NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Swedish, Population-based, Anti-Rheumatic Treatment in Sweden (ARTIS) register
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Medicinal Product	Xeljanz® (tofacitinib)
Product Reference	EMEA/H/C/004214
Procedure Number	EMA/PAM/0000261850
Marketing Authorisation Holder (MAH)	Pfizer Europe
Joint PASS	No
Research Question and Objectives	**Research Question:** What are the rates of safety events of interest in RA patients treated with tofacitinib and among RA patients treated with other advanced targeted therapies?

	Objectives: To estimate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, MACE, MI, VTE (DVT and PE) and other safety events of interest, including fractures, among patients with RA in Sweden who initiate tofacitinib. Rates will also be estimated among 1) patients with RA who have not been treated with biologic or targeted synthetic disease modifying antirheumatic drugs (DMARDs), 2) patients with RA who initiate biologic DMARDs (bDMARDs) and 3) the general population to provide context for rates observed on tofacitinib. Further, event rates will be estimated in elderly patients aged 65 years and older. Pending feasibility, rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE and other event rates, including fractures, will be compared between tofacitinib treated RA patients and other comparator cohorts using multivariable Cox regressions adjusting for sex, age, year of treatment start, treatment history, disease severity, comorbidities and other potential confounders for more refined evaluation of safety concerns.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
ARTIS	Anti-Rheumatic Treatment in Sweden
BID	bis in die (twice daily)
AS	ankylosing spondylitis
bDMARD	biologic disease modifying antirheumatic drug
CABG	coronary artery bypass graft
CI	confidence interval
CLL	chronic lymphocytic leukemia
COPD	chronic obstructive pulmonary disease
CRP	c-reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DAS 28	disease activity score 28
DMARD	disease modifying antirheumatic drug
DVT	deep vein thrombosis
EC	European Commission
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	health assessment questionnaire
HR	hazard ratio
Hx	history
HZ	herpes zoster
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
ICD10	International Classification of Diseases version 10
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEA	International Epidemiological Association
IEC	independent ethics committee
IQR	interquartile range
ISPE	International Society for Pharmacoepidemiology
IL	Interleukin
IR	incident rate
IRB	institutional review board
JA	juvenile arthritis
JAK	janus kinase
LTE	long term extension
MI	myocardial infarction
MACE	major adverse cardiovascular event
MTX	methotrexate

Abbreviation	Definition
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NI	non-interventional
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
OT	other rheumatic disease
PA	polyarthritis
PAS	post-authorization study
PASS	Post-Authorization Safety Study
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PPV	positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	psoriatic arthritis
PY	person-years
RA	rheumatoid arthritis
RMP	risk management plan
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SIR	standardized incidence rate
SJC	swollen joint count
SmPC	Summary of Product Characteristics
SpA	spondyloarthropathies
SRQ	Swedish Rheumatology Quality Register
Std	standardized
TB	tuberculosis
TJC	tender joint count
TNFi	tumor necrosis factor inhibitor
tsDMARD	targeted synthetic disease modifying antirheumatic drug
VAS	visual analog scale
VTE	venous thromboembolism
Yrs	years

3. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

Title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Swedish, Population-based, Anti-Rheumatic Treatment in Sweden (ARTIS) register.

Version: Final Protocol (V6.0)

Date: 06 July 2025

Name and Affiliation of Main Author: Shahar Shmuel, Pfizer. Inc.

Rationale and Background: Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome. Tofacitinib was approved in the European Union (EU) in March 2017 at a dose of 5 milligrams (mg) administered twice daily (BID) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). To enable assessment of safety events of interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data included in the ARTIS register.

Research Question: What are the rates of safety events of interest in RA patients treated with tofacitinib and among RA patients treated with other advanced targeted therapies?

Objectives: To estimate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, major adverse cardiovascular events (MACE), myocardial infarction (MI), venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]) and other safety events of interest, including fractures, among patients with RA in Sweden who initiate tofacitinib. Rates will also be estimated among RA patients who initiate biologic DMARDs (bDMARDs), bDMARD and targeted synthetic DMARD (tsDMARD) naïve RA patients, and the general population to provide context for tofacitinib rates. Pending feasibility, a comparative analysis is planned as a secondary objective. Pending feasibility, rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE, and other event rates, including fracture, will be compared between tofacitinib-treated RA patients and the comparator cohort using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and MACE have been added as study endpoints (MI and lymphoma (overall) were already included as a study endpoints). Further, rates of events, including serious infections, MACE, MI, VTE and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

Study Design: This active surveillance study will use existing data from the existing ARTIS register, an ongoing, prospective, observational, disease-based cohort started in 1999 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use.

Population: The study population will comprise all patients with RA enrolled within the ARTIS register who receive tofacitinib following EU approval and marketing, through the end of the study period. Three comparator cohorts will be assembled for risk characterization purposes: (1) RA patients who are treated with bDMARD (2) RA patients who are naïve to bDMARDs and tsDMARDs, and (3) a general population cohort.

Variables: The study variables include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies) and safety events of interest including, but are not restricted to, the following: serious infections, malignancies (including lymphoma subtypes and lung cancer), CV events (including MACE), and VTE (DVT and PE).

Data Sources: Core baseline and follow up data, including patient demographics, disease characteristics, and treatment will be based on data from the ARTIS register, the Swedish Patient Register, and Swedish Rheumatology Quality Register (SRQ). ARTIS data will be augmented with linkages to the Swedish Patient, Prescribed Drug, Cancer, Medical Birth, Contagious Disease, Total Population, and Causes of Death Registers.

Study Size: This is a descriptive study without pre-specified hypotheses. All eligible patients in the Swedish registers will be included, with no upper limit on the sample size. The feasibility of more refined comparative analyses to evaluate safety concerns that adequately adjust for patient channeling and confounders will be assessed at an interim time point and after 7 years will be based on statistical power.

Data Analysis: The initial analyses will consist of descriptive comparisons of baseline status and crude event rates between the different cohorts. The final analysis of endpoints will provide the rates of events overall and in subgroups defined by baseline characteristics. Pending feasibility, rates of malignancy (overall, excluding NMSC), lymphoma (overall and by subtype), lung cancer, serious infection, CV events, VTE, and other event rates will be compared between tofacitinib-treated RA patients and the comparator cohorts using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders. For lymphoma, incidence rates will be stratified by lymphoma subtypes; not limited to but including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphatic leukemia. Similarly, CV (e.g. myocardial infarction (MI), MACE, serious congestive heart failure) and VTE (DVT and PE) event rates will be stratified by type of event. Further, for the outcomes of MI and MACE, incidence rates of the safety events of interest will be stratified by patients with ≥1 CV risk factors versus no CV risk factors. Similarly, for the outcome of VTE, incidence rates of the safety events of interest will be stratified by patients with ≥1 VTE risk factors versus no VTE risk factors.

Milestones: Interim reports will be provided at 2, 4, 6 years after the start of data collection. A final report, including linked data, will include 7 years of data after start of data collection.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	September 2021	Substantial	Title Page	Updated to replace old Pfizer logo with new one Updated to include EU PAS Register Number Updated contact information for a protocol author. Updated contact information for the MAH Contact Person Updated objectives to align with changes in protocol.	Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor Editorial change.
			Section 2	Updated to include new abbreviations	Editorial change
			Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principal investigator.
			Section 4	Revised version and date. Updated Objective, Variables, and Data Analysis to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated Variables to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes.	PRAC request and clarification.
			Section 7	Updated to include information on changes to protocol resulting from June 2021 signal evaluation procedures	Editorial changes

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				Updated to include fractures as an additional safety event of interest	Based on available data, Pfizer has identified fractures as a potential risk
			Section 8	Updated objectives to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated objective to include estimation of event rates in the elderly aged 65 years and older.	PRAC request and clarifications
			Section 9.3.1	Updated to include CV risk factors	PRAC request and clarifications
			Section 9.3.2	Updated Risk Window to include sensitivity analysis for the 90-extension period.	
			Section 9.3.3	Updated to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated to include fracture as additional safety endpoint.	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk
			Section 9.7	Updated analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes. Updated to specify 'elderly' as aged 65 years and older.	PRAC request and clarifications Editorial change.
			Section 9.9	Updated limitations to research methods to include limitations in data capture of characteristics that may influence VTE	PRAC request and clarification

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				and CV outcomes and risk.	
			Annex 2	Author name changed. Signature and signature date updated. Instructions for form completion removed.	Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Editorial change.
			Appendix 2	Added baseline VTE risk factors to table.	Editorial change.
			Appendix 4	Updated to include definitions for additional endpoints.	PRAC request and clarifications
3.0	February 2022	Substantial	Title Page	Updated Research Questions and Objectives to include change in terminology from 'lymphoproliferative malignancy' to 'lymphoma' and to include VTE as an outcome of interest (VTE was already included as an outcome in the previous version of protocol. Included VTE in this section for consistency with the rest of protocol).	PRAC request and clarification
			Section 2	Updated abbreviations	Editorial change
			Section 4	Revised version and date. Updated Objective and Variables to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added VTE as an outcome of interest for consistency with other sections of the protocol (VTE was an outcome of interest in the previous version of the protocol).	Editorial change PRAC request and clarification

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				Updated Data Analysis to include stratified analysis for VTE incidence rates by ≥1 VTE risk factors versus no VTE risk factors. Removed 6-monthly reports from the Milestones.	PRAC request and clarification
			Section 7.3	Updated the Cardiovascular Disease section to remove MACE as an "important identified risk".	PRAC request and clarification
			Section 8	Updated Objective to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added VTE (DVT and PE) as an outcome of interest for consistency with other sections of the protocol (VTE was an outcome of interest in the previous version of the protocol).	PRAC request and clarification
			Section 9.3.1	Updated Baseline Data to clarify the CV risk factor information that will be evaluated at baseline, including the recent addition of chronic kidney failure and statin use as a proxy for history of hypercholesterolemia	PRAC request and clarification
			Section 9.3.3	Updated the Endpoints of Interest to replace the term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
			Section 9.7.2	Updated Data Analysis to include stratified analysis for VTE incidence rates by ≥1 VTE risk factors versus no VTE risk factors.	PRAC request and clarification

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
			Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
			All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
			Annex 2	Signature date updated	Editorial change
4.0	February 2023	Substantial	Section 6	Added footnote to milestone table to indicate anticipated data availability	Updated to accommodate data lag
			Section 9.2.1 and all sections where applicable	Removed the inclusion criteria of "diagnosis of RA must have occurred after 01 January 2012."	To limit potential bias
			All sections where applicable	Updated language to 'safety events of interest' to be consistent with the study title	Editorial change
5.0	January 2025	Substantial	Cover page	Updated MAH Contact Person	Study staff transition for the MAH Contact Person
			Section 9.7.2	Added sensitivity analysis for the final report to assess potential confounding by prior non-tofacitinib JAKis	To assess potential confounding via stratification (since excluding patients with prior non-tofacitinib JAKi use would reduce sample size substantially)
			Section 9.2.2	Added exclusion criterion to exclude patients with prior history of the specific safety event of interest being analyzed.	Patients with prior history of the safety event are often at increased risk of experiencing the safety event of interest again. This will replace model adjustment for baseline comorbidities.
			Section 9.2.1.1. and Section 9.2.1.3	Added inclusion criterion of age 18 years and above (to match Section 9.2.1.2)	Same age inclusion criterion across the study cohorts

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
			Appendix 2	Revised the table shells to reflect the tables provided in the reports	Table shells in the protocol did not match those in the reports
			Appendix 3	Removed Appendix 3. List of References provided by ARTIS	This reference list is a sample reference list from ARTIS and is not specific to this protocol
6.0	06 July 2025	Substantial	Section 9.2.2	Removed exclusion criterion to exclude patients with prior history of the specific safety event of interest being analyzed.	Per PRAC request. Prior history will be accounted for using model adjustment for baseline comorbidities.
			Section 9.7.2	Corrected reference from Appendix 4 to Appendix 3	Reference needed to be updated

6. MILESTONES

Milestone	Planned date
Registration in the HMA-Catalogues of RWD studies	01 September 2019
Start of data collection	15 September 2019
Interim report	14 March 2021
Interim report	14 March 2023
Interim report	14 March 2025
End of data collection	14 September 2025
Final Study Report	14 August 2026*

*Anticipated to include data from 01 September 2019 – 31 December 2024 for all outcomes to accommodate 1 year lag in data linkage between registries

7. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[1] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities. Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma). These patients are also treated with multiple classes of agents, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and DMARDs including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral JAK inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[17,36] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[18] Unlike biological therapies, such as tumour necrosis factor (TNF) inhibitor (TNFi) and anti-interleukin (IL)-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome.

