be included in the cohort. This limitation is mitigated in part by the fact that, regardless of whether a patient uses the drug, all patients should receive the recommended screening tests prior to receiving a tofacitinib prescription. Additionally, in some analyses, the patient population will be restricted to patients with ≥2 tofacitinib prescription dispensings to further assure actual use.

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 will be developed. This may lead to misclassification of drug exposure. Additionally, the selected databases do not record ADD of a prescription. For Hungary, the NHIFA administrative claims database is unable to estimate ADD, either directly or by proxy, due to how tofacitinib is captured in the database. Specifically, because tofacitinib is in a special category of medications that are administered through the hospital channel in Hungary, there is no milligram information available for tofacitinib prescriptions that are captured in NHIFA. Without milligram information for the tofacitinib prescriptions, the MAH is unable to directly or indirectly calculate ADD. Thus, NHIFA cannot be used to assess any study outcomes with an ADD component. In the high-budget impact medication dataset of the PHARMO Database Network, neither ADD nor the number of pills per prescription is captured. For Sweden, the MAH will estimate ADD using 8-week intervals throughout the follow-up period, which will result in imprecision of the ADD estimates that may worsen over the course of the follow-up period, particularly with respect to patients diagnosed with UC. For example, over the first

8 weeks of follow-up (Weeks 0-7), an ADD over 20 mg (over 10 mg BID) will be indicative of inappropriate use of tofacitinib. However, during Weeks 8-15, the estimated ADD will be more challenging to interpret, as the protocol will not be able distinguish patients who continue to take 10 mg BID for the full 8 weeks from patients who continue to take 10 mg BID at the start of the interval and then transition to 5 mg BID by the end of the 8-week interval or from patients who start the interval at 5 mg BID, experience a loss of response, and then go back to the 10 mg BID induction. For Weeks 17+, the MAH expects that most patients will receive the 10 mg ADD (5 mg BID) maintenance dose; however, the MAH will not be able to distinguish patients who inappropriately receive the 20 mg ADD (10 mg BID) induction dosing from patients who stopped and subsequently restarted tofacitinib at the appropriate 20 mg ADD (10 mg BID) induction dosing.

Misclassification of diagnoses is also a potential issue. For example, it may not be possible to distinguish between mild, moderate, and severe hepatic and renal impairment without laboratory test results (which are unavailable in the majority of data sources). Therefore, the severity of hepatic and renal impairment, as measured by diagnostic codes alone, may be misclassified for some patients. Additionally, the proposed databases do not provide explicit information regarding the indication for which a medication is prescribed. Therefore, a proxy will be used to determine indication, which may result in an inaccurate (or no) indication(s) being assigned to the index tofacitinib dispensing. Mild conditions, such as mild renal impairment, may not be brought to a healthcare provider's attention and thus may not be recorded. Additionally, the 12-month baseline period may be too short for the ascertainment of chronic conditions, as patients may not have had a healthcare encounter during this timeframe for which a diagnosis could be recorded and thus may be incorrectly categorized as not having the condition (e.g., malignancies occurring more than 12 months prior to tofacitinib initiation will be missed). Conversely, if the ascertainment interval is too long, conditions may resolve prior to tofacitinib initiation. For example, the 12-month baseline period may identify patients with severe hepatic impairment that has resolved prior to tofacitinib initiation. In the outpatient setting, some conditions may be recorded as a rule-out diagnosis and patients may be incorrectly categorised as having these conditions. Rule-out diagnoses will be minimised to the extent possible, for example, by requiring 2 diagnosis codes for a condition, a diagnosis code and therapy (e.g., a diagnosis code for type 2 diabetes and anti-diabetic therapy), or a diagnosis code followed by a code for a test, followed by a diagnosis code. The SAP will elaborate on these strategies, as appropriate. Ascertainment intervals and algorithms for disease classification will be carefully determined based on prior literature (where available) to reduce the potential for misclassification.

