NON-INTERVENTIONAL STUDY FINAL REPORT 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

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Keywords: Rheumatoid arthritis, tofacitinib, serious infection, malignancy, cardiovascular

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 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 outcomes of interest including rare events and endpoints with long latency periods, Pfizer implemented a post approval, active surveillance study of tofacitinib exposed patients using actively collected prospective data included in the Anti Rheumatic Treatment in Sweden (ARTIS) register.

This non-interventional, active surveillance study, embedded within the ARTIS register, is designated as a post-authorization safety study (PASS) and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA). This study is one of four registry-based PASS, which are being conducted in the United Kingdom, Sweden, Spain and Germany.

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 biologic DMARD (bDMARD) therapies, and whether these rates differ between patients treated with tofacitinib and patients in comparator cohorts. The objectives are to estimate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, cardiovascular (CV) events, major adverse cardiovascular events (MACE), myocardial infarction (MI), venous thromboembolism (VTE: deep venous thrombosis [DVT] and pulmonary embolisms [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 targeted synthetic DMARD (tsDMARD), 2) patients with RA who initiate bDMARDs, and 3) the general population to provide context for rates observed in tofacitinib. Rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE, and other event rates, including fracture, are compared between tofacitinib-treated RA patients and the other comparator cohorts using

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multivariable Cox regressions adjusting for sex, age, year of treatment start, DMARD treatment history, disease severity, comorbidities and other potential confounders for more refined evaluation of safety concerns.

Study design: This active surveillance study used 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 in Sweden.

Setting: Swedish healthcare is tax-funded and offers universal access. Hospital referral is based on geography, rather than insurance-status. Patients with arthritis are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics. Health and demographic information is recorded in a series of registers with a very high degree of completeness resulting from mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible, which allows for the evaluation of baseline comorbidities, outcomes and prescription drug use for this study.

Subjects and study size, including dropouts: The study population comprised all patients with RA enrolled within the ARTIS register who receive tofacitinib following EU approval and marketing (01 January 2017), through the end of the study period (31 December 2024). Three comparator cohorts were assembled for risk characterization purposes: (1) RA patients who were treated with bDMARDs, (2) RA patients who were naïve to bDMARDs and tsDMARDs, and (3) a general population cohort. This study did not have pre-specified hypotheses. All eligible patients in the Swedish registers were included, with no upper limit on the sample size.

Variables and data sources: The study variables included baseline patient characteristics (i.e., clinical and demographic characteristics, comorbidities and current and past therapies) and safety events of interest including, but were not restricted to, the following: serious infections, malignancies, and CV events. Core baseline and follow up data, including patient demographics, disease characteristics, and treatment were based on data from the ARTIS register, that includes data from the Swedish Rheumatology Quality Register (SRQ). ARTIS data were augmented with linkages to the Swedish Patient, Prescribed Drug, Cancer, Basal Cell Cancer, Medical Birth, Total Population, and Causes of Death Registers.

Results: As of 31 December 2024, there were 557, 18,201, 59,959, and 93,782 subjects in the tofacitinib, bDMARD, b/tsDMARD-naïve, and general population cohorts, respectively. The median age of first tofacitinib initiation was 59 years (vs. 61 years for bDMARD initiation, and 69 for b/tsDMARD naïve cohort). Among the tofacitinib cohort, 80% of patients were female (vs. 77% for the bDMARD cohort, and 69% for the b/tsDMARD naïve cohort). In the tofacitinib cohort, 70% had rheumatoid factor (RF)-positive RA (vs. 74% in the bDMARD cohort). Around half (52%) of RA patients initiating tofacitinib were prescribed concomitant oral steroids or had recorded concomitant conventional synthetic DMARDs (47%), but fewer were recorded as also being treated with an NSAID (32%). Percentages were lower in the bDMARD cohort for concomitant use of these therapies (38% and 19%, respectively) The median disease activity score 28 (DAS28) in the tofacitinib and the bDMARD cohort at treatment start were 4.7 and 4.5, respectively. Most patients had RA for

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a relatively long time before initiating tofacitinib treatment (median time since disease onset was 13.1 years). This was longer than the bDMARD cohort who had a median time since disease onset of 9.8 years.

There were few events (ranging from 0 to 65, the latter for hospitalized infection) across the safety events of interested that were monitored in the tofacitinib cohort, and crude incidence rates ranged from 0 to 44.01 per 1000 person-years (hospitalized infection).

There were elevated incidence rates for hospitalized infections, NMSC, PE, congestive heart failure, and GI perforations. Statistically significant differences were observed when comparing the tofacitinib cohort to the bDMARD cohort using adjusted Cox proportional hazards regression for NMSC (fully adjusted hazard ratio (HR) = 1.89, 95% confidence interval (CI) = 1.41–2.53, ever exposed follow-up setting; HR = 2.23, 95% CI 1.56–3.20, treatment-switch follow-up setting) and lung cancer (HR = 3.45, 95% CI 1.32–9.04, treatment-switch follow-up setting).

Discussion: In summary, this final study report describes the relative occurrence of a series of pre-defined safety events of interest in Swedish patients with RA treated with tofacitinib or with other anti-rheumatic treatments. In the fully adjustment models, under an on-drug approach, there was a statistically significant, increased risk forNMSC, and lung cancer in those patients initiating tofacitinib in comparison to bDMARDs. Using the ever-exposed approach, the increased risks of only NMSC remained statistically significant. However, future surveillance is necessary for these potential safety concerns, which should be interpreted in light of the few recorded events. Any crude comparisons of incidence rates for the tofacitinib and the comparison cohorts should be interpreted with caution, as comparisons may be confounded by baseline differences between cohorts, such as disease duration, comorbidities, and medication use, despite adjustments for these in the Cox analyses. Further studies would be required to draw any final conclusions, especially for outcomes with long latency.

No new safety signals identified from this study. These results are consistent with the known safety profile of tofacitinib, as NMSC and lung cancer are important identified risks in the EU RMP.