In March 2017, XELJANZ® (tofacitinib citrate) was approved in the EU at a dose of 5 mg administered BID for the treatment of adult patients with moderately to severely active RA who have who have responded inadequately to, or who are intolerant to, one or more DMARDs. Tofacitinib citrate is also approved in more than 80 additional countries as of August 2017, including the United States, Canada, Australia, Switzerland, and Japan.

Careful observation of large cohorts of patients is needed to detect any increase in risk either of malignancy or infection, possibly due to tofacitinib treatment. Furthermore, it is important that surveillance also examines the occurrence of other co-morbidities and mortality. It is possible that long-term effective disease suppression might actually reduce all-cause mortality and the risk of lymphoma.

It therefore follows that for all new biologic and other targeted therapies there is a need for active surveillance to identify higher than expected rates of such safety events overall and within strata of disease severity, treatment history, and other concomitant therapy. To enable assessment of safety events of interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data included in the ARTIS register. Long term morbidity and mortality event-tracking of these cohorts over 7 years is an appropriate method for evaluating the risk associated with these treatments.

There is an increased risk of premature mortality, serious infection and lymphoma in patients with RA and other connective tissue diseases, independent of the treatment they have

received.[21] Thus, the patients on newly approved therapies without a well-established record of safety are already at increased background risk of premature mortality, infection and malignancy. Additionally, following the result of the June 2021 signal evaluation procedure (EPITT 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 rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma (overall) were already included as study endpoints prior to the signal evaluation). It is therefore fundamentally important to describe the occurrence of these events among patients treated with newly approved therapies and among patients who remained on "conventional" therapy or received a different targeted agent.

This non-interventional, active surveillance study, embedded within the ARTIS register, is designated as a PASS and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

7.1. Serious Infections

The risk of infections among RA patients depends on the environmental distribution of the organism of interest, inherent patient characteristics and treatment for RA. Persons with RA ≥65 years of age are found to be at increased risk of serious infections relative to those <65 years of age in both clinical trial and observational data.[6,13] The mechanism by which infection risk is increased in RA patients is likely to be multifactorial. In addition to the underlying disease (RA), therapies used to treat the disease have suppressive effects on the immune system. For example, TNFi may affect host defense against infection since TNF mediates inflammation and modulates cellular immune response. Tofacitinib inhibits cytokines that are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

Risk of infections is reportedly higher among TNFi-treated patients than those on DMARDs,[4,9,13,27] however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.[3,31] The decline may reflect a change in the risk profile of the population as a result of at-risk patients switching therapies, reduced co-administration of corticosteroids, in addition to any impact of TNFi therapy on overall health.[31]

Tuberculosis (TB) is the most common opportunistic infection (OI) in the RA population, with risks approximating 10-20 times that of the general population, likely due in part to RA therapy.[2,7,8]

Studies comparing the background risk of herpes zoster in RA and general population cohorts have been inconsistent, with some showing no increased risk and some showing modestly elevated risk.[16,29,32,37]

Serious infections, including tuberculosis and herpes zoster are important identified risks for RA patients taking tofacitinib.

7.2. Malignancies

Certain types of cancers may occur in higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer.[25,28] In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

Due to the immunosuppressive properties of approved RA therapies, researchers have investigated the risk of lymphopoietic and hematopoietic cancers in men and women with RA. It is not clear whether the risk of lymphoma in RA patients is increased further by methotrexate (MTX) or TNFi agents, although initial reports from large epidemiological studies have not found an increased risk among TNFi treated patients.[19]

Malignancy is an important potential risk for patients taking tofacitinib for the treatment of rheumatoid arthritis. As part of the June 2021 signal procedure (EPITT No. 19832), lung cancer and lymphoma were categorized as important identified risks for tofacitinib.

7.3. Cardiovascular Disease

Patients with RA have higher rates of CVD than the general population.[26] The body of published evidence for increased risk of serious CV events among RA patients is more extensive than the published information on lipid patterns; the extent to which adverse lipid profiles contribute to increased CV risk in patients with RA is unclear.

CV risk is an important potential risk for patients taking tofacitinib for the treatment of rheumatoid arthritis. In 2019, venous thromboembolism (VTE) was determined to be an important identified risk for tofacitinib. In January 2020, as a result of a reassessment of the benefit-risk of tofacitinib, the European Commission (EC) approved several revisions to the Summary of Product Characteristics (SmPC), including addition of VTE as an important identified risk associated with the use of tofacitinib. As part of the June 2021 signal procedure (EPITT No. 19382), MI was categorized as an important identified risk for tofacitinib.

7.4. Other Safety Events of Interest

The ARTIS register includes data on other safety events of interest in the RA population including central nervous system events, fractures, pregnancy and mortality. Rates these events will also be estimated to potentially identify new safety signals.

8. RESEARCH QUESTION AND OBJECTIVES

This study asks what are the rates of safety events of interest among RA patients treated with tofacitinib and among RA patients treated with other advanced targeted therapies?

Objectives:

To estimate the rates of serious infections, malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, CV events MACE and MI, VTE (DVT and PE) and other safety events of interest, including fractures, among patients with RA in Sweden who initiate tofacitinib. Rates will also be estimated among 1) patients with RA who have not been treated with bDMARD or tsDMARD, 2) patients with RA who initiate bDMARDs, and 3) the general population to provide context for rates observed on tofacitinib. Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE MI, VTE, and other event rates, including fractures, will be compared between tofacitinib-treated RA patients and other comparator cohorts using multivariable Cox regressions adjusting for sex, age, year of treatment start, treatment history, disease severity, comorbidities and other potential confounders for more refined evaluation of safety concerns. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and MACE have been added as study endpoints (MI and lymphoma (overall) were already included as a study endpoints). Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

9. RESEARCH METHODS

9.1. Study Design

This is an active surveillance study of existing nationwide cohorts in Sweden using linkages between drug-based registers, disease-based registers, national death register, cancer register, inpatient register, and outpatient register. All linkages are deterministic based on unique patient identifiers.

Rates of safety events of interest will be calculated in the four cohorts with 95% confidence intervals (CI) and reported as descriptive analyses. Data capture and follow-up methods are the same for all four cohorts within the Swedish Registers. This study will adhere to the ARTIS analytical protocol. No a priori hypotheses will be specified. Pending adequate sample size to permit adjustment for important variables for comparative analyses, 95% CI will be reported around hazard ratio (HR) estimates.

9.2. Setting

Sweden is a Scandinavian country with 10 million inhabitants. The prevalence of RA in Sweden is around 0.7% and the overall incidence 41/100,000 per year.[12,24]

Swedish health-care is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance-status. Patients with RA are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics.

Health and demographic information is collected in a series of registers with a high degree of completeness resulting from the mandatory and semi-automated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registers is possible.[14] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

Use of a RA treatment for a particular patient in Sweden has never been subject to a formal approval process (with the exception of a period during 2002-2003, when manufacturing issues led to reduced availability of etanercept), mandatory treatment history, or disease activity indices. Instead, the Swedish Society for Rheumatology has issued guidelines for the use of biologics, which are revised on an annual basis, but the ultimate decision to treat with biologics and which biologic to use have always resided with the treating rheumatologist.

The SRQ and ARTIS

The SRQ was started in 1995 by the Swedish Society of Rheumatology to improve the healthcare and treatment for patients with RA.[12] SRQ followed on regional register initiatives, to enable a national real-world documentation of many different aspects of RA, and developed over time into a harmonized national register. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), myositis, and systemic lupus erythematosus. Initially focusing on early RA, SRQ has gradually come to include also other segments. Data entry into SRQ is provided by the patient and the rheumatologist in conjunction with visits. Visits are scheduled according to treatment guidelines and clinical practice, which means at 0 and 3 to 6 months after the initiation of a new anti-rheumatic therapy, and thereafter in relation to the level of disease activity, according to an overall treat to target paradigm. Data are routinely captured as patients must visit their physician annually to renew prescriptions and must refill prescriptions every three months.

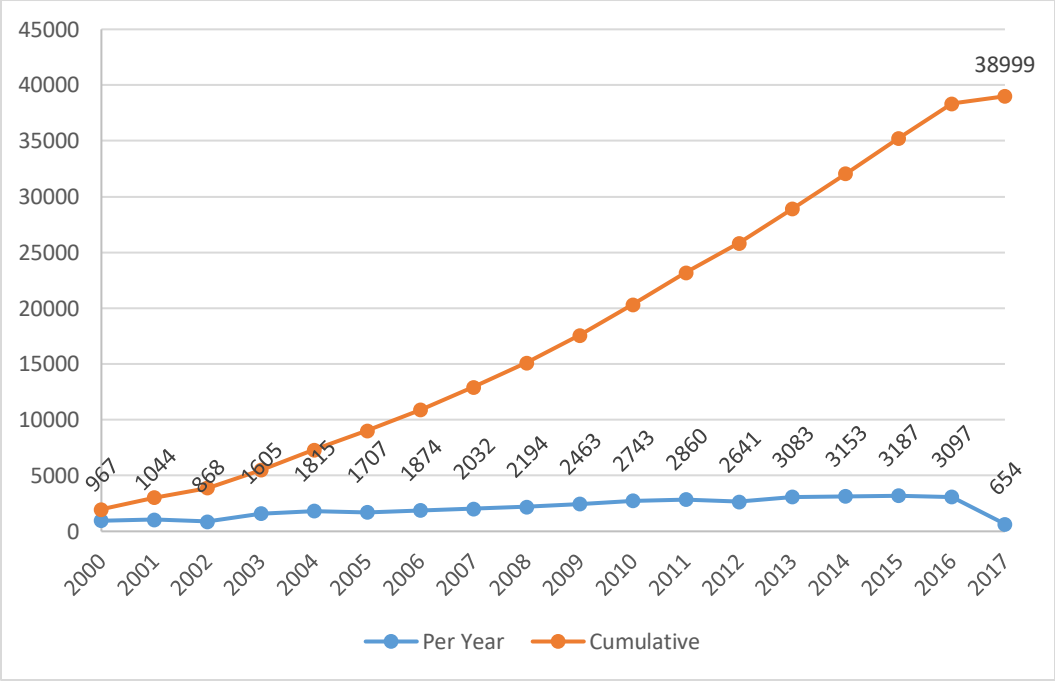
Since 1999, ARTIS has conducted a prospective, observational disease-based cohort study safety surveillance programme with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use based on SRQ linked to additional registers, and includes all presently available biologics used for the treatment of patients with inflammatory rheumatic diseases. It covers around 90% of all biologic initiations in Sweden after 1999.[23,35]

To maintain this high amount of data capture, and to improve the completeness further, the Swedish Society for Rheumatology regularly holds scientific meetings during which the surveillance data is presented. The managers and research nurses of ARTIS regularly visit participating centers to support the clinicians in managing the web-based forms and/or entering information. In each of the six geographical regions, at least one rheumatologist is

assigned as responsible for the registration in SRQ. Similarly, the ARTIS steering committee has a geographical representation.