The ability to ascertain whether the recommended screenings or monitoring described in the prescriber treatment initiation and maintenance checklists took place is limited when using automated health databases. This is because many of the recommendations are at the discretion of the healthcare professional and/or because they will not be captured in administrative claims or register data. For example, it is not possible to assess whether the physician ensured that the woman was using effective contraception, was lactating, or whether the risks and benefits of treatment were considered among patients who have resided or travelled in areas of endemic TB. Additionally, it will not be possible to robustly assess whether HCPs discontinued tofacitinib in response to a patient developing an infection

because, for some infections, it will be challenging to assess severity and, depending on the length of the drug holiday, the MAH might not be able to capture a discontinuation in response to an infection (e.g., if it was shorter than the anticipated duration of the prescription). Therefore, the screening and monitoring recommendations proposed for assessment in the current study represent only those which can be objectively captured in automated health databases, such as laboratory tests for key clinical values. Given the use of data sources from two distinct EU countries, there will be variability in data capture. For example, the Swedish national health registers do not capture the laboratory tests of interest. In GKV claims, some codes will not be specific enough to allow for differentiation between an ALC laboratory test and an ANC laboratory test, or an ALT laboratory test and an AST laboratory test. In the PHARMO Database Network, TB screening and viral hepatitis B and C testing are not captured for the study population when sub-cohort analysis is not of interest. The MAH acknowledges that this is a limitation of the proposed data sources. 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 owners. If procedure codes are not available for a given data source, this will be noted in the SAP. Additional variations in data capture may exist given different procedure coding schemes, patterns of patient care, and reimbursement schemes; these limitations will be described in greater detail in the study report after the MAH is able to contract with the data sources.

The study will aim to describe how implementation of the 2019 Article 20 referral aRMM materials (which incorporate guidelines for reducing the increased risk of VTE and mortality on tofacitinib) and the 2021 signal evaluation procedure aRMM materials (which incorporate guidelines for reducing the increased risk of CV-related outcomes and malignancy-related outcomes on tofacitinib) is associated with use of tofacitinib within vulnerable populations. While many of the VTE, CV, and malignancy risk factors will be assessed, some risk factors, such as immobilisation and obesity are under-captured in administrative databases and thus will not be reported due to the concern of a high level of missingness. Additionally, there are operational challenges associated with trying to assess the effect of acquiring a VTE risk factor post-tofacitinib initiation (e.g., it will not be feasible to assess whether a patient discontinued a prescription that they already filled in response to developing a VTE risk factor or if they took the entire prescription); thus, changes in prescribing patterns in response to acquiring a VTE risk factor post-index (e.g., initiation of oral contraceptives or hormone replacement therapy) will be reported with limitations. In Sweden, prior VTE cannot be reliably distinguished from new VTE unless there is a ≥12-month period between the two events (i.e., if a patient with a history of VTE experiences a new VTE after initiating treatment with tofacitinib, it will only be possible to distinguish which VTE occurred *prior to* the index date and which VTE occurred *after* the index date if the two VTE events are separated by ≥12 months) due to the nature of the Swedish health registers and their use of ICD-10 diagnosis codes. The CV and malignancy risk factor of current or past smoker are likely under captured, leading to low sensitivity and misclassification. In Sweden, for instance, tobacco use disorder would typically be addressed as part of primary care, and the NPR does not contain primary care information. Regarding anti-smoking prescriptions, it is likely that most patients purchase nicotine replacement products over the counter, which would not be captured in the PDR, resulting in misclassification. Similar to many of the screening and monitoring guidelines above, the ability to assess guidelines which rely on the

discretion of the healthcare provider will be limited. For example, assessment of whether tofacitinib is being "used with caution in patients with known risk factors for VTE, regardless of indication and dosage" cannot be done directly in this study. This assessment will be approximated using the number and proportion of patients who had VTE risk factors (≥1 and ≥2) and were prescribed tofacitinib before and after the 2019 Article 20 referral aRMM materials were implemented. However, this assessment is limited in the sense that if the proportion of patients with VTE risk factors prescribed tofacitinib does not decline over time, it does not necessarily mean that prescribers were not prescribing tofacitinib with caution among patients with VTE risk factors.