Marketing Authorization Holder(s): Pfizer Limited

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NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

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
Protocol number	A3921314
Version identifier of the study report	1.0
Date	28 July 2026
EU Post Authorization Study (PAS) register number	EUPAS31157
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-004
Procedure number	EMEA/H/C/0004214
Marketing Authorization Holder (MAH)	Pfizer Limited
Joint Post-Authorization Safety Study (PASS)	No

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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 are also 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 are estimated in elderly patients aged 65 years and older.
Country(-ies) of study	Sweden
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Marketing Authorization Holder(s)

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Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES

Appendix 2.1 Protocol

Appendix 2.2 Protocol administrative change letter (PACL)

Not applicable

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Not applicable

Appendix 3.1. List of Investigators by Country

Not applicable

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Not applicable

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF)/DATA COLLECTION TOOL (DCT)

Not applicable

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable

Appendix 7.1 Withdrawn Subjects

Not applicable

Appendix 7.2 Protocol Deviations

Not applicable

Appendix 7.3 Subjects Excluded from the Analysis

Not applicable

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Appendix 7.4 Demographic Data

Not applicable

Appendix 7.5 Medication/Treatment Data

Not applicable

Appendix 7.6 Endpoint Data

Not applicable

Appendix 7.7 Adverse Events

Not applicable

Appendix 7.8 Laboratory listings

Not applicable

Appendix 8. ADDITIONAL DOCUMENTS

Meta-analysis for tofacitinib RA PASS

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ARTIS	Anti-Rheumatic Treatment in Sweden
ATC	Anatomical Therapeutic Chemical
bDMARD	biologic disease modifying antirheumatic drug
BID	twice daily
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
csDMARD	conventional synthetic DMARD
CV	cardiovascular
CVD	cardiovascular disease
DAS28	disease activity score 28
DMARD	disease modifying antirheumatic drug
DVT	deep vein thrombosis
EC	European Commission
EMA	European Medicines Agency
EU	European Union
GEP	Good Epidemiological Practice
GI	gastrointestinal

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Abbreviation	Definition
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	health assessment questionnaire
HR	hazard ratio
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICD7	International Classification of Diseases version 7
ICD10	International Classification of Diseases version 10
IEA	International Epidemiological Association
IEC	independent ethics committee
ISPE	International Society for Pharmacoepidemiology
IL	interleukin
IQR	interquartile range
IR	incident rate
IRB	institutional review board
JAK	janus kinase
LoT	line of therapy
MI	myocardial infarction
MACE	major adverse cardiovascular event
MAH	market authorization holder
MTX	methotrexate
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	post-authorization study

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Abbreviation	Definition
PASS	Post-Authorization Safety Study
PE	pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PY	person-years
RA	rheumatoid arthritis
RF	rheumatoid factor
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SmPC	Summary of Product Characteristics
SRQ	Swedish Rheumatology Quality Register
TB	tuberculosis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
tsDMARD	targeted synthetic disease modifying antirheumatic drug
US	United States
VTE	venous thromboembolism

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3. INVESTIGATORS

Name, degree(s)	Title	Affiliation
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Johan Askling, MD, PhD	Professor of Rheumatology	Clinical Epidemiology Unit, Dept of Medicine Solna, Karolinska Institutet and Dept of Rheumatology, Karolinska University Hospital, Stockholm

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Shahar Shmuel, PhD	Epidemiologist and Safety Surveillance Research Scientist	Pfizer, Inc.
Johan Askling, MD, PhD	Professor of Rheumatology	Clinical Epidemiology Unit, Dept of Medicine Solna, Karolinska Institutet and Dept of Rheumatology, Karolinska University Hospital, Stockholm

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the HMA-EMA Catalogues of RWD Studies	01 September 2019	28 August 2019	
Start of data collection	15 September 2019	01 September 2019	
Interim report 1	14 March 2021	04 March 2021	
Interim report 2	14 March 2023	22 February 2023	
Interim report 3	14 March 2025	14 March 2025	
End of data collection	14 September 2025	14 September 2025	
Final Study Report	14 August 2026		

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6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (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 characterized 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 disease modifying antirheumatic drugs (DMARDs) including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral Janus kinase (JAK) inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[2,3] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[4] 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 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 European Union (EU) at a dose of 5 mg administered BID (twice a day) 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 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 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 outcomes of interest including rare events and endpoints with long latency periods, Pfizer implemented a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected data in the Anti Rheumatic Treatment in Sweden (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.

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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.[4] 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 the 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 is one of four registry-based post-authorization safety study (PASS), which are being conducted in the United Kingdom, Sweden, Spain, and Germany. This non-interventional, active surveillance study, embedded within the ARTIS register, is designated as a post-authorization safety study (PASS) and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

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 were found to be at increased risk of serious infections relative to those <65 years of age in both clinical trial and observational data.[5,6] 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, tumour necrosis factor inhibitors (TNFis) may affect host defense against infection since TNF mediates inflammation and modulates cellular immune response. Tofacitinib, a JAK inhibitor, 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,[6,7,8,9] however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.[10,11] 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.[11]

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.[2,8,12]

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.[13,14,15,16]

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

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.[14,17] 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.[18]

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.

Cardiovascular Disease

Patients with RA have higher rates of CVD than does the general population.[19] The body of published evidence for increased risk of serious cardiovascular (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.

Other Safety Events of Interest

The ARTIS register collects data on other safety events of interest in the RA population including central nervous system (CNS) events, pregnancy, and mortality. The full list of safety events of interest is provided in 9.4.2.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was a commitment to EMA.

7. 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

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7.1. Primary Objectives

a) To estimate the rates of serious infections, malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, 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 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 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.

b) To estimate the rates of the same events of interest among the comparator groups:

- Patients with RA who have not been treated with bDMARD or tsDMARD

- Patients with RA who initiate bDMARDs

- The general population to provide context for rates observed on tofacitinib.

7.2. Secondary Objectives

To compare the rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE MI, VTE, and other event rates, including fractures between tofacitinib-treated RA patients and other comparator cohorts, if feasible.

Further, rates of a subset of events (e.g., serious infections, MACE, MI, VTE, malignancies excluding NMSC), will be estimated stratified by age (in patients younger than 65 years and in older adult patients aged 65 years and older), by previous tofacitinib use, by VTE risk factors, by CV risk factors, by time periods defined by the changes in SmPC for tofacitinib use in patients with VTE risk factors, and finally by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	September 2021	Administrative	Title Page	Updated to replace old Pfizer logo with new one	Editorial change

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				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 Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor Editorial change.
	September 2021	Administrative	Section 2	Updated to include new abbreviations	Editorial change
	September 2021	Administrative	Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principal investigator.
	September 2021	Substantial	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	PRAC request and clarification.