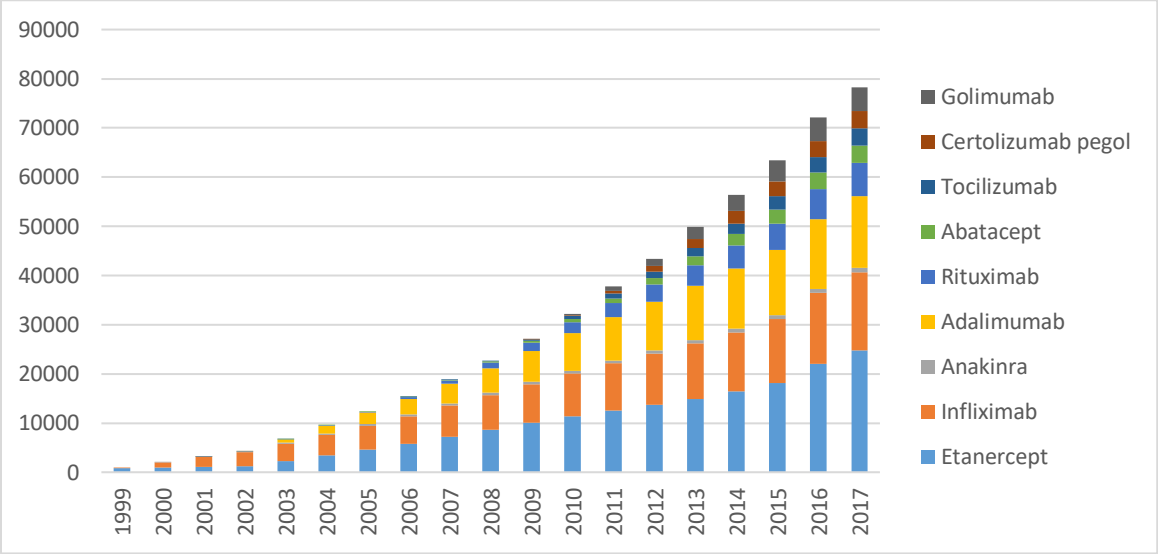
By August 2017, the follow-up within ARTIS included over 40,000 patients (65% women), and almost 80,000 biologics treatment initializations. Mean age at start of biological treatment is around 50 years. The treatment indication is RA or polyarthritis among 52% of the patients, PsA 15% [n=5995], AS 9% [3515], spondyloarthropathies (SpA) 8% [n=3302], juvenile arthritis 5% [n=1958], and the remainder being other rheumatic diseases. Figure 1 shows the accumulated number of biologic starts across all rheumatology indications in the SRQ. Figure 2 shows the total number of treatment episodes and their distribution across specific drugs.

Figure 1. Accumulated Number of First Ever Biologics Starts Across All Rheumatology Indications Registered in the Swedish Rheumatology Quality Register (SRQ) and Amenable for Monitoring in the ARTIS Programme.



Note: Orange line = cumulative numbers, across all rheumatology indications, blue line = annual number of new starts. Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is yet higher.

Figure 2. Cumulative Number of Treatment Starts in the Swedish Follow-up on Biologics Treatment Among Patients with Rheumatic Diseases.



The treating physicians enter the information into the study data-base via a web-based interface. Optionally, it is possible to send the data to the study secretariat on a pre-designed paper form. Patients can enter his/her data through internet ahead of the visit, at touch-screens in the waiting room, or on paper. The clinical information can be accessed by the treating physician and has been found to be a very useful tool in the management of individual patients. Currently, the overwhelming majority of the rheumatologist-derived data are entered directly via the internet in direct conjunction with the visit, and over half of the patient derived data are also entered electronically, ahead of the visit.

Safety outcomes included in ARTIS derive from two sources; spontaneous reports of adverse drug reactions (ADRs), and linkage to the national health care registers of Sweden (Section 9.4.2).

Matched general population subjects, and additional health and demographic information are derived from the mandatory, semi-automated data registration within population registers maintained by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden.

9.2.1. Inclusion Criteria

The active surveillance population includes RA patients enrolled in the ARTIS register who are newly treated with tofacitinib following EMA approval and Swedish launch of the product (product fully available April 2017). For contextualization purposes, the study population will also include the comparator cohorts as defined in inclusion/exclusion criteria. Patient consent is not applicable; planned analyses use data from existing data sources that do not include patient identifiers. Patients are eligible to move between cohorts if inclusion/exclusion criteria are met.

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

9.2.1.1. RA Patient Treated with Tofacitinib

1. Initiation of tofacitinib as captured in ARTIS/SRQ.
2. Diagnosis of rheumatoid arthritis by a consulting rheumatologist.[1]
3. Aged 18 years and older

9.2.1.2. RA Patients Treated with bDMARD:

1. Initiation of a bDMARD therapy as captured in ARTIS/SRQ.
2. Diagnosis of rheumatoid arthritis by a consulting rheumatologist.[1]
3. Aged 18 years and older.

9.2.1.3. ts/bDMARD-naïve RA Cohort

1. At least two separate visits documented in Swedish Patient Register listing RA as a diagnosis code for the visit, with at least one visit at a unit of Rheumatology or Internal Medicine.
2. Patients are censored from this cohort when they start tfofacitinib or a bDMARD, but are eligible for subsequent inclusion into the respective drug-based cohorts defined above.
3. Aged 18 years or older

9.2.1.4. General Population Cohort

Randomly selected from general population and region-, age- and gender-matched to RA patient cohorts, up to 5 population controls per tofacitinib exposed patient.

9.2.2. Exclusion Criteria

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

1. Patients not meeting the inclusion criteria for the respective cohorts will be excluded.

9.3. Variables

The study variables include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies) and safety events of interest including, but are not restricted to, the following: serious infections, malignancies (including

[1] Diagnosis of RA by a consulting rheumatologist is possible for all patients with the exception of the bio-naïve patients and the general population cohorts proposed as comparator populations.

lymphoma subtypes and lung cancer), CV events (including MACE), and VTE (DVT and PE).

9.3.1. Baseline Data

Examples of baseline data captured in ARTIS can be found in Appendices 1 and 2, respectively. The data captured include, but are not restricted to, the following: age, sex, years since diagnosis, disease severity, drug history, comorbidities (eg, history of malignancies), current concomitant medications, history of serious infection, history of opportunistic infection, history of herpes zoster, history of fractures, ever malignancy events (i.e. history of malignancy excluding NMSC, and specifically history of NMSC, history of lymphoma and history of lung cancer), and history of therapeutic procedures.

To facilitate the evaluation of the safety endpoints of MI and MACE, the following CV risk factors will also be evaluated at baseline: age (patients ≥65 years versus <65 years) and history of the following conditions: chronic kidney failure, diabetes, hypertension, statin use (as a proxy for history of hypercholesterolemia), previous MI, coronary heart disease, stable angina pectoris, and history of therapeutic procedures to treat cardiovascular disease (e.g. coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI)).

To facilitate the evaluation of the primary endpoint of VTE, the following VTE risk factors will be evaluated at baseline and/or, for some risk factors, within specific time periods prior to index date as specified: age, previous VTE, undergoing major surgery from date of hospital admission to one month after date of discharge, MI within previous 3 months prior to index date, heart failure, use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date, malignancy, diabetes mellitus, hypertension, inpatient care because of RA (i.e., RA as main diagnostic listing; from date of admission to date after discharge).

9.3.2. Follow-Up

Subjects will be followed from treatment start (or for comparator cohorts not defined by therapy: from an index date) until each outcome of interest, with death and emigration from Sweden treated as censoring events.

Some outcomes of interest in this study are thought to potentially occur at a higher rate while on drug, but that increased risk subsides after the drug is discontinued (ie, serious infections, herpes zoster, CV events, gastrointestinal (GI) perforation, progressive multifocal leukoencephalopathy (PML)).[2] Those events will be evaluated over a risk window that includes time from drug initiation until 90 days after end of treatment. When a patient initiates a new therapy within the 90-day extension, the time and events during the overlapping period will be assigned to both treatments. The 90-day extension period is implemented in part to accommodate ongoing exposure to treatments with longer half-lives, and in part to ensure that any subclinical or undiagnosed illness at time of end of treatment is

[2] The potential mechanism for increased PML risk is poorly understood. PML will be evaluated using both on drug and once-exposed always at risk approaches.

captured. As an additional sensitivity analysis for MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events with a 90-day extension period applied after treatment discontinuation, if a new medication is started during the 90-day window after discontinuation of a previous medication, initiation of the new medication will stop the 90-day risk window, and any event prior to the new medication start will be assigned to the discontinued medication. Similarly, as part of the primary analysis, for malignancy and all-cause mortality events, a 90-day risk window will be applied to the censoring at switch approach (i.e., if a malignancy or death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy).

For non-melanoma skin cancer (NMSC), lung cancer, lymphoma and malignancies excluding NMSC, and all-cause mortality, the manifestation of which is expected to be delayed relative to the time of exposure, the outcomes will be evaluated using two different approaches, a once exposed always at risk approach as the primary analysis and a censor at switch approach as a secondary analysis. PML rates will also be described using this approach.

The primary analysis will assume a once exposed always at risk paradigm, as is frequently used in study of malignancy risk due to bDMARDs.[19,20,32,35] Under this approach, follow up for each cohort continues from the cohort index date until the first of a malignancy event, loss to follow up, death or end of study. Follow up for each exposure cohort continues after switching to a new drug or discontinuation of treatment. This approach maximizes follow up time and the ability to capture long latency events, ie, events that occur or are detected years after exposure. Under this approach, events will be double-counted if a patient indexed to bDMARD switches to tofacitinib and a malignancy occurs subsequent to tofacitinib exposure. That is, the event will be assigned to both the bDMARD and the tofacitinib exposure cohorts as will the corresponding person years since index to the respective cohorts. Because tofacitinib is expected to be used as a later line therapy, switching is expected to be non-random with most tofacitinib patients having been included in the bDMARD cohort prior to initiation of tofacitinib. In such cases, the bDMARD rate will have more associated person-years and thus a relatively lower rate than the corresponding rate in the tofacitinib cohort.