The results from this study may not be generalizable to other member states of the EU (e.g., prescribing patterns and implementation of the recommended screenings and monitorings may vary by country). Finally, only the RA indication has received full reimbursement in Hungary (in May 2019), with the PsA and UC indications available only via the Named Patient Program. Thus, Hungary will not have a VTE Reporting Period 1 for any indication and also will not have a VTE Reporting Period 2 for the PsA and UC indications, nor will Hungary have a CV and Malignancy Reporting Period 1 or a CV and Malignancy Reporting Period 2 for the PsA and UC indications, which limits the MAH's ability to examine changes in the utilisation of tofacitinib among patients with VTE risk factors, among elderly patients, and among patients with CV or malignancy risk factors in Hungary following the updated recommendations and limitations for use. Additionally, there may be smaller patient numbers for these two indications relative to the RA indication in Hungary. However, there will be more comprehensive data across indications from Sweden. In the Netherlands, the PHARMO Database Network requires linkage between different data sources. As the same patients may not be captured by all databases and the initial number of tofacitinib patients is not high, patient counts may be affected by linkage.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

As per Module VIII of the EMA's *Guideline on good pharmacovigilance practices (GVP) – Post-authorisation safety studies*,[19] this study will be included in the EU Post-Authorisation Studies (PAS) Register® prior to the start of data collection.

The study will be submitted to ethics committees for approval as required by local law. Regulatory authorities will be notified, and approval will be sought as required by local laws and regulations.

10.1. Patient information

The Swedish national registers contain personal identifiers; however, when the data are released for research purposes, it is pseudonymised by the NBHW. NHIFA contains pseudonymised data, which is maintained by the NHIF, who are responsible for anonymising the data. For the PHARMO Database Network and GKV Claims, third parties cannot have

access to anonymised patient level data and analyses are performed by the data owner with only aggregate results shared externally.

10.2. Patient consent

The Swedish national registers collect data without informed consent but in compliance with local legislation. Local legislation states that data from the national registers can be used for research purposes as long as it is confirmed that it will not harm or identify the individual. The assessment of privacy (or confidentiality assessment), which evaluates the need for the data for the project against the individual's privacy rights, is done by the NBHW, the data holder. Patient consent is not required for NHIFA or GKV Claims. The PHARMO Institute uses de-identified data from existing databases without any direct enrolment of subjects. Ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet Medisch-wetenschappelijk Onderzoek met mensen [WMO]), which is enforced by the Central Committee of Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek [CCMO]).

10.3. Patient withdrawal

Not applicable.

10.4. 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 (not applicable for this study) or independent ethics committees (IECs; Sweden). All correspondence with the IRB or IEC must be retained. Copies of IRB or IEC approvals must be forwarded to Pfizer. IRB or IEC approval is not required for NHIFA or GKV claims because neither the MAH nor their vendor will have access to any patient-level data (i.e., the data owner will conduct the study analyses and provide the aggregated results to the MAH). However, permission from SHI providers is required for studies using GKV claims. Studies using the PHARMO Database Network require permission of the Compliance Committee.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements:

- The study protocol and information about the study will be sent to the Swedish Medical Products Agency (Läkemedelsverket) prior to study initiation.

The study will be conducted in accordance with scientific purpose, value, and rigor and follow the generally accepted research practices described in the following documents:

- Module XVI of the EMA's *Guideline on good pharmacovigilance practices (GVP) – Risk minimisation measures: selection of tools and effectiveness indicators*;[20]

- *Guidelines for Good Pharmacoepidemiology Practices (GPP)* issued by the International Society for Pharmacoepidemiology (ISPE);[21]

- *Guidelines for Good Epidemiological Practice (GEP)* issued by the International Epidemiological Association (IEA);[22]

- *Good Practices for Outcomes Research* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR);[22]

- *International Ethical Guidelines for Health-related Research Involving Humans* issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO);[23]

- *Guide on Methodological Standards in Pharmacoepidemiology* issued by ENCePP;[24] and

- The United States Food and Drug Administration's (FDA) Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.[25]

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 (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 the party responsible for collecting data is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

The study will be registered in the EU PAS Register by the MAH.