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				malignancy subtypes.	
	September 2021	Substantial	Section 7	Updated to include information on changes to protocol resulting from June 2021 signal evaluation procedures Updated to include fractures as an additional safety event of interest	Editorial changes Based on available data, Pfizer has identified fractures as a potential risk
	September 2021	Substantial	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
	September 2021	Substantial	Section 9.3.1	Updated to include CV risk factors	PRAC request and clarifications
	September 2021	Substantial	Section 9.3.2	Updated Risk Window to include sensitivity analysis for the 90- extension period.	
	September 2021	Substantial	Section 9.3.3	Updated to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints.	PRAC request and clarifications Based on available data, Pfizer has

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Updated to include fracture as additional safety endpoint.	identified fractures as a potential risk
	September 2021	Substantial	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.
	September 2021	Substantial	Section 9.9	Updated limitations to research methods to include limitations in data capture of characteristics that may influence VTE and CV outcomes and risk.	PRAC request and clarification
	September 2021	Administrative	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.
	September 2021	Administrative	Appendix 2	Added baseline VTE risk factors to table.	Editorial change.
	September 2021	Substantial	Appendix 4	Updated to include definitions for additional endpoints.	PRAC request and clarifications

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
2.0	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
	February 2022	Administrative	Section 2	Updated abbreviations	Editorial change
	February 2022	Substantial	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). Updated Data Analysis to include stratified analysis for VTE incidence rates by ≥1 VTE risk factors versus no VTE risk factors.	Editorial change PRAC request and clarification

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Removed 6-monthly reports from the Milestones.	PRAC request and clarification
	February 2022	Substantial	Section 7.3	Updated the Cardiovascular Disease section to remove MACE as an “important identified risk”.	PRAC request and clarification
	February 2022	Substantial	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
	February 2022	Substantial	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
	February 2022	Substantial	Section 9.3.3	Updated the Endpoints of Interest to replace the term ‘lymphoproliferative malignancy’ with ‘lymphoma’.	PRAC request and clarification
	February 2022	Substantial	Section 9.7.2	Updated Data Analysis to include stratified analysis for VTE incidence rates	PRAC request and clarification

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				by ≥1 VTE risk factors versus no VTE risk factors.	
	February 2022	Substantial	Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
	February 2022	Substantial	All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
	February 2022	Administrative	Annex 2	Signature date updated	Editorial change
3.0	February 2023	Substantial	Section 6	Added footnote to milestone table to indicate data availability	Updated to accommodate data lag
	February 2023	Substantial	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
	February 2023	Administrative	All sections where applicable	Updated language to 'safety events of interest' to be consistent with the study title	Editorial change
4.0	January 2025		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 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

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Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
					baseline comorbidities.
5.0	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

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 are calculated in the four cohorts with 95% confidence intervals (CIs) and reported as descriptive analyses. Data capture and follow-up methods are the same for all four cohorts within the Swedish Registers. This study adheres to the study protocol (V6.0, 06 July 2025) and statistical analysis plan (V1.0, 24 June 2025). No a priori hypotheses are specified. Pending adequate sample size to permit adjustment for important variables, comparative analyses will be conducted, and hazard ratio (HR) estimates with corresponding 95% CIs will be reported.

9.2. Setting

Swedish healthcare is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance status. Patients with inflammatory arthritis are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics. Health and demographic information is recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible. 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.[28]

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9.3. Subjects

RA Patients Treated with Tofacitinib (Main cohort). The main cohort includes all patients with RA initiating tofacitinib in 2017- 2024. This cohort was defined as all RA patients identified in the Swedish Rheumatology Quality Register (SRQ) who started tofacitinib as their first or later b/tsDMARD treatment as recorded in the SRQ. Entry was defined as date of treatment start. No exclusion was used based on previous tofacitinib or b/tsDMARD use. Inclusion criteria were:

1. Initiation of tofacitinib as captured in ARTIS/SRQ.
2. Diagnosis of rheumatoid arthritis by a consulting rheumatologist.

Comparator cohorts. In addition to the main cohort, three comparator cohorts were studied: a cohort of RA patients treated with a bDMARD, a ts/bDMARD-naïve RA cohort, and a general population cohort. For the comparator cohorts, treatments with one and the same b/tsDMARD (i.e., the originator b/tsDMARD and its biosimilar not being distinguished from each other) were counted as separate b/tsDMARD treatments if the previous treatment was registered as discontinued, and more than 90 days (183 days for rituximab) had passed between discontinuation and the next initiation. Entry was defined as date of treatment start.

RA patients treated with a bDMARD. This cohort was defined as all patients with RA as recorded in the SRQ who had a recorded initiation of a bDMARD therapy in the SRQ. bDMARD therapies are defined in Table 2. Entry was defined as the first date when all inclusion criteria are fulfilled 2017-2024. Inclusion criteria for this cohort were:

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

No exclusion was used based on previous (or later) tofacitinib or b/tsDMARD use.

ts/bDMARD-naïve RA cohort. This cohort was defined as all patients with RA, defined as those with at least two diagnoses of RA (ICD10: M05, M060, M062, M063, M068, M069, M123) recorded in the Swedish Patient Register with at least one being recorded in a unit of rheumatology or internal medicine; this definition has been used in previous ARTIS publications. Patients were followed from the date when all inclusion criteria were met from 2017-2024.These patients were censored on the date of initiation of tofacitinib or another b/tsDMARD, but were eligible for subsequent inclusion into the respective drug based cohorts defined above.

General population cohort. The collective study population in the tofacitinib- and bDMARD-cohorts were matched (1:5, by year of birth, sex, and vital status at the date of first identification of arthritis 2001 onwards) to the Swedish Population Register. Date of entry in the general population comparator cohorts was set to the date of entry of their corresponding RA patient. These patients were censored at RA diagnosis date, if RA diagnosis occurred.

Note that follow-up was available until 31 December 2024 for all outcomes except malignancy outcomes where the data from the Cancer Register was only available to 31 December 2023. Thus, analyses for malignancy outcomes included only patients with RA treatment initiations between 2017-2023, rather than 2017-2024.

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Table 2. Classification of Medications (ATC codes) for the Treatment of RA

Abatacept (L04AA24)	Anakinra (L04AC03)	Tofacitinib (L04AA29)
Adalimumab (L04AB04)	Certolizumab pegol (L04AB05)	Baricitinib (L04AA37)
Etanercept (L04AB01)	Golimumab (L04AB06)	Upadacitinib (L04AA44)
Infliximab (L04AB02)	Rituximab (L01XC02)	
Sarilumab (L04AC14)	Tocilizumab (L04AC07)	

Abbreviations: ATC = Anatomical Therapeutic Chemical, bDMARD = biologic disease modifying antirheumatic drug, tsDMARD = targeted synthetic disease modifying antirheumatic drug

9.4. Variables

9.4.1. Outcomes

The following outcomes were analyzed:

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.

Outcome definitions, including ICD-codes and data source, are presented in Table 3. The first outcome occurrence per treatment course (per the above outcomes 1 through 21) during follow-up was recorded. Individuals with a history of the outcome at start of follow-up were not excluded, however, in comparative analyses, prior history was accounted for using model adjustment for baseline comorbidities (Section 9.4.3).