Using this primary analytic approach, if neither tofacitinib nor bDMARDs cause an increased risk of malignancy both exposure cohort rates will reflect the background rates of malignancy from the time of index to the end of the study period and the comparative effect measure will indicate no difference in rates. If tofacitinib does cause an increased rate of malignancy, which is the effect we are most interested in detecting, a relatively higher rate will be observed in the tofacitinib exposed cohort. The once exposed always at risk approach is therefore able to detect an increased rate given the non-random switching expected to occur given use of bDMARDs prior to tofacitinib and is consistent with previous studies evaluating the risk of individual biologics.[19,20,32,35] Additional analyses will be conducted to evaluate potential confounders and the impact of different latency assumptions as will be described in the statistical analysis plan (SAP). Sensitivity analyses will be conducted that restrict the bDMARD comparator cohort to patients who were never exposed to tofacitinib or

other non-biologic advanced therapies and compare the characteristics of those bDMARD patients ever and never exposed to tofacitinib.

Secondary analyses that censor follow up time after a switch to a different treatment class will also be performed. Among patients indexed to a bDMARD cohort, follow up will begin at index and continue until the first of an event, switch to tofacitinib or other non-biologic advanced systemic therapy, loss to follow up, death, or study end date. Similarly, for tofacitinib, follow up will begin at index and continue until the first of an event, switch to a non-JAK inhibitor-based advanced systemic therapy, loss to follow up, death or study end date. While this approach eliminates the problem of double counting, it may not allow sufficient follow up time to allow for latent effects or detection and decreases the number of events included reducing the statistical power to detect a higher risk of malignancy in tofacitinib treated patients. However, under an assumption of no latency or a very short latent period as in an aggressive tumor promoter, this approach would detect an increased risk of disease on tofacitinib relative to the risk due to bDMARDs.

Of note, several studies compared a once-exposed approach to a time on drug and other approaches and found similar rates of malignancy using an on-drug and ever-exposed approach.[19,20,32,35]

The schematic below provides examples of patterns of event and treatment patterns to illustrate resulting contribution to rate calculation in the once exposed always at risk and censoring at switch analytic models:

*: bDMARD index date;
~: year on bDMARD;
^: tofacitinib index date;
-: year on tofacitinib;
O: discontinuation of advanced systemic therapies;
=: year not on systemic therapy;
X: event.

	Once-exposed always at risk		Censoring at Switch	
Treatment/Event pattern	bDMARD rate contribution (events/person years)	Tofacitinib rate contribution (events/person years)	bDMARD rate contribution (events/person years)	Tofacitinib rate contribution (events/person years)
* ~ ~ ~ ^ - - X	1/5	1/2	0/3	1/2
* ~ ~ ~ X	1/3	0/0	1/3	0/0
^ - - - O = = = X	0/0	1/6	0/0	1/6[a]
*~ ~ ~ ^ - - - ~ ~ ~ X	1/9	1/6	0/3	0/3
^ - - - - ~ ~ ~ X	0/0[b]	1/7	0/0[b]	0/4

a. Patients continue to be followed after index exposure discontinuation if they do not initiate another systemic therapy in a different class.
b. Patients are ineligible for bDMARD cohort index after tofacitinib index.
Note: if an event does not occur, person time will be allocated to rate denominator as described in table without corresponding event.

9.3.3. Endpoints of Interest

The endpoints of interest captured in the semi-annual reports are the following safety events of interest.

For the interim feasibility analysis and final safety report (where also information on patients, co-variates and outcomes, from SRQ as well as from the linked Patient/Prescribed Drug and other registers will be included) of pre-specified safety outcomes, the following events of interest have been pre-specified.

1. Hospitalized infections overall.
2. Opportunistic infections.
3. Herpes zoster (hospitalized).
4. Hepatitis.
5. Fractures.
6. NMSC.
7. Malignancies (overall, excluding NMSC).
8. Lung Cancer.
9. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia).
10. CV events, including deep vein thrombosis/pulmonary embolism (DVT/PE).

11. Major Adverse Cardiovascular Events (MACE).
12. Myocardial infarction (MI)
13. Gastrointestinal (GI) perforations.
14. Progressive multifocal leukoencephalopathy (PML).
15. Interstitial lung disease, pending feasibility.
16. All-cause Mortality.

Given the age-dependent rate events of interest, analysis will be conducted in elderly patents aged ≥65 years.

This list may be extended with a reasonable number of additional sub-diagnoses or new health related outcomes as agreed to by ARTIS researchers and Sponsor before the interim feasibility analysis and final safety report. These decisions will be made prior to initiation of analyses and documented in a statistical analysis plan (SAP) kept on file by the Sponsor.

In addition, the final safety reports will include the number of tofacitinib-exposed pregnancies.

9.4. Data Sources

9.4.1. SRQ

SRQ is the source of disease activity information, measured by C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ), number of swollen and tender joints, and patient's global assessment of disease (on a visual analog scale(VAS)) and doctor's evaluation on a Likert type scale. In addition, disease activity scores -28 (DAS 28), the European League Against Rheumatism (EULAR) response criteria, and the American College of Rheumatology criterion of improvement (ACR) can be calculated. Reflecting the changes in treatment paradigm, Table 1 shows how the disease activity in RA at the time of first biologic start has decreased over time. Although the system was originally developed for RA, clinical variables of importance for specific rheumatic diseases have been added incrementally.

Table 1. Temporal Trends in Average Disease Severity Scores at First Biologics Initiation in Swedish Patients with RA.

	DAS28	HAQ	VAS	SJC	TJC	ESR	CRP
1998	6.6	1.6	55.6	15.0	14.4	47.0	43.7
1999	6.0	1.6	64.0	11.8	10.5	45.0	45.6
2000	5.7	1.5	62.6	10.3	9.4	39.3	38.5
2001	5.6	1.4	60.9	10.2	9.4	37.9	35.8
2002	5.6	1.4	59.1	9.8	9.0	38.6	35.5
2003	5.5	1.3	57.8	9.5	8.7	36.1	31.9
2004	5.4	1.3	58.1	9.2	8.6	35.7	30.7
2005	5.3	1.2	55.5	8.6	8.4	32.9	25.0

Table 1. Temporal Trends in Average Disease Severity Scores at First Biologics Initiation in Swedish Patients with RA.

	DAS28	HAQ	VAS	SJC	TJC	ESR	CRP
2006	5.2	1.2	56.6	8.4	8.0	31.5	23.8
2007	5.1	1.2	56.2	8.1	7.6	31.2	23.0
2008	5.1	1.2	56.4	7.8	8.0	28.4	18.7
2009	5.0	1.1	54.9	7.5	7.8	28.3	20.7
2010	4.9	1.1	55.7	7.0	7.4	27.4	18.0
2011	4.8	1.1	54.7	6.8	7.2	26.9	18.1
2012	4.9	1.1	58.0	6.8	7.4	25.6	18.1
2013	4.9	1.0	56.0	6.6	7.4	25.7	16.8
2014	4.8	1.1	54.7	6.1	6.9	25.9	17.0
2015	4.5	1.0	53.8	5.4	6.4	23.7	15.6
2016	4.5	1.0	54.4	5.2	6.6	24.5	14.2

CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; SJC = Swollen joint count, TJC = tender joint count, VAS = Visual analog score.

9.4.2. SRQ/ARTIS Linkage

Endpoint information also derives from the linkage of SRQ/ARTIS to nationwide Swedish health care registers. Compared to the ADR reports, the register linkage has many advantages in providing data on all comorbidities that have been diagnosed, unbiased by incomplete reporting from physicians or by subjective assessments on causality. Importantly, it also allows us to obtain data on comparator cohorts, so that any potential risk increases can be evaluated in light of risks among patients on other treatments, and the general Swedish population. The drawback is a lag time of between 1 and 2 years from when an event occurs until it can be analyzed and reported using the national health care registers. This delay is caused by the annual curation of the Patient and Cancer registers by the National Board of Health and Welfare (ie, data from each year is only made available after internal processing, usually 9 to 12 months later, and the processing of data requests).

9.4.3. The Patient Register and the Prescribed Drug Register

The Swedish Patient Register provides information on all hospitalized (inpatient treated) patients, and all visits to non-primary outpatient care (such as a visit to a rheumatologist). Diagnoses are assigned by the discharging physician, as well as date of discharge, discharging hospital and department. Diagnoses are coded according to the International Classification of Diseases (ICD), with version 8 used until 1986, version 9 1987 to 1996 and version 10 (ICD10) since 1997.

In addition to data on safety outcomes and baseline comorbidities or disease history, the patient register is the source of comparator cohorts defined by diagnosis, but untreated with biologic agents.

The Prescribed Drug Register provides all retrievals of prescribed drugs in Sweden from July 2005, and may be used to aid correct classification of patients by their history of retrieved DMARDs, or to define subcohorts based on switches in treatment.

9.4.4. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and provides data on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.[5]

9.4.5. The Contagious Disease Register

The Contagious Disease Register provides events reported according the Communicable Diseases Act and the Communicable Diseases Ordinance on diseases that have mandatory reporting Sweden. The notifiable diseases also fall into different categories: subject to mandatory contact tracing, dangerous to public health and dangerous to society.

9.4.6. The Medical Birth Register

The Medical Birth Register contains prospectively provides data from antenatal, obstetric, and neonatal records since 1973, and covers all live and still births (but not all miscarriages) in Sweden.[10] Among the variables covered are maternal age, parity, smoking and family situation in early pregnancy, and the infant's birth weight and length, gestational age (primarily based on ultrasound dating), and Apgar score. Complications and mother's and infant's morbidities are coded according to the ICD, with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

9.4.7. The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. Although the register was started in 1952, the data is considered complete since 1961.

9.4.8. The Total Population Register

The Total Population Register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961. This register thus provides information on censoring (death and emigration) of study subjects, and can also be used to identify a general population comparison cohort.

9.5. Study Size

All eligible patients in the Swedish registers will be included, with no upper limit on the sample size. The feasibility of more refined comparative analyses to evaluate safety concerns that adequately adjust for patient channeling and confounders will be assessed at an interim time point and after 7 years will be based on statistical power. Since the comparator groups will be a magnitude larger than the tofacitinib treated group, statistical power will be limited by the uptake of tofacitinib, which is difficult to estimate a priori. While the primary

objective of the protocols is active surveillance, conducting quantitative, confounding controlled comparisons will depend on having a sufficient sample.

Table 2 and Table 3 below describe the power to detect a 2-fold difference in event rates between tofacitinib-initiators and bDMARD-initiators assuming the following:

α=0.05;

3 different bDMARD-treated patient population sizes (reflecting roughly range of EU registers): n=11100, n=5050, n=1650;

4 different tofacitinib-treated patient population sizes: n=100, n=250, n=500, n=1000;

Estimated rates on bDMARD of 30/1000 person years (PY) (eg, serious infection), 10/1000 PY (eg, malignancy excluding NMSC), and 6/1000 PY (eg, major adverse cardiovascular event (MACE)) based on previous analysis with registers (Pfizer, internal data);

7-year study period;

Constant rate of accrual;

5% annual loss to follow up among tofacitinib-treated patients.