The interim and final study reports describing the study results will be disseminated to the tofacitinib clinical program teams and to the regulators (i.e., 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) in the European Union Using Secondary Data Sources

EU PAS Register® number: Pending
Study reference number (if applicable):
Protocol #: A3921321

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[xx]	☒	☐	☐	6
1.1.2 End of data collection[yy]	☒	☐	☐	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, 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:

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

[yy] 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, 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, 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, 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 9.4
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 follow-up	☒	☐	☐	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, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	n/a
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.3 9.3.4
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?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2 9.3.3 9.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, 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, health care services utilisation, burden of disease or treatment, compliance, 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

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

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, sub-group analyses, 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, 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, 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, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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?	☐	☐	☒	n/a
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
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 anti-fraud protection, 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

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, 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, precision of the estimates)	☒	☐	☐	9.5, 9.5.1

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?	☒	☐	☐	10.4
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: Nana Koram

Date: 11/02/2022

Signature :

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

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

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

ANNEX 4. LIST OF DIAGNOSIS AND PROCEDURE CODES FOR INTERSTITIAL LUNG DISEASE

A majority of the following codes were derived from Curtis et al. (2015).[26] All codes will be verified for each data source prior to study initiation.

Interstitial lung disease (ILD) diagnosis description	ICD-10 diagnosis code
Codes in the standard, specific definition of ILD	
Pulmonary fibrosis, unspecified	J8410
Other specified interstitial pulmonary diseases	J8489
Idiopathic interstitial pneumonia, not otherwise specified	J84111
Idiopathic pulmonary fibrosis	J84112
Idiopathic non-specific interstitial pneumonitis	J84113
Acute interstitial pheumonitis	J84114
Respiratory bronchiolitis interstitial lung disease	J84115
Lymphoid interstitial pneumonia	J842
Cryptogenic organizing pneumonia	J84116
Desquamative interstitial pneumonia	J84117
Lymphangioleiomyomatosis	J8481
Adult pulmonary langerhans cell histiocytosis	J8482
Alveolar proteinosis	J8401
Neuroendocrine cell hyperplasia of infancy	J84841
Pulmonary interstitial gycogenosis	J84842
Surfactant mutations of the lung	J8483
Alveolar capillary dysplasia with vein misalignment	J84843
Other interstitial lung disease of childhood	J84848
Additional codes added in the sensitive definition	
Other alveolar and parietoalveolar conditions	J8409
Interstitial pulmonary disease, unspecified	J849
Rheumatoid lung disease with rheumatoid arthritis of unspecified site	M0510

Abbreviations: ICD-10 = International Classification of Disease, 10th Revision; ILD = interstitial lung disease.

Interstitial lung disease (ILD) procedure description (codes to be provided in the SAP)

Computed tomography of the thorax

Computed tomography of the thorax

Interstitial lung disease (ILD) procedure description (codes to be provided in the SAP)

Computed tomography of the thorax

Computed tomography of the thorax

Computerized 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, incisional), unilateral

Thoracotomy, with diagnostic biopsy of lung nodule/mass (e.g., wedge, 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, incisional), unilateral

Thoracoscopy; with diagnostic biopsy of lung nodule/mass (e.g., wedge, incisional), unilateral

Thoracoscopy; with biopsy(ies) of pleura

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

All codes will be verified for each data source 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

Abbreviations: ICD-10 = International Classification of Disease, 10th Edition.