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Table 3. Outcome definitions

Outcome	ICD10 codes	Data sources
Hospitalized Infections	A00-B99, D73.3, E06.0, 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, J38.3, 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, N10, N11, N12, 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	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA then contributory diagnoses were also allowed.
Opportunistic infections	A02, A15, A16, A17, A18, A19, A31, A32, A43, A481, B02, B38, B39, B40, B44, B45, B58, B69	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA then contributory diagnoses were also allowed.
Herpes zoster (hospitalized)	B02	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA then contributory diagnoses were also allowed.
Hepatitis	B15-B19	Main diagnosis in inpatient component of Patient Register. If main diagnosis was RA then contributory diagnoses were also allowed.
Fractures	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92; T02, T08, T10, T12, T14.2, M48.5, M80, M84	Any diagnosis in the inpatient or outpatient component of the Patient Register
Non-melanoma skin cancer (NMSC), including basal cell cancer	C44 and D04 (ICD7=191)	The Cancer Register. Basal cell cancers will be identified using The Swedish Basal Cell Cancer Register.
All primary invasive cancers excluding non-melanoma skin cancers	All non-benign tumors, except C44 and D04 (ICD7=191).	The Cancer Register, invasive cancers only.
Lung cancer	ICD7=162.1	The Cancer Register
Lymphoma (overall)	All non-Hodgkin Lymphoma: ICD-7: 200,202 All Hodgkin Lymphoma: ICD-7: 201 Chronic lymphocytic leukemia: ICD-7: 204.1	The Cancer Register
Non-Hodgkin lymphoma	ICD-7: 200,202	The Cancer Register
Hodgkin lymphoma	ICD-7: 201	The Cancer Register
Chronic lymphocytic leukemia (CLL)	ICD-7: 204.1	The Cancer Register
MACE event	I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis	Main diagnosis in the Patient register, in- or outpatient component.

Table 3. Outcome definitions

Outcome	ICD10 codes	Data sources
	(combines MI, stroke and fatal CV events)	The underlying (main) cause recorded in the Cause of Death Register.
Myocardial infarction (MI)	I20.0, I21	Main diagnosis in the inpatient Patient Register
Venous thrombotic event (VTE)	I26, I80-I82 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the VTE ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.	Main diagnosis in the Patient Register (in- or outpatient component), plus I26.0 as main cause of death in the Cause of Death Register. Anti-coagulants identified using the prescribed drug register.
Deep vein thrombosis (DVT)	I80-I82 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the DVT ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.	Main diagnosis in the Patient Register (in- or outpatient component), Anti-coagulants identified using the prescribed drug register.
Pulmonary embolism (PE)	I26 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the VTE ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.	Main diagnosis in the Patient Register (in- or out-patient component), plus I26.0 as main cause of death in the Cause of Death Register. Anti-coagulants identified using the prescribed drug register.
Gastrointestinal (GI) perforations	K223, K251, K252, K255, K256, K261, K262, K265, K266, K271, K272, K275, K276, K281, K282, K285, K286, K316, K570, K572 K574, K578, K630, K631, K632	Any diagnosis in the Patient register, in- or outpatient component.
Progressive multifocal leukoencephalopathy (PML)	A81.2	Any diagnosis in the Patient register, in- or outpatient component.
Interstitial lung disease	J80-J84	Main diagnoses in the Patient register, in- or outpatient component.
All-cause mortality	-	The Cause of Death Register

Abbreviations: ATC, anatomical therapeutic chemical; ICD10, international classification of diseases version 10; RA, rheumatoid arthritis; RF, rheumatoid factor; DAS28, disease activity score 28; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NMSC, non-melanoma skin cancer; CHD, coronary heart disease; CKD, chronic kidney failure; CV, cardiovascular; VTE, venous thrombotic event; ICD-7, international classification of diseases version 7.
*Note these are Swedish surgical intervention codes

9.4.2. Follow up Definitions

For each cohort, follow-up time began at the date of entry (as specified in Section 9.4.2) and ended as described below.

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Non-malignancy and non-mortality outcomes

Non-malignancy and non-mortality outcomes (see below for outcome definitions; outcomes 1-5, 13-20) were followed up until the first of the following time points:

- event of interest
- first date of emigration from Sweden,
- date of death,
- 31-DEC-2024
- end of treatment + 90 days

End of treatment was defined as the end of treatment date recorded by the treating rheumatologist in the SRQ. When a patient initiated a new therapy within the 90-day extension, the follow-up time and events during the overlapping period was assigned to both treatments.

Malignancy and mortality outcomes

Malignancy outcomes (including NMSC; outcomes 6-12) and all-cause mortality (outcome 21) were evaluated using two approaches: an ever-exposed analysis as per the primary analysis, and a censor at switch approach as the secondary analysis. PML was analyzed as described in the non-malignancy outcomes above, and as per the malignancy outcomes described here resulting in three separate definitions of follow-up for this outcome.

For the ever-exposed approach end of follow-up was defined as the first of the following:

- event of interest
- first date of emigration from Sweden,
- date of death,
- 31-DEC-2023 (31-DEC-2024 for death)

For the censor at switch approach end of follow-up was defined as the first of the following dates:

- event of interest
- first date of emigration from Sweden,
- date of death,
- 31-DEC-2023 (31-DEC-2024 for death)
- date of switch to a tsDMARD (in the non-tofacitinib cohorts; tsDMARDs are listed in Table 1), or date of switch to another JAK inhibitor, or switch to a non-JAK-inhibitor based advanced systemic therapy (in the tofacitinib cohort).

Switch is defined differently in each cohort:

1. **Tofacitinib cohort:** switch to another JAK inhibitor, or switch to a non-JAK-inhibitor based advanced systemic therapy

2. **bDMARD cohort:** switch to tofacitinib or other non-biological advanced systemic therapy

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3. **ts/bDMARD naïve cohort:** switch to a b/tsDMARD therapy

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).

9.4.3. Covariates and Adjustments

All analyses used attained age as the time scale and were adjusted for age, sex (M/F) and number of previous b/tsDMARDs (0, 1-2, 3+). In addition, the following covariates (measured at start of follow-up) were investigated as potential confounders. To avoid over-parameterization of models, these covariates were categorized relatively broadly:

1. Seropositive disease: rheumatoid factor (RF) positive or negative
2. RA disease duration: <5, 5+ years
3. Calendar year of entry into cohort
4. Disease activity score on 28 joints (DAS28): continuous
5. Health assessment questionnaire disability index (HAQ): continuous
6. Concomitant conventional synthetic DMARD (csDMARD) use at the time point of cohort entry: Y/N
7. Concomitant oral steroids at the time point of cohort entry: Y/N
8. History of malignancy: Y/N
9. History of hospitalization listing infection, ever: Y/N
10. History of knee/hip joint replacement surgery, ever Y/N
11. History of chronic obstructive pulmonary disease (COPD), last 5 years: Y/N
12. History of myocardial infarction (MI), last 5 years: Y/N
13. History of diabetes, last 5 years: Y/N
14. Total number of days spent in hospital during the last five years
15. (Where applicable) Reason for discontinuation of most recent b/tsDMARD (safety/inefficacy/other)

DAS28 and its components are considered indicators of disease severity. Note that clinical variables (covariates 1-2, 4-7, above) were only available for the b/tsDMARD-treated cohorts (i.e., the tofacitinib and bDMARD cohorts) defined through ARTIS. ICD codes used to define baseline disease history included as confounders are summarized in Table 4.