Additionally, Table 2 assumes a 0% annual rate of switching off tofacitinib, as would be true for a drug with very high persistence or for an analysis following the once exposed always at risk paradigm. Table 3 assumes a 30% annual rate of switching from tofacitinib to a bDMARD over the study period, as previously demonstrated in the EU for bDMARDs in Italy.[38]

For an event with a rate of 30/1000 PY, such as serious infections, 250 patients would allow sufficient power to detect a 2-fold difference in rates between tofacitinib and bDMARD-exposed patients assuming very high persistence (Table 2), while 500 tofacitinib exposed patients would be nearly sufficient if 30% of tofacitinib treated patients switched off of tofacitinib annually.

For an event with a rate of 10 cases per 1000 PY, such as malignancy excluding NMSC, a sample of 500 patients approaches 80% power in a medium (n=5050) to large (n=11,100) register when patient time continues to accrue after drug discontinuation (Table 2). It will be a challenge to achieve sufficient power in a register with fewer bDMARD exposed patients. Nonetheless, replication of a similar trend in an underpowered sample could be locally informative.

For an endpoint with an event rate of 6/1000 PY, such as MACE, even assuming high persistence (Table 2) a sample size of 1000 tofacitinib patients within a registry with more than 5000 bDMARD patients would be required to make well-powered comparison. In a scenario with a 30% annual rate of switching off of tofacitinib, 1000 tofacitinib treated patients and 11 100 bDMARD patients would only provide 40% power to detect a 2-fold difference (Table 3).

Prior to conducting any analyses, a feasibility assessment will be conducted to determine the approximate power of planned comparative analyses.

Table 2. The Power To Detect A Two Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5 Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm

Number of tofacitinib exposed patients	~11100 bDMARD-treated patients	~5050 bDMARD-treated patients	~1650 bDMARD-treated patients
bDMARD rate ~ 30/1000 PY (eg, serious infections)			
100	0.46	0.45	0.44
250	0.92	0.91	0.88
500	1.00	1.00	0.9
1000	1.00	1.00	1.00
bDMARD rate ~10/1000 PY (eg, malignancy)			
100	0.11	0.12	0.12
250	0.38	0.38	0.36
500	0.75	0.73	0.66
1000	0.98	0.96	0.89
bDMARD rate ~ 6/1000 PY (eg, MACE)			
100	0.06	0.06	0.06
250	0.20	0.20	0.20
500	0.47	0.46	0.41
1000	0.83	0.79	0.68

Table 3. The Power To Detect A Two Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5 year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, 30% Switch From Tofacitinib to bDMARD Per Year

Number of tofacitinib exposed patients	~11100 bDMARD-treated patients	~5050 bDMARD-treated patients	~1650 bDMARD-treated patients
bDMARD rate ~ 30/1000 PY (eg, serious infections)			
100	0.18	0.18	0.18
250	0.50	0.49	0.46
500	0.84	0.82	0.75
1000	0.99	0.98	0.93
bDMARD rate ~10/1000 PY (eg, malignancy)			
100	0.06	0.06	0.06
250	0.16	0.16	0.15

Table 3. The Power To Detect A Two Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5 year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, 30% Switch From Tofacitinib to bDMARD Per Year

Number of tofacitinib exposed patients	~11100 bDMARD-treated patients	~5050 bDMARD-treated patients	~1650 bDMARD-treated patients
500	0.33	0.32	0.30
1000	0.64	0.60	0.50
bDMARD rate ~ 6/1000 PY (eg, MACE)			
100	0.04	0.04	0.04
250	0.09	0.09	0.09
500	0.19	0.19	0.18
1000	0.40	0.38	0.32

Based on the first 9 months of enrolment of tofacitinib-exposed patients in ARTIS, 344 patients are projected to be enrolled in the first 24 months, allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remains constant over the period.

9.6. Data Management

This study analyzes data existing with the ongoing ARTIS register. The ARTIS researchers are responsible for the data management of this study. As previously described, health and demographic information within Sweden is collected in a series of registers with a high degree of completeness resulting from the mandatory and semi-automated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registers is possible.[14] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

The data warehouses of ARTIS reside on restricted, double backed-up, servers at the Clinical Epidemiology unit at the Karolinska University Hospital Campus. All work with these data ware houses is done by trained staff in adherence with local guidelines on good programming and data management practices, and on archiving. Data, programs, and documents related to study reports will be maintained for a minimum of ten years.

9.7. Data Analysis

All statistical analyses will be performed by ARTIS using Statistical Analysis Software (SAS) version 9.4 or later.

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

9.7.1. Semi-Annual Reports

Reports summarizing the rate of safety events of interest will be provided by ARTIS to Pfizer on a semi-annual basis, with tables corresponding to the template Appendix 1. These will provide data from SRQ/ARTIS on the patients treated with tofacitinib and rates "on drug" and "ever since treatment start", but they will not contain comparator cohorts or adjusted comparisons.

9.7.2. Final Safety Report

The feasibility of conducting a final comparative study will be evaluated at an interim time point and at 7-years of follow up based on statistical power and suitable overlap in patient populations in the exposure groups. The feasibility assessment, like the final report, will be conducted using safety events of interest identified through linkages with the patient, cancer and death registers, as appropriate. ARTIS will apply an ICD-code based algorithm to identify serious infections, GI perforations, herpes zoster, and CV events (MACE), in the Swedish patient register. Appendix 3 describes the algorithms used to identify these endpoints in ARTIS and relevant validation references, along with definitions used by other EU registers. The specific algorithms for defining those endpoints have not been validated, though the Swedish patient register has been validated several times (Ludviggson 2011).[39] The overall positive predictive value (PPV) of the inpatient diagnoses generally ranged from 85% to 95%. A regional validation study of hospitalized acute MI and stroke (components of the MACE endpoint) found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987 (Lindblad, 1993).[40] An ICD-9 code based algorithm applied to inpatient diagnoses of GI perforations in the US demonstrated high PPV (89.1-100) (Curtis, 2011).[41] While the ICD algorithms used by ARTIS to define the endpoints of interest may not be validated, their use can be justified given the importance to contextualize the study results with historical findings. ARTIS has previously conducted and published studies of serious infections (Askling, 2007),[42] PML (Arkema, 2012),[43] and MACE (Michaud, 2016)[44] events in RA patients.

The Swedish national register for contagious diseases, will serve as source of information on TB and other possibly serious contagious diseases for which there is a mandatory registration in Sweden. These reports will be based on a standardized analytical scheme, with some but limited flexibility to add additional endpoints and stratification, and will contain populated tables in line with the shells in Appendix 2. Whether these reports include formal comparisons of patients exposed to tofacitinib and bDMARDS will be determined a priori based on adequate power.

For these analyses, the exposure cohorts will be analyzed overall, by previous biologics use and monotherapy and combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs). Increased risk of malignancy (excluding

NMSC), MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events, as well as an increase in mortality, in patients treated with a combination therapy with MTX specifically will be described if sample sizes are sufficient, in the interim and final reports. These and potentially other agreed upon strata will be determined a priori and included in SAP filed with Sponsor. The general analytic approach will be descriptive and include rates of events of interest within stratified treatment cohorts. Data will be presented as number of events, crude and age/sex-standardized incidence rates.

Any final comparative report will adjust for differences in severity of disease and other confounders will be completed using appropriate multivariate, propensity score matching, or inverse probability weighting. The final report will also evaluate the rates of safety events of interest within the elderly. The outcomes reported will include hospitalized infections, OI, herpes zoster, fractures, hepatitis, GI perforations, malignancies, CV events, and all-cause mortality, with subgroupings and selected additional outcomes per agreement. HRs from multivariable Cox regressions adjusting for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders to be agreed upon by ARTIS and the Sponsor and defined in an SAP prior to analysis. The final SAP will also specify an ICD-algorithm harmonised with other registers conducting similar analyses for serious infections, CV events, GI perforations, and herpes zoster (HZ).

Any comparative safety reports will leverage data linkages to obtain data on all comorbidities that have led to hospitalization, cancer or death. Data on malformations and perinatal morbidities and mortality can also be obtained from the birth register.

For lymphoma, incidence rates will be stratified by lymphoma subtypes; not limited but including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphatic leukemia. Similarly, CV event rates will be stratified by type of event (e.g. myocardial infarction (MI), MACE, serious congestive heart failure). Further, for the outcomes of MI and MACE, incidence rates of the safety events of interest will be stratified by patients with ≥1 CV risk factors versus no CV risk factors. The rates of safety events of interest, including infections, MACE, MI, and malignancies excluding NMSC, will also be evaluated within the elderly aged ≥65 years. Descriptive data will be presented in the interim reports. Likewise, VTE event rates will be stratified by type of event (DVT and PE). Further, for the outcomes of VTE, incidence rates of the safety events of interest will be stratified by patients with ≥1 VTE risk factors versus no VTE risk factors.

At study completion, all descriptive and comparative data analyses will be presented in the final report.

If feasible, stratified analyses to estimate the incidence rates for VTE stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors will also be conducted (i.e., time period prior to 31 January 2020 vs. time period after 31 January 2020). Additionally, if feasible, stratification of the incidence rates for malignancy excluding NMSC, lung cancer, lymphoma, MACE and MI by time periods defined by changes in the SmPC for use in patients with malignancy and CV risk factors will be conducted (i.e. time period after June 2021).

To evaluate and account for potential confounding by prior non-tofacitinib JAK inhibitors, in the final report, a sensitivity analyses with stratified results by the presence versus absence of prior non-tofacitinib JAK inhibitors will be conducted.

Meta-analytic methods that attempt to combine the results of this study with results from other participating European registers will be used to summarize the findings across studies. A quantitative meta-analysis would permit an estimate of an average effect across the studies with more statistical power than the individual studies, provided a formal evaluation did not reveal substantial heterogeneity. Meta-analysis may reveal between-study heterogeneity such that a subset of more comparable studies could be included in a single estimate. Heterogeneity may be expected, for example due to differences in local prescribing practices, patient populations, competing risks, and prevalence of comorbidities and risk factors. Such heterogeneity would exist even if the coding for endpoint definitions and reporting could be harmonized across registers. In the presence of such heterogeneity, pooling across the registers is not informative as the generalizability of such an estimate is unknown. Pending feasibility of comparative analysis, meta-analytic methods will be determined a prior and described in an approved SAP.

9.8. Quality Control

This study uses data existing within ARTIS. ARTIS works mainly with data from the SRQ, a quality of care register with several guidelines in place to monitor and maintain data quality. Physicians working with the SRQ have access to an online portal in which they can monitor all their patients and the information on them. Regional representatives encourage/remind the physicians to check the quality of the information by accessing the "Data Quality" section of the "Visit monitoring" tool: in this section a series of questions guide the doctor in checking the quality of the registered information of their patients. Moreover, the data coordinator of SRQ periodically check the quality of the data overall in the region.

9.9. Limitations of the Research Methods

This study is designed to monitor the safety of tofacitinib within the clinical practice setting utilizing the ARTIS Register, a well-established Swedish-based rheumatology register. Despite the strengths of the register, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling and endpoint misclassification, are of concern in interpreting findings.