ANNEX 6. LIST OF ATC CODES FOR MEDICATIONS OF INTEREST TO AVOID WHILE TAKING TOFACITINIB

All codes will be verified for each data source 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
Other DMARDS	Balsalazide	A07EC04
	Olsalazine	A07EC03
	Sulfasalazine[a]	A07EC01

Class of drug	Drug	ATC code
Selected potent immunosuppressant	6-Mercaptopurine	L01BB02
	Azathioprine[a]	L04AX01
	Cyclosporine[a]	L04AD01
	Tacrolimus	L04AD02

Abbreviations: ATC = Anatomical Therapeutic Chemical; cs = conventional synthetic; DMAID = disease-modifying anti-inflammatory bowel disease drug; DMARD = disease-modifying antirheumatic drug.

a. Denotes that the medicine may also be classified as a csDMARD.

ANNEX 7. LIST OF ATC CODES FOR COMEDICATIONS OF INTEREST

All codes will be verified for each data source 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
	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	Somatostatin	H01CB01
	Atorvastatin	C10AA05
	Atorvastatin and acetylsalicylic acid	C10BX08
	Atorvastatin and amlodipine	C10BX03
	Atorvastatin and ezetimibe	C10BA05
	Atorvastatin and perindopril	C10BX15

Class of drug	Drug	ATC code
	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
	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
	Somatostatin	H01CB01
Vaccinations	Anthrax antigen	J07AC01
	Brucella antigen	J07AD01

Class of drug	Drug	ATC code
	Cholera, inactivated, whole cell	J07AE01
	Cholera, live attenuated	J07AE02
	Cholera, combinations with typhoid vaccine, inactivated, whole cell	J07AE51
	Diphtheria toxoid	J07AF01
	Hemophilus influenzae B, purified antigen conjugated	J07AG01
	Hemophilus influenzae B, combinations with toxoids	J07AG51
	Hemophilus influenzae B, combinations with pertussis and toxoids	J07AG52
	Hemophilus 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
	Pertussis, inactivated, whole cell, combinations with toxoids	J07AJ51
	Pertussis, purified antigen, combinations with toxoids	J07AJ52
	Plague, inactivated, whole cell	J07AK01

Class of drug	Drug	ATC code
	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

Class of drug	Drug	ATC code
	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, 18)	J07BM01
	Papillomavirus (human types 16, 18)	J07BM02
	Papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	J07BM03
	Smallpox, live attenuated	J07BX01
	Diphtheria-poliomyelitis-tetanus	J07CA01
	Diphtheria-pertussis-poliomyelitis-tetanus	J07CA02
	Diphtheria-rubella-tetanus	J07CA03
	Hemophilus influenzae B and poliomyelitis	J07CA04
	Diphtheria-hepatitis B-pertussis-tetanus	J07CA05
	Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus	J07CA06
	Diphtheria-hepatitis B-tetanus	J07CA07
	Hemophilus influenzae B and hepatitis B	J07CA08
	Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	J07CA09
	Typhoid-hepatitis A	J07CA10

Class of drug	Drug	ATC code
	Diphtheria-hemophilus influenzae B-pertussis-tetanus-hepatitis B	J07CA11
	Diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B	J07CA12
	Diphtheria-hemophilus influenzae B-pertussis-tetanus-hepatitis B-meningococcus A + C	J07CA13

Abbreviations: ATC = Anatomical Therapeutic Chemical.

ANNEX 8. LIST OF ATC CODES FOR ANTIHYPERTENSIVES

All codes will be verified for each data source 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

Class of drug	Drug	ATC code
	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
	ambrisentan	C02KX02
	sitaxentan	C02KX03
	macitentan	C02KX04
	riociguat	C02KX05
	ambrisentan and tadalafil	C02KX52

ANNEX 9. LIST OF ATC CODES FOR ANTIHYPERLIPIDAEMICS

All codes will be verified for each data source 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

Class of drug	Drug	ATC code
	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
	inclisiran	C10AX16
	evinacumab	C10AX17
	volanesorsen	C10AX18

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