Table 4. Definitions of Baseline Covariates included in Descriptive Statistics and/or Considered as Potential Confounders

Covariate	ICD10	Data source
Seropositive disease (rheumatoid factor (RF)+/RF-)	N/A	SRQ
RA disease duration (<5, 5+ yrs)	N/A	SRQ
Calendar year of entry into cohort	N/A	SRQ

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Table 4. Definitions of Baseline Covariates included in Descriptive Statistics and/or Considered as Potential Confounders

Covariate	ICD10	Data source
Disease activity score 28 (DAS28)	N/A	SRQ
Health assessment questionnaire (HAQ)	N/A	SRQ
History of malignancy	All except non-invasive malignancies	The Cancer register. Diagnoses ever prior to entry.
History of infection	A00-B99, D73.3, E06.0, 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, J38.3, 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, N10, N11, N12, 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	Main diagnoses from the inpatient component of Patient Register. Diagnoses ever prior to entry.
History of knee or hip replacement	Operation codes: NGB, NFB	Operation codes from the Patient register. Diagnoses ever prior to entry.
History of chronic obstructive pulmonary disease (COPD)	J41-J44	The Patient Register (any diagnosis, in- and outpatient component). Diagnoses in the 5 years prior to entry.
History of diabetes	E10-E14, O24	The Patient Register (any diagnosis, in- and outpatient component). Diagnoses in the 5 years prior to entry.
History of myocardial infarction (MI)	I21, I22	The Patient Register (any diagnosis, in- and outpatient component). Diagnoses in the 5 years prior to entry.
Baseline covariates presented in descriptive statistics only		
History of opportunistic infections	A02, A15, A16, A17, A18, A19, A31, A32, A43, A481, B02, B38, B39, B40, B44, B45, B58, B69	Main diagnosis in the inpatient component of the National Patient Register. Diagnoses in the 5 years prior to entry.
History of herpes zoster	B02	Main diagnosis in the inpatient component of the National Patient Register. Diagnoses in the 5 years prior to entry.
History of fractures	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92; T02, T08, T10, T12, T14.2, M48.5, M80, M84	Any diagnosis in the in- or outpatient component of the National Patient Register. Diagnoses in the 5 years prior to entry.
History of non-melanoma skin cancer (NMSC)	C44 and D04 (ICD7=191)	Any previous diagnosis recorded in the Cancer Register.
History of lymphoma	ICD7: 200, 201, 202, 204.1	Any previous diagnosis recorded in the Cancer Register.

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Table 4. Definitions of Baseline Covariates included in Descriptive Statistics and/or Considered as Potential Confounders

Covariate	ICD10	Data source
History of lung cancer	ICD7: 162.1	Any previous diagnosis recorded in the Cancer Register.
History of hypertension	I10-I15	Any diagnosis in the in- or outpatient component of the National Patient Register. Diagnoses in the 5 years prior to entry.
History of statin use	ATC=C10AA	The Prescribed Drug Register. Dispensations in the year prior to entry.
History of coronary heart disease (CHD)	I20-I25	Any diagnosis from the in- and outpatient components of the Patient Register. Diagnoses in the 5 years prior to entry.
History of chronic kidney failure (CKD)	N17-N19	Any diagnosis from the in- and outpatient components of the Patient Register. Diagnoses in the 5 years prior to entry.
History of stable angina pectoris	I20 (minus I20.0)	Any diagnosis from the in- and outpatient components of the Patient Register. Diagnoses in the 5 years prior to entry.
History of therapeutic procedures to treat cardiovascular disease (CV procedures)	FN*	Surgical intervention codes recorded in the National Patient Register. Ever recorded.
History of venous thrombotic event (VTE)	I26, I80-I82	Main diagnosis in the in- or outpatient component of the National Patient Register. Diagnoses in the 5 years prior to entry.
History of major surgery	Operation codes: J*, F*, L*, N*	Operation codes from the Patient register. Records in the 90 days prior to entry.
History of heart failure	I50	Main diagnosis in the in- or outpatient component of the National Patient Register, Diagnoses in the 5 years prior to entry.
History of hormone replacement therapy or oral contraceptives	G03A, G03CA	Dispensation in the Prescribed Drug Register in the 90 days prior to entry.
Inpatient care due to RA	M05, M060, M062, M068, M069, M123	Main diagnoses in the inpatient component of the National Patient Register. Ever recorded

Abbreviations: ATC, anatomical therapeutic chemical; ICD10, international classification of diseases version 10; RA, rheumatoid arthritis; RF, rheumatoid factor; DAS28, disease activity score 28; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NMSC, non-melanoma skin cancer; CHD, coronary heart disease; CKD, chronic kidney failure; CV, cardiovascular; VTE, venous thrombotic events.
*Note these are Swedish surgical intervention codes

9.5. Data Sources and Measurement

Tofacitinib-treated patients were identified through the Swedish Rheumatology Quality Register SRQ (www.srq.nu), with comparator cohorts identified through a combination of SRQ, the Swedish Patient Register, the Prescribed Drug Register, and the Total Population register. Baseline comorbidities and outcomes during follow-up were identified by linking

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individuals in these cohorts to Swedish Patient Register, the Swedish Cancer Register, and the Cause of Death Register.

9.5.1. The Swedish Rheumatology Quality Register (SRQ) and Anti-Rheumatic Therapy in Sweden (ARTIS)

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Rheumatology Society to improve the healthcare and treatment for patients with rheumatoid arthritis (RA). The SRQ initially only contained RA patients followed from their first RA diagnosis and onwards. SRQ followed on regional registry initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national clinical registry. For instance, SRQ covers close to 90% of all biologic initiations in Swedish Rheumatology after 1999, and currently contains data on around 85% of all patients with RA in Sweden.[23] SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis, myositis, systemic lupus erythematosus and additional conditions. Currently, approximately 30,000 patients with RA or polyarthritis initiating over 80,000 biological treatments have been enrolled in SRQ. In conjunction with each patient visit, the treating rheumatologist enters data on disease activity and anti-rheumatic treatment. Data from SRQ has been linked to other national registers (described below), using the unique Swedish personal identity number, to create the ARTIS database.