As a new therapy in the RA treatment armamentarium, it is possible that patients treated with tofacitinib will represent those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at risk for events. Biases resulting from channeling may present as increased rates of safety events of interest in the early phases of the study. Comparison to internal comparators may illuminate such channeling. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualization. Trend analyses may be conducted to evaluate rates in tofacitinib patients over time.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to patient management. The rates of safety events of interest and their distribution among patient-types may have changed over time. The comparators in this study are not exclusively contemporaneous to tofacitinib treated patients. Analysis may be unable to identify or control for any changes in rates due to changes in the treatment landscape.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While ARTIS has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, linkage to national health care registers allows the register to obtain data on all safety events of interest (regardless of suspected causal relationship to the treatments), and on comparator cohorts, so that any potential risk increases can be evaluated in light of risks among patients and with other treatments, and the general Swedish population.

Certain patient characteristics which may influence VTE outcomes (e.g., smoking status, obesity and immobilisation), cannot be reliably captured, and thus may limit data interpretation. Inherited coagulation disorders encompass a broad range of conditions, and only a limited number of these can be reliably captured in the Swedish registers. While immobilisation cannot be captured in the Swedish registers, including inpatient care due to RA (i.e., RA as main diagnostic listing) will capture hospitalized patients who will be immobilized, and who will also be at a potentially higher risk for VTE (consensus guidelines recommend thromboprophylaxis for all admitted patients with inflammatory bowel disease (IBD) in the absence of contraindications). Additionally, some CV risk factors such as smoking status (as previously mentioned) and baseline total cholesterol/HDL ratio cannot be adequately captured within the Swedish registers, and thus will limit the assessment of the MACE and MI endpoints. For the outcome of lymphoma, the 3 main subtypes that can be adequately be captured in the Swedish registers are NHL, Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). Other lymphoma subtypes that do not fit into these 3 main categories will not be captured in the study and thus may limit the assessment of this outcome.

This study will follow patients for a period of 7-years from therapy initiation. Conclusions may not be generalizable outside of the 7-year period since initiation of therapy.

9.10. Other Aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where

required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

10.2. Patient Consent

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

10.3. Patient Withdrawal

Not applicable; analyses planned utilize data from secondary data sources that do not include patient identifiers.

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 (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

This register-linkage database does not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files. This comparative safety study has been approved by the Ethics Committee in Stockholm (DNR: 2015/1844-31/2, renewed approval will be sought as needed for the duration of the study).

10.4.1. Ethical Permits

In accordance with Swedish law, non-interventional studies of register-based data (including "quality of care" registers such as SRQ/ARTIS) do not usually require informed consent by the individual study subjects. Instead, regional ethics committees are mandated to provide permission for such studies, after weighing the subjects' potential benefit from the research against the potential risks to the subjects' personal privacy. ARTIS has ethical approval for the studies described in this protocol as outlined above, but is subject to strict rules and regulations regarding the maintenance, analysis and reporting of personal data. Patient consent is not required for this study as data already exist within ARTIS register.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), and the Karolinska Institutet's guidelines on Research Conduct.

Per Pfizer's subscription to the ARTIS database, analyses will be conducted by ARTIS researchers and in accordance with ARTIS scientific review policies. The database does not

contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim reports summarizing the patient characteristics and crude event rates will be submitted to EMA to reflect 2, 4, and 6, years of the study period. Analysis using linked register data through 7 years of follow up will be the basis for a final report to be submitted to EMA. The final report will be included in risk management plan (RMP) updates. Data may be used in regulatory communications external to Sweden for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for external publication purposes.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the party responsible for collecting data from the participant 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.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Swedish, Population-based, Anti-Rheumatic Treatment in Sweden (ARTIS) register

EU PAS Register® number: EUPAS31157
Study reference number (if applicable): A3921314

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	6
1.1.2 End of data collection[4]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
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:	☐	☐	☒	8
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)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

[3] 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.

[4] 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?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.2
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))	☐	☐	☒	
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)	☐	☐	☒	

Comments:

No measure of association will be determined in this descriptive study.

This is a secondary database study using structured data, no reporting of adverse events is required for this protocol.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.3.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1/9.2.2

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)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

Exposure is assumed after index until report of discontinuation during risk window for interim reports. Final study SAP will describe methods for accounting for exposure.

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?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.2
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)	☒	☐	☐	9.7.2
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)	☐	☐	☒	

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)	☒	☐	☐	9.7.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.2

Comments:

Interim reports are crude analyses, final study analyses will be determined by SAP.

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)	☐	☒	☐	

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)	☐	☒	☐	
9.2.2 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)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4,9.7.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	9.4,9.7.2

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?	☐	☐	☒	
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?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.2.4

Comments:

This is a descriptive study. SAP to govern final adjusted analyses pending feasibility.

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?	☒	☐	☐	9.8

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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).	☒	☐	☐	9.9
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)	☒	☐	☐	8. 9.3.3, 9.5. 9.7.2

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?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

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: Shahar Shmuel

Date: 06 July 2025

Signature:

Appendix 1. TABLE SHELLS FOR SAFETY REPORTS

XXXX Data report		
DD Month YYYY		
Table no.	Description	Comment
1	Demographics	Demographic data not included in Table 3a
1b	Person-years of follow-up and treatment	By sex and treatment indication.
3a-3b	Manchester template	Table 3a describing the surveillance cohort. Table 3b with characteristics at first treatment start with the present biologic drug, all patients registered, and patients with Rheumatoid Arthritis (RA) or Polyarthritis (PA).

The Template Of Semiannual Reports

Table 1. Number Of Patients Ever Treated, And Currently On Drug, By Treatment Indication

	Treatment indication[a]							
	Overall	**RA**	**JA**	**PA**	**PsA**	**AS**	**OT**	**Missing**
Patients ever on drug – n (%)								
Male								
Female								
All								
Patients currently on drug [b] – n (%)								
Male								
Female								
All								

a. RA=rheumatoid arthritis, JA=juvenile arthritis, PA=polyarthritis, PsA=psoriatic arthritis, AS=ankylosing spondylitis, OT=other rheumatic disease.
b. It is acknowledged that data at time of data lock may be incomplete, and thus information on exposure may lag.

Table 1b. Number of Person-years of Follow-up and of Time on Biologic Treatment; by Sex and Treatment Indication

Person-years	Treatment indication[a]						
of follow-up	**Total**	**RA**	**JA**	**PA**	**PsA**	**AS**	**OT**
Male							
Female							
All							
on treatment							
Male							
Female							
All							

a. RA=rheumatoid arthritis, JA=juvenile arthritis, PA=polyarthritis, PsA=psoriatic arthritis, AS=ankylosing spondylitis, OT=other rheumatic disease

Table 2. Distribution of Safety Events Of Interest By Seriousness, And Treatment Indication - Cumulatively During The Follow-Up Period

Report according to a revised version of the template			
Period of observation	Cumulatively	From	
	This period	From	
		To	

Table 3a. Variables Describing The Surveillance Cohort

Variable		N	%
New treatments			
New treatments in this time period			
Newly recorded treatments before this period			
Previously reported cumulative number of treatments			
Current cumulative number of treatments			
Cumulative number of treatments by gender			
	Males		
	Females		
	Unknown		
Cumulative number of patients by gender			
	Males		
	Females		
	Unknown		
Cumulative Number of patients by Age at registration			
	<18		
	18-34		
	35-44		
	45-54		
	55-64		
	65-74		
	75+		
	Unknown		
Person Years - Time on actual biologic therapy			
	Male		
	Females		
	All		

Table 3a. Variables Describing The Surveillance Cohort

Variable		N	%
Person Years - Total follow-up			
	Male		
	Female		
	All		

Table 3b. Characteristics At First Treatment Start With The Present Biologic Drug, All Patients Registered, And Patients With Rheumatoid Arthritis (RA)

Variable	**Mean**	**SD**
Year since diagnosis		
HAQ among RA		
Female		
Male		
Total		
DAS28 among RA		
Female		
Male		
Total		
PAIN VAS among RA		
Female		
Male		
Total		
Tender joint count among RA or PA patients		
Female		
Male		
Total		
Swollen joint count among RA or PA patients		
Female		
Male		
Total		

Table 3b. Characteristics At First Treatment Start With The Present Biologic Drug, All Patients Registered, And Patients With Rheumatoid Arthritis (RA)

Variable	Mean	SD
CRP among all patients		
Female		
Male		
Total		
CRP among RA or PA patients		
Female		
Male		
Total		
ESR among all patients		
Female		
Male		
Total		
ESR among RA or PA patients		
Female		
Male		
Total		
Global Health VAS in all patients		
Female		
Male		
Total		
Global Health VAS in RA or PA patients		
Female		
Male		
Total		
Ever treated with any other biologics		
All		
Males		
Females		

Table 3b. Characteristics At First Treatment Start With The Present Biologic Drug, All Patients Registered, And Patients With Rheumatoid Arthritis (RA)

Variable	Mean	SD
Previously treated with any other biologics		
All		
Males		
Females		

CRP=c-reactive protein; DAS=disease activity scale ESR=erythrocyte sedimentation rate; HAQ=health assessment questionnaire; PA=polyarthritis; RA=rheumatoid arthritis; SD=standard deviation; VAS=visual analog scale

Appendix 2. Table Shells For Comparative Safety Reports

These table shells describe the general outline and contents of tables in comparative safety reports based on register-linkage data. Details of outcome definitions will be agreed upon before each report.

Table I. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts

	Main cohort	Comparator cohorts		
Status at entry	**Tofacitinib**	**bDMARD**	**Bio-naïve**	**General population**
N observations				
N patients				
Demographics				
Age (median, IQR)				
Sex (% females)				
Disease-related characteristics				
Rheumatoid factor positive (%)				
Rheumatoid factor missing (%)				
Disease duration (median, IQR)				
Disease duration missing (%)				
Calendar year (median)				
DAS28 (median, IQR)				
DAS28 missing (%)				
HAQ (median, IQR)				
HAQ missing (%)				
Concomitant DMARDs (%)				
Concomitant csDMARD missing (%)				
Oral steroids (%)				
Oral steroid missing (%)				
Combination therapy with MTX (%)				
NSAIDs (%)				

Table I. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts				
	Main cohort	**Comparator cohorts**		
NSAID missing (%)				
Smoking				
Ever, of non-missing (%)				
Missing, of total (%)				
Number of previous b/tsDMARDs				
0				
1-2				
3+				
Disease history				
Hospitalized infections (%)				
Opportunistic infections (%)				
Herpes zoster (%)				
Fractures (%)				
Malignancy (%)				
NMSC (%)				
Lymphoma (%)				
Lung cancer (%)				
Joint replacement surgery (%)				
COPD (%)				
Diabetes mellitus (%)				
MI (%)				
Hypertension (%)				
Statin use (%)				
Coronary heart disease (%)				
Chronic kidney failure (%)				
Stable angina pectoris (%)				

Table I. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts

	Main cohort	Comparator cohorts		
CV procedures (%)				
VTE (%)				
Major surgery (%)				
Heart failure (%)				
HRT/oral contraceptives (%)				
RA hospitalization (%)				
Total days in hospital during previous year (median, IQR)				
Reason for discontinuing previous b/tsDMARD				
Safety, of non-missing. (%)				
Inefficacy, of non-missing (%)				
Non-medical switch, of non-missing (%)				
Other, of non-missing (%)				
Missing, of total (%)				