9.5.2. The Swedish Patient Register and the Prescribed Drug Register

The Swedish Patient Register collects 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 International Classification of Diseases 10 (ICD10) since 1997.

The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. Validation against medical files has demonstrated an overall error rate in the main diagnoses of 4% at the ICD chapter level, and 12% at the three-digit level.[29]

The outpatient component of the Patient Register was initiated with nationwide coverage in 2001. Overall, 13% of outpatient visits lack records, but coverage is higher for somatic public care (including most rheumatology care). Chart reviews and validation of the RA diagnosis based on different algorithms applied to the register data indicate a positive predictive value for a register-based diagnosis of RA around 90%.[24,25]

The Prescribed Drug Register was established in July 2005 and contains data with unique patient identifiers for all filled prescriptions to patients in ambulatory care for the whole population. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units for utilization of prescription medications are prescriptions, and DDDs. Information on drugs administrated in hospitals or nursing homes, and drugs sold over-the counter is not captured. The Prescribed Drug Register provides all retrievals of prescribed drugs in Sweden from July 2005, and may be used to aid correct

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classification of patients by their history of retrieved DMARDs, or to define subcohorts based on switches in treatment.

9.5.3. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and contains information 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%.[26, 27] Data until 31-DEC-2023 were available from the Cancer Register for use in this report.

9.5.4. The Swedish Basal Cell Cancer Register

The Swedish Basal Cell Cancer Register was established in 2004, and is linked to the Swedish Cancer Register.[30] Approximately 50,000 individuals are diagnosed with basal cell carcinoma each year in Sweden.

9.5.5. 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.[31] 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 coding system, with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

9.5.6. 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. The register was started in 1952, and the data are considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three-digit level of the ICD-coded underlying cause of death.[32]

9.5.7. 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 residing in Sweden since 1961. This register was used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

9.6. Bias

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing ARTIS, a well-established Swedish rheumatology register. Despite the strengths of the register, the data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, residual confounding and generalizability are of concern when comparing incidence rates. At the beginning of the study period, as a new therapy in the RA treatment

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armamentarium, it is possible that patients treated with tofacitinib represented those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at increased risk for adverse events (AEs). Biases resulting from channeling in the early phases of the study may present as increased rates of AEs. Comparison to internal comparators may illuminate such channeling.

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

Event misclassification may be a 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, it is not feasible in such an observational study to verify all events via source documentation.

9.7. Study Size

This active surveillance study is not intended to test a pre-specified statistical hypothesis. The size of the active surveillance population depends largely on use of tofacitinib in Sweden. All eligible patients in the Swedish registers will be included, with no upper limit on the sample size.

9.8. Data transformation

Number of previous b/tsDMARD has been categorized as 0, 1-2, 3+. Smoking was categorized as ever smoking vs. non-smoking. Concomitant treatments were classified as 1 (presence) or 0. Patients with each of the comorbidities and outcome of interest were classified as 1 if they had at least one of code presented in Table 3 and Table 4, and 0 otherwise.

9.9. Statistical methods

9.9.1. Main Summary Measures

Descriptive statistics for each cohort are presented for all covariates which were described in Section 9.4.3. Descriptive statistics for the b/tsDMARD-exposed cohorts (i.e., the tofacitinib and bDMARD cohorts) are additionally displayed separately by the three categories defined by the number of previous b/tsDMARDs (0, 1-2, 3+).

The number of events and crude incidence rates were estimated for each cohort and outcome. These rates were also stratified by the number of previous b/tsDMARDs for the tofacitinib and bDMARD cohorts. Age- and sex-standardized rates were calculated for each outcome, using the distribution of person-time by age and sex in the tofacitinib cohort as standard. Rates were also presented separately according to the number of previous b/tsDMARDs (0, 1-2, 3+) at the time of treatment start. Moreover, hazard ratios were estimated using Cox proportional hazards models.

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9.9.2. Main Statistical Methods

Hazard ratios were estimated with Cox proportional hazards models using attained age as the time scale. To assess the potential confounding effect of baseline covariates and potential impact of missingness, four models were fit. The first model adjusted for sex, number of previous b/tsDMARDs and calendar year of entry. The second model adjusted for sex, number of previous b/tsDMARDs, calendar year of entry and additionally for pre-baseline comorbidities and healthcare utilization: prior number of days in inpatient care, and history of comorbidities (infection, cancer, MI, diabetes, COPD, and joint replacement surgery). The third model adjusted for all these covariates, but also included RA-specific covariates (measured at treatment start): RF, HAQ, disease duration, DAS28, use of csDMARDs and steroids.

Models 1-4 were additionally fit within categories of previous number of b/tsDMARDs (0, 1-2, 3+) comparing the tofacitinib and bDMARD cohorts for each outcome. Stratified Cox regression models were additionally estimated using the previous number of b/tsDMARDs as the strata variable for each outcome within the b/tsDMARD cohorts.

Covariates were parameterized as described in Section 9.4.3. Cohort-outcome combinations with fewer than 5 events were not included in Cox proportional hazard regression analyses; in these cases, only event numbers and crude and age/sex-adjusted incidence rates were estimated.

Crude incidence rates and number of events were also tabulated by age subgroups for all cohorts; for those patients aged less than 65 years at cohort entry, and those aged 65 years and over at cohort entry. Furthermore, they were tabulated by (1) previous tofacitinib use, (2) VTE risk factors, (3) CV risk factors, (4) time periods defined by the changes in SmPC for tofacitinib use in patients with VTE risk factors, and (5) by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors.

SAS version 9.4 was used for all analyses.

As mentioned previously, this is one of four registry-based PASS, which are being conducted in the United Kingdom, Sweden, Spain, and Germany. To attempt to combine the results of this study with results from other participating European registers, a meta-analysis was conducted to summarize the findings across studies (Appendix 8). Meta-analytic methods are summarized in the meta-analysis report (Appendix 8) and in the meta-analysis SAP (included as an appendix to the meta-analysis report).

9.9.3. Missing Values

No imputation of missing values was performed. For baseline tables, a missing category was added for patients with missing a characteristic (categorical) of interest. For the multivariable Cox proportional hazard regressions, two models were provided: (1) a complete case analysis and (2) a missing category analysis.

9.9.4. Sensitivity Analyses

In order to determine the difference between bDMARD patients who have and have not previously been exposed to tofacitinib, the descriptive statistics of the bDMARD cohort with and without a previous record of tofacitinib use recorded in the SRQ were compared.

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9.9.5. Amendments to the Statistical Analysis Plan

None.

9.10. 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 checks the quality of the data overall in the region.

9.11. Protection of Human Subjects

Subject information and consent

As this study involved 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.

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

There was 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 was 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: 2023-03804-01).

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), the Karolinska Institutet’s guidelines on Research Conduct and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Per Pfizer’s subscription to the ARTIS database, analyses are conducted by ARTIS researchers and in accordance with ARTIS scientific review policies. The database does not contain any patient identification information (e.g., name), except for a unique number assigned for the purpose of linking files.

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10. RESULTS

10.1. Participants

Between 01-JAN-2017 and 31-DEC-2024, 557 initiations of tofacitinib were observed among eligible Swedish RA patients. Of these, 494 initiations occured prior to the end of 2023, and were thus included in the malignancy outcomes analyses (where data were available only up to the end of 2023).

10.2. Descriptive Data

Table 5 describes demographic and clinical characteristics of Swedish RA patients initiating tofacitinib and comparator cohorts. We identified a total of 542 (unique) RA patients initiating tofacitinib treatment between 2017 and 2024. The median age of first tofacitinib initiation was 59 years (vs. 61 years for bDMARD initiation, and 69 for b/tsDMARD naïve cohort Among the tofacitinib cohort, 80% of patients were female (vs. 77% for the bDMARD cohort, and 69% for the b/tsDMARD naïve cohort). In the tofacitinib cohort, 70% had rheumatoid factor (RF)-positive RA (vs. 74% in the bDMARD cohort). The median DAS28 disease activity in the tofacitinib and the bDMARD cohort at treatment start were 4.7 and 4.5, respectively.

Most patients had had RA for a relatively long time before initiating tofacitinib treatment (median time since disease onset was 13.1 years), and this was slightly longer than the bDMARD cohort, which had a median time since disease onset of 9.8 years.

Disease related characteristics were not available for the b/tsDMARD naïve cohort, nor (by definition)for the general population comparator cohort as both populations are defined based on the national patient register (NPR) and not the SRQ. Disease characteristics and smoking are information available only in SRQ.

Relative to the comparative cohorts, the tofacitinib-treated cohort had a slightly larger proportion of females. Compared with the bDMARD cohort, fewer patients in the tofacitinib cohort receiving concomitant DMARDs (47% vs. 63%). There was also a large difference in the number of previous b/tsDMARDs in the tofacitinib cohort in comparison to the bDMARD cohort; 49% of the tofacitinib group had received three of more previous b/tsDMARDs, whereas this figure was only 15% in the bDMARD group. Patients in the tofacitinib cohort tended to have a more extensive history of disease as compared to those the bDMARD cohort, notably for serious infections (30.3% vs 22.8%) and inpatient care because of RA (36.8% vs 20.7%).

Compared to the general population cohort (age and sex matched to the cohorts defined by b/tsDMARDs initiation), the tofacitinib cohort had generally a higher rate of comorbid conditions at baseline; however, there were some exceptions (e.g., cancer, NMSC, lung cancer, MI).

The reason for discontinuing a previous b/tsDMARD (where applicable) did not differ markedly between the tofacitinib and the bDMARD cohort for safety reason, while 57% of tofacitinib patients had discontinued their previous b/ts-DMARD due to inefficacy vs. 47% in the bDMARD cohort.

Additionally, there were 12 tofacitinib-exposed births or pregnancies surviving up to 25 weeks of gestation (data not shown).

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Table 6 describes the demographic and clinical characteristics of the tofacitinib and comparator cohorts stratified by number of previous b/tsDMARDs. Patients who had taken 3 or more b/ts-DMARDs previously were more often females compared to patients on their first line of b/ts-DMARDs , both for the tofacitinib (86% vs 70%) and for the bDMARDs cohort (83% vs 74%).. Patients previously exposed to 3 or more b/ts-DMARDs tended to have a more extensive history of disease compared to those with 0 previous b/ts-DMARDs, most notably for serious infections (35.4 vs 15% for tofacitinib, 34.7% vs 17.5% for bDMARDs).

Table 5. Baseline characteristics of Swedish RA patients initiating tofacitinib, and comparator cohorts

	Main cohort	Comparator Cohorts		
Status at entry	**Tofacitinib**	**bDMARD**	**b/tsDMARD-naïve**	**General population**
N observations	557	18201	59969	93782
N patients	542	13521	59969	79495
Demographics				
Age (median, IQR)	59 (49-68)	61 (50-71)	69 (57-77)	60 (50-71)
Sex (% females)	80%	77%	69%	77%
Disease-related characteristics				
Rheumatoid factor positive (%)	70%	74%	0%	N/A
Rheumatoid factor positive missing (%)	3%	2%	100%	100%
Disease duration (median, IQR)	13.1 (6.8-23.1)	9.8 (3.5-19.1)	N/A	N/A
Disease duration missing (%)	1%	0%	100%	100%
Calendar year of dx (median)	2019	2021	2017	2021
DAS28 (median, IQR)	4.7 (3.6-5.8)	4.5 (3.6-5.4)	N/A	N/A
DAS28 missing (%)	55%	55%	100%	100%
HAQ (median, IQR)	1.3 (0.8-1.8)	1.0 (0.5-1.5)	N/A	N/A
HAQ missing (%)	51%	51%	100%	100%
Concomitant csDMARDs (%)	47%	63%	N/A	N/A
Concomitant csDMARDs missing (%)	33%	34%	100%	100%
Oral steroids (%)	52%	38%	N/A	N/A
Oral steroids missing (%)	33%	34%	100%	100%
Combination therapy with MTX (%)	38%	54%	N/A	N/A
NSAIDs (%)	32%	19%	N/A	N/A
NSAIDs missing (%)	33%	34%	100%	100%
Smoking				

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Table 5. Baseline characteristics of Swedish RA patients initiating tofacitinib, and comparator cohorts