Abbreviations: b/tsDMARD=biological/targeted synthetic disease-modifying anti-rheumatic drug; COPD=chronic obstructive pulmonary disease; CV=cardiovascular; DAS28= disease activity score on 28 joints; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; HAQ= health assessment questionnaire disability index; HRT=hormone replacement therapy; IQR=interquartile range (25th-75th); MI=myocardial infarction; MTX=methotrexate; N= number; NMSC= non-melanoma skin cancer; NSAID=non-steroidal anti-inflammatory drug; RA=rheumatoid arthritis; VTE= venous thrombotic event

Table II. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Number of Previous b/tsDMARDs

	0 previous b/tsDMARDs		1-2 previous b/tsDMARDs		3+ previous b/tsDMARDs	
Status at entry	**Tofacitinib**	**bDMARD**	**Tofacitinib**	**bDMARD**	**Tofacitinib**	**bDMARD**
N patients						
Demographics						
Age (median, IQR)						
Sex (% females)						
Disease characteristics						
Rheumatoid factor positive (%)						
Rheumatoid factor missing (%)						
Disease duration (median, IQR)						
Disease duration missing (%)						
Calendar year (median)						
DAS28 (median, IQR)						
DAS28 missing (%)						
HAQ (median, IQR)						
HAQ missing (%)						
Concomitant csDMARD use, of non-missing (%)						
Oral steroid use (%)						
Oral steroid missing (%)						
NSAIDs (%)						
NSAID missing (%)						
Smoking						
Ever, of non-missing (%)						
Missing (%)						
Disease history						
Hospitalized infections (%)						
Opportunistic infections (%)						

Table II. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Number of Previous b/tsDMARDs

	0 previous b/tsDMARDs		1-2 previous b/tsDMARDs		3+ previous b/tsDMARDs	
Herpes zoster (%)						
Fractures (%)						
Malignancy (%)						
NMSC (%)						
Lymphoma (%)						
Lung cancer (%)						
Joint replacement surgery (%)						
COPD (%)						
Diabetes mellitus (%)						
MI (%)						
Hypertension (%)						
Statin use (%)						
Coronary heart disease (%)						
Chronic kidney failure (%)						
Stable angina pectoris (%)						
CV procedures (%)						
VTE (%)						
Major surgery (%)						
Heart failure (%)						
HRT/oral contraceptives (%)						
RA hospitalization (%)						
Total days in hospital during previous year (median, IQR)						
Reason for discontinuing previous bDMARD						
Safety, of non-missing (%)						
Inefficacy, of non-missing (%)						
Non-medical switch, of non-missing (%)						

Table II. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Number of Previous b/tsDMARDs						
	0 previous b/tsDMARDs		**1-2 previous b/tsDMARDs**		**3+ previous b/tsDMARDs**	
Other, of non-missing (%)						
Missing, of total (%)						

Abbreviations: N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire, DMARDS, disease modifying antirheumatic drugs, NSAIDS, non-steroidal anti-inflammatory drugs; Hosp, hospital; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction, n/r = information not relevant

Table III. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person- Years)								
Cohort	**Number of previous biologics**	**Patients**	**Events**	**Person-Years**	**IR**	**95% CI**	**Std IR**	**Mean follow-up, years**
Event								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	bDMARD							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	b/tsDMARD-naïve Patients							
	General Population							

***ever-exposed: follow-up time is until event of interest, death, migration or end of follow-up; whichever occurs first.**
****treatment switch: follow-up time is until treatment switch (bDMARDs to tsDMARD, or tofacitinib to bDMARD), event of interest, death, migration or end of follow-up; whichever occurs first.**

Abbreviations: b/tsDMARD=biological/targeted synthetic disease-modifying anti-rheumatic drug; CI=confidence interval; CLL=chronic lymphatic leukemia; DVT=deep vein thrombosis; GI=gastrointestinal; IR=incidence rate; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PE=pulmonary embolism; PML=progressive multifocal leukoencephalopathy; Std IR=age- and sex-standardized incidence rate (to the tofacitinib cohort distribution); VTE=venous thrombotic event

Table IV. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib initiators vs.	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI

***ever-exposed: follow-up time is until event of interest, death, migration or end of follow-up; whichever occurs first.**
****treatment switch: follow-up time is until treatment switch (bDMARDs to tsDMARD, or Xeljanz to another b/tsDMARD), event of interest, death, migration or end of follow-up; whichever occurs first.**
Notes: Analyses were performed only where both cohorts had at least 5 observed events, some outcome rows are missing for this reason (denoted n/a).
HRa: adjusted for sex, calendar year and number of previous b/tsDMARDs
HRb: additionally adjusted for history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, and number of hospitalization days.
HRc: additionally adjusted for RF status, HAQ (linear), RA disease duration, DAS28 (linear), DMARDs and steroids. Complete case analysis.
HRd: as HRc but using a missing indicator and quartiles for HAQ and DAS28.
b/tsDMARD=biologic/targeted synthetic disease-modifying anti-rheumatic drug; CI=confidence interval; COPD=chronic obstructive pulmonary disease; DAS28=disease activity score on 28 joints; GI=gastrointestinal perforation; HAQ=health assessment questionnaire disability index; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PE=pulmonary embolism; RA=rheumatoid arthritis; RF=rheumatoid factor; VTE=venous thrombotic event.

Table V. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous b/tsDMARDs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Each event	0								
	1								
	2								
	Aggregate estimate								

***ever-exposed: follow-up time is until event of interest, death, migration or end of follow-up; whichever occurs first.**
****treatment switch: follow-up time is until treatment switch (bDMARDs to tsDMARD, or tofacitinib to another b/tsDMARD), event of interest, death, migration or end of follow-up; whichever occurs first.**
Notes: Analyses were performed only where both cohorts had at least 5 observed events, some outcome rows are missing for this reason (denoted n/a).
#Aggregate estimates were estimated using a stratified Cox regression model with the number of previous b/tsDMARDs as the strata variable.
HRa: adjusted for sex, calendar year and number of previous b/tsDMARDs
HRb: additionally adjusted for history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, and number of hospitalization days.
HRc: additionally adjusted for RF status, HAQ (linear), RA disease duration, DAS28 (linear), DMARDs and steroids. Complete case analysis.
HRd: as HRc but using a missing indicator and quartiles for HAQ and DAS28.
b/tsDMARD=biologic/targeted synthetic disease-modifying anti-rheumatic drug; CI=confidence interval; COPD=chronic obstructive pulmonary disease; DAS28=disease activity score on 28 joints; GI=gastrointestinal perforation; HAQ=health assessment questionnaire disability index; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PE=pulmonary embolism; RA=rheumatoid arthritis; RF=rheumatoid factor; VTE=venous thrombotic event.
Note: Table V is also presented stratified by age 65.

Appendix 3. ICD and MedDRA Codes For Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
Serious infections	Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1	This algorithm has not been specifically validated in ARTIS, but the register itself is subject to strict quality assurance routines and has been validated several times. Refs: Ludvigsson et al. External Review and Validation of the Swedish National Inpatient Register, BMC Public Health, 2011 (11):450. http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish.	Hospitalization and/or use of parenteral antibiotics+ MedDRA Infections and Infestations SOC 10021881.
HZ reactivation	Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes B00 and B02. If main diagnosis is RA, contributory diagnoses are also considered.	The algorithm used to identify this endpoint in ARTIS has not been validated and is expected to only identify the most severe cases.	10019974 Herpes zoster, 10019983 Herpes zoster ophthalmic, 10030865 Ophthalmic herpes zoster, 10058428 Herpes zoster multi-dermatomal, 10063491 Herpes zoster oticus, 10065038 Herpes zoster disseminated, 10065119 Necrotising herpetic retinopathy, 10072210 Genital herpes zoster, 10074241 Varicella zoster gastritis, 10074245 Herpes zoster pharyngitis, 10074248 Herpes zoster meningoencephalitis, 10074253 Herpes zoster necrotising retinopathy, 10074254 Varicella zoster pneumonia, 10074254 Varicella zoster pneumonia, 10074259 Herpes zoster meningitis, 10074297 Herpes zoster cutaneous disseminated.

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
CV risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care.	See Serious Infections 'Outcome' was defined as any first-ever ACS event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the underlying cause of death. For discharge diagnoses, the date of admission to hospital was considered the event date. This outcome definition has previously been validated in a Swedish early RA cohort, with a positive predictive value of 95%. In addition, a regional validation study of hospitalized acute MI and stroke found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987. Lindblad et al. Validity of register data on acute myocardial infarction and acute stroke. Scandinavian Journal of Public health 1993; 21 (1):3-9.	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism; Fatal only 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type; 10006145 Brain stem haemorrhage; 10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus;

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
			10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage; 10008076 Cerebral aneurysm ruptured syphilitic; 10008086 Cerebral arteriovenous malformation haemorrhagic; 10008089 Cerebral artery occlusion; 10008092 Cerebral artery thrombosis; 10008111 Cerebral haemorrhage; 10008118 Cerebral infarction; 10008132 Cerebral thrombosis; 10018985 Haemorrhage intracranial; 10022758 Intracranial aneurysm; 10022840 Intraventricular haemorrhage; 10022841 Intraventricular haemorrhage neonatal; 10024119 Left ventricular failure; 10024242 Leriche syndrome; 10034476 Pericardial haemorrhage; 10036511 Precerebral artery occlusion; 10039163 Right ventricular failure; 10039330 Ruptured cerebral aneurysm; 10042316 Subarachnoid haemorrhage; 10042434 Sudden death; 10047279 Ventricle rupture; 10048380 Aneurysm ruptured; 10048761 Atrial rupture; 10049418 Sudden cardiac death; 10049993 Cardiac death; 10050403 Carotid artery dissection; 10051093 Cardiopulmonary failure; 10051328 Carotid aneurysm rupture; 10052019 Femoral artery occlusion; 10053633 Cerebellar artery occlusion; 10053649 Vascular rupture; 10053949 Vascular pseudoaneurysm ruptured; 10055803 Haemorrhage coronary artery; 10058178 Aortic occlusion; 10060874 Aortic rupture; 10060953 Ventricular failure; 10060964 Arterial haemorrhage; 10062585 Peripheral arterial occlusive disease; 10062599 Arterial occlusive disease; 10063081 Acute left ventricular failure; 10063082 Acute right ventricular failure; 10063083 Chronic left ventricular failure; 10063084 Chronic right ventricular failure; 10064595 Haemorrhagic arteriovenous malformation; 10064601 Iliac artery occlusion; 10065441 Venous haemorrhage; 10065558 Aortic arteriosclerosis; 10067057 Basal ganglia haemorrhage; 10067116 Carotid arteriosclerosis; 10068119 Aortic dissection rupture; 10068119 Aortic dissection rupture; 10068230

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Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
			Cardiorenal syndrome; 10069694 Brachiocephalic artery occlusion; 10069695 Subclavian artery occlusion; 10069696 Coeliac artery occlusion;10071716 Vertebral artery dissection; 10072043 Central nervous system haemorrhage; 10072789 Iliac artery rupture; 10073565 Intracranial artery dissection; 10073565 Intracranial artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure.
GI perforation	Hospitalizations in the Patient Register listing ICD10-codes: K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K31.6, K35.0, K35.1, K57.0, K57.2, K57.4, K57.8, K63.0, K63.1, K63.2.	See Serious Infections; Pharmacoepidemiol Drug Saf. 2011 Nov;20(11):1150-8. doi: 10.1002/pds.2215. Epub 2011 Aug 27. Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients.	10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheo-oesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924 Aorto-duodenal fistula; 10003012 Appendicitis perforated; 10009995 Colonic fistula; 10013536 Diverticular fistula; 10013538 Diverticulitis; 10013541 Diverticulitis intestinal haemorrhagic; 10013828 Duodenal fistula; 10013832 Duodenal perforation; 10013849 Duodenal ulcer perforation; 10013849 Duodenal ulcer perforation; 10013850 Duodenal ulcer perforation, nobstructive; 10017815 Gastric perforation; 10017835 Gastric ulcer perforation; 10017836 Gastric ulcer perforation, obstructive; 10017866 Gastritis haemorrhagic; 10017877 Gastrointestinal fistula; 10017954 Gastrointestinal gangrene; 10017955 Gastrointestinal haemorrhage; 10018001 Gastrointestinal perforation; 10021305 Ileal perforation; 10021310 Ileal ulcer perforation; 10022647 Intestinal fistula; 10022694 Intestinal perforation; 10023174 Jejunal perforation; 10023178 Jejunal ulcer perforation; 10023804 Large intestine perforation; 10030181 Oesophageal perforation; 10034354 Peptic ulcer perforation; 10034358 Peptic ulcer perforation, obstructive; 10034397 Perforated peptic ulcer oversewing; 10034649 Peritoneal abscess; 10034674 Peritonitis; 10038073 Rectal perforation; 10038975 Retroperitoneal abscess; 10041103 Small intestinal perforation; 10046274 Upper gastrointestinal

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			haemorrhage; 10048946 Anal abscess; 10048947 Rectal abscess; 10049583 Douglas' abscess; 10049764 Appendiceal abscess; 10050362 Anovulvar fistula; 10050953 Lower gastrointestinal haemorrhage; 10051425 Enterocutaneous fistula; 10052211 Oesophageal rupture; 10052457 Perineal abscess; 10052488 Oesophageal ulcer perforation; 10052814 Perirectal abscess; 10052931 Colon fistula repair; 10052991 Intestinal fistula repair; 10053267 Rectal fistula repair; 10056086 Paraoesophageal abscess; 10056346 Anastomotic haemorrhage; 10056991 Enterocolonic fistula; 10056992 Oesophagobronchial fistula; 10058381 Oesophageal fistula repair; 10059175 Intestinal haemorrhage; 10060921 Abdominal abscess; 10061248 Intestinal ulcer perforation; 10061249 Intra-abdominal haemorrhage; 10061820 Diverticular perforation; 10061975 Gastrointestinal ulcer perforation; 10062065 Perforated ulcer; 10062070 Peritonitis bacterial; 10062570 Enterovesical fistula; 10065713 Gastric fistula; 10065879 Gastrointestinal anastomotic leak; 10066870 Aorto-oesophageal fistula; 10066892 Rectourethral fistula; 10067091 Gastropleural fistula; 10068792 Gastrosplenic fistula; 10071647 Infectious peritonitis.
PML	Hospitalizations in the Patient Register listing ICD10-codes: A81.2.	See Serious Infections.	TBD based on reported events.
NMSC	Identified through the Cancer register as all malignancies with ICD-O/2 code C44, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers Alt: all invasive NMSC, identified as non-benign ICD-O/2 code C44, and no basal cell cancers.	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%.	10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059 Bowen's disease; 10007390 Carcinoma in situ of skin; 10064055 Lip squamous cell carcinoma; 10063693 Malignant neoplasm of eyelid; 10040808 Skin cancer; 10055115 Skin cancer metastatic 10041834 Squamous cell carcinoma of skin.
Malignancy	All invasive malignancies recorded in the cancer register, excluding NMSC.	See NMSC.	Malignant or unspecified tumours (SMQ).

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Lung Cancer	Identified through the Cancer Register. ICD-7: 162.1		HLTs: 10038723 Respiratory tract and pleural neoplasms malignant cell type unspecified NEC; 10024973 Lower respiratory tract neoplasms. LLT: 10023292 Kaposi's sarcoma, lung; Exclude PTs: 10043515 throat cancer; 10004280 benign lung neoplasm; 10061002 benign respiratory tract neoplasm, 10052247 bronchial neoplasm benign; 10014654 endobronchial lipoma; 10081106 sclerosing pneumocytoma.
Lymphoma	Identified through the Cancer Register. All non-Hodgkin Lymphoma: ICD-7: 200,202 All Hodgkin Lymphoma: ICD-7: 201 Chronic lymphocytic leukemia: ICD-7: 204.1	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%	Non-Hodgkin's lymphoma 10029547; Non-Hodgkin's lymphoma metastatic 10071535; Non-Hodgkin's lymphoma recurrent 10029600; Non-Hodgkin's lymphoma refractory 10029601; Non-Hodgkin's lymphoma stage I 10029602; Non-Hodgkin's lymphoma stage II 10029603; Non-Hodgkin's lymphoma stage III 10029604; Non-Hodgkin's lymphoma stage IV 10029605; Non-Hodgkin's lymphoma transformed recurrent 10061871; Non-Hodgkin's lymphoma unspecified histology aggressive 10063908; Non-Hodgkin's lymphoma unspecified histology aggressive recurrent 10029609; Non-Hodgkin's lymphoma unspecified histology aggressive refractory 10029610; Non-Hodgkin's lymphoma unspecified histology aggressive stage I 10029611; Non-Hodgkin's lymphoma unspecified histology aggressive stage II 10029612; Non-Hodgkin's lymphoma unspecified histology aggressive stage III 10029613; Non-Hodgkin's lymphoma unspecified histology aggressive stage IV 10029614; Non-Hodgkin's lymphoma unspecified histology indolent 10065856; Non-Hodgkin's lymphoma unspecified histology indolent stage I 10029622; Non-Hodgkin's lymphoma unspecified histology indolent stage II 10029623; Non-Hodgkin's lymphoma unspecified histology indolent stage III 10029624;

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			Non-Hodgkin's lymphoma unspecified histology indolent stage IV 10029625; Hodgkin's disease 10020206; Hodgkin's disease lymphocyte depletion stage I site unspecified 10020208; Hodgkin's disease lymphocyte depletion stage I subdiaphragm 10020209; Hodgkin's disease lymphocyte depletion stage I supradiaphragm 10020210; Hodgkin's disease lymphocyte depletion stage II site unspecified 10020211; Hodgkin's disease lymphocyte depletion stage II subdiaphragm 10020212; Hodgkin's disease lymphocyte depletion stage II supradiaphragm 10020213; Hodgkin's disease lymphocyte depletion type recurrent 10020215; Hodgkin's disease lymphocyte depletion type refractory10020216; Hodgkin's disease lymphocyte depletion type stage III 10020217; Hodgkin's disease lymphocyte depletion type stage IV 10020218; Hodgkin's disease lymphocyte depletion type stage unspecified 10020219; Hodgkin's disease lymphocyte predominance stage I site unspec 10020220; Hodgkin's disease lymphocyte predominance stage I subdiaphragm 10020221; Hodgkin's disease lymphocyte predominance stage I supradiaphragm 10020222; Hodgkin's disease lymphocyte predominance stage II site unspec 10020223; Hodgkin's disease lymphocyte predominance stage II subdiaphragm 10020224; Hodgkin's disease lymphocyte predominance stage II supradiaphragm 10020225; Hodgkin's disease lymphocyte predominance type recurrent 10020227; Hodgkin's disease lymphocyte predominance type refractory 10020228; Hodgkin's disease lymphocyte predominance type stage III 10020229; Hodgkin's disease lymphocyte predominance type stage IV 10020230; Hodgkin's disease lymphocyte predominance type stage unspecified 10020231; Hodgkin's disease mixed cellularity recurrent 10020233; Hodgkin's disease mixed cellularity refractory 10020234; Hodgkin's disease mixed cellularity stage I site unspecified 10020235; Hodgkin's disease mixed cellularity stage I subdiaphragmatic 10020236; Hodgkin's

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			disease mixed cellularity stage I supradiaphragmatic 10020237; Hodgkin's disease mixed cellularity stage II subdiaphragmatic 10020238; Hodgkin's disease mixed cellularity stage II supradiaphragmatic 10020239; Hodgkin's disease mixed cellularity stage III 10020240; Hodgkin's disease mixed cellularity stage IV 10020241; Hodgkin's disease mixed cellularity stage unspecified 10020242; Hodgkin's disease nodular sclerosis 10020244; Hodgkin's disease nodular sclerosis recurrent 10020245; Hodgkin's disease nodular sclerosis refractory 10020246; Hodgkin's disease nodular sclerosis stage I 10073535; Hodgkin's disease nodular sclerosis stage II 10073534; Hodgkin's disease nodular sclerosis stage III 10020252; Hodgkin's disease nodular sclerosis stage IV 10020253; Hodgkin's disease recurrent 10020266; Hodgkin's disease refractory 10020267; Hodgkin's disease stage I 10020268; Hodgkin's disease stage II 10020269; Hodgkin's disease stage III 10020270; Hodgkin's disease stage IV 10061597; Hodgkin's disease unclassifiable 10020271; Chronic lymphocytic leukaemia 10008958; Chronic lymphocytic leukaemia (in remission) 10008959; Chronic lymphocytic leukaemia recurrent 10008961; Chronic lymphocytic leukaemia refractory 10008962; Chronic lymphocytic leukaemia stage 0 10008963; Chronic lymphocytic leukaemia stage 1 10008964; Chronic lymphocytic leukaemia stage 2 10008965; Chronic lymphocytic leukaemia stage 3 10008966; Chronic lymphocytic leukaemia stage 4 10008967; Chronic lymphocytic leukaemia transformation 10058717;
Fractures	Identified in patient register, in- or outpatient component. Skull/face: S02 Neck: S12 Ribs/chest: S22	The PPV for fractures in the Swedish NPR is extremely high: a validation of 647 patient charts the PPV of fracture in	HLGT | Bone and joint injuries (Primary Path) • Exclude all PTs within HLT Bone and joint injuries NEC • Exclude the following individual PTs from other HLTs: Bone fissure, Cuboid syndrome, Fractured

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	Lumbar spine/pelvis: S32 Shoulder/humerus: S42 Forearm: S52 Wrist/hand: S62 Femur: S72 Ankle/wrist: S82 Foot: S92 Fractures on multiple body parts: T02 Location of fracture not defined in detail: T08, T10, T12, T14.2.	Swedish patient records was 1.00. There is high accuracy for both a diagnosis of hip fracture and a fracture of any type in the Swedish Patient Register	delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner fracture, Pathological fracture, Pseudoarthrosis, Pseudofracture, Anterior labroligamentous periosteal sleeve avulsion lesion, Bankart lesion, Fracture of clavicle due to birth trauma, Radial head dislocation, Scapulothoracic disassociation, Dislocation of vertebra, Intervertebral disc injury, Spinal fusion fracture, Costal cartilage fracture, Costochondral separation, Dislocation of the sternum. HLGT | Fractures (Primary Path) • Exclude all PTs within HLT Fracture complications • Exclude the following individual PTs from other HLTs: Bone fissure, Metaphyseal corner fracture, Pathological fracture, Pseudofracture, Fracture of clavicle due to birth trauma, Scapulothoracic disassociation, Spinal fusion fracture, Costal cartilage fracture.