	Main cohort	Comparator Cohorts		
Status at entry	**Tofacitinib**	**bDMARD**	**b/tsDMARD-naïve**	**General population**
Ever	53%	54%	N/A	N/A
Never	43%	42%	N/A	N/A
Missing	4%	4%	100%	100%
Number of previous b/tsDMARDs				
0	14%	50%	100%	N/A
1-2	37%	35%	N/A	N/A
3+	49%	15%	N/A	N/A
Disease history				
Serious infection (%)	30.3%	22.8%	21.4%	11.3%
Opportunistic infection (%)	0.4%	0.2%	0.3%	0.1%
Herpes zoster (%)	0.2%	0.1%	0.2%	0%
Fracture (%)	14.5%	12.7%	14.3%	8.4%
Malignancies, excl. NMSC (%)	6.6%	9%	14.4%	10%
NMSC (%)	5.9%	7%	8.5%	5.5%
Lymphoma (%)	0.9%	0.6%	0.8%	0.4%
Lung cancer (%)	0%	0.3%	0.6%	0.3%
Joint replacement surgery (%)	17.6%	13%	13.7%	5.3%
COPD (%)	4.1%	3.7%	5.2%	1.7%
Diabetes mellitus (%)	8.6%	8.3%	9.8%	5%
MI (%)	1.1%	1.7%	2.8%	1%
Hypertension (%)	21.9%	20.3%	27.8%	12.3%
Statin use (%)	17.4%	18.9%	23.7%	17.2%
CHD (%)	3.4%	3.5%	6%	2.1%
CKD (%)	2.2%	2%	3%	1.2%
Stable angina pectoris (%)	2.3%	1.9%	3.7%	1.1%
Procedures to treat CVD (%)	2.2%	2.8%	3%	1.8%
VTE	3.2%	2.9%	2.8%	1.2%
Undergoing major surgery from date of hospital admission to one month after date of discharge (%)	2.7%	3%	3.1%	1.8%
Heart failure (%)	1.6%	1.6%	3.1%	1%
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)	9.9%	8.4%	6.4%	7%
Inpatient care because of RA (%)	36.8%	20.7%	11.5%	0.1%
Total days in hosp (median, IQR)	1 (0-5)	0 (0-4)	0 (0-6)	0 (0-1)

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Table 5. Baseline characteristics of Swedish RA patients initiating tofacitinib, and comparator cohorts

	Main cohort	Comparator Cohorts		
Status at entry	**Tofacitinib**	**bDMARD**	**b/tsDMARD-naïve**	**General population**
Reason for discontinuing previous b/tsDMARD				
Safety, of those with info. on reason for discontinuation (%)	23%	19%	N/A	N/A
Inefficacy, of those with info. (%)	57%	47%	N/A	N/A
Non-medical switch, of those with info. (%)	0%	4%	N/A	N/A
Other, of those with info. (%)	20%	29%	N/A	N/A
Missing, of total (%)	2%	2%	N/A	N/A

Notes: Procedures to treat CVD include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI).
Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire; DMARDs, disease modifying antirheumatic drugs; MI: myocardial infarction; NSAIDS, non-steroidal anti-inflammatory drugs; Hosp, hospital; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; MTX, methotrexate; RA, rheumatoid arthritis

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Table 6. 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	80	9092	206	6353	271	2756
Demographics						
Age (median, IQR)	55 (45-67)	60 (48-70)	58 (49-67)	62 (51-71)	60 (51-68)	61 (51-71)
Sex (% females)	70%	74%	77%	79%	86%	83%
Disease characteristics						
Rheumatoid factor positive (%)	66%	71%	64%	76%	76%	78%
Rheumatoid factor positive missing (%)	1%	2%	5%	2%	1%	2%
Disease duration (median, IQR)	5.7 (2.4-12.6)	5.0 (1.6-12.6)	11.6 (5.3-22.0)	12.9 (6.8-21.8)	16.6 (10.3-25.3)	17.7 (11.4-26.2)
Disease duration missing (%)	0%	0%	1%	1%	1%	1%
Calendar year of dx (median)	2019	2021	2019	2021	2019	2021
DAS28 (median, IQR)	4.6 (3.2-5.7)	4.4 (3.5-5.3)	4.8 (3.6-5.6)	4.6 (3.6-5.4)	4.8 (3.9-6.0)	4.9 (3.9-5.7)
DAS28 missing (%)	64%	53%	56%	57%	51%	59%
HAQ (median, IQR)	1.0 (0.5-1.6)	0.9 (0.4-1.3)	1.0 (0.6-1.6)	1.0 (0.6-1.5)	1.4 (1.0-2.0)	1.4 (0.9-1.8)
HAQ missing (%)	61%	49%	50%	53%	50%	55%
Concomitant DMARDs (%)	50%	69%	51%	58%	42%	51%
Concomitant DMARDs missing (%)	45%	32%	31%	36%	31%	37%
Oral steroids (%)	48%	35%	44%	37%	59%	50%
Oral steroids missing (%)	45%	32%	31%	36%	31%	37%
Combination therapy with MTX (%)	43%	61%	41%	49%	35%	40%
NSAIDs (%)	7%	13%	33%	22%	37%	31%

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Table 6. 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	
NSAIDS missing (%)	45%	32%	31%	36%	31%	37%
Smoking						
Ever	54%	56%	54%	57%	56%	56%
Disease history						
Serious infection (%)	15%	17.5%	29.6%	25.2%	35.4%	34.7%
Opportunistic infection (%)	0%	0.1%	0.5%	0.3%	0.4%	0.4%
Herpes zoster (%)	0%	0%	0%	0.1%	0.4%	0.3%
Fracture (%)	12.5%	10.8%	14.1%	13.6%	15.5%	16.8%
Malignancies, excl. NMSC (%)	1.3%	8.3%	7.3%	9.8%	7.7%	9.6%
NMSC (%)	1.3%	5.7%	4.9%	8%	8.1%	9.1%
Lymphoma (%)	0%	0.5%	1.5%	0.8%	0.7%	0.4%
Lung cancer (%)	0%	0.3%	0%	0.4%	0%	0.3%
Joint replacement surgery (%)	3.8%	9.3%	15.5%	14.4%	23.2%	21.7%
COPD (%)	5%	3.4%	4.9%	3.9%	3.3%	4%
Diabetes mellitus (%)	3.8%	7.6%	9.7%	8.5%	9.2%	10.1%
MI (%)	0%	1.5%	1%	1.7%	1.5%	2.2%
Hypertension (%)	20%	17.7%	17%	21.8%	26.2%	25.5%
Statin use (%)	12.5%	17.6%	16%	19.8%	19.9%	21.3%
CHD (%)	1.3%	3.1%	2.4%	3.8%	4.8%	4.4%
CKD (%)	2.5%	1.9%	2.9%	2.1%	1.5%	2.1%
Stable angina pectoris (%)	1.3%	1.7%	1.5%	2.1%	3.3%	2.4%
Procedures to treat CVD (%)	2.5%	2.4%	3.4%	3%	1.1%	3.5%
VTE (%)	0%	2.3%	4.4%	3%	3.3%	4.7%
Undergoing major surgery from date of hospital admission to one month after date of discharge (%)	2.5%	2.5%	1.5%	3.4%	3.7%	4%
Heart failure (%)	2.5%	1.4%	1.9%	1.7%	1.1%	1.9%

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Table 6. 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	
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)	8.8%	7.8%	9.7%	8.2%	10.3%	10.6%
Inpatient care because of RA (%)	13.8%	9.2%	25.7%	26.1%	52%	46.3%
Total days in hosp (median, IQR)	0 (0-1)	0 (0-3)	0 (0-4)	0 (0-5)	2 (0-8)	2 (0-8)
Reason for discontinuing previous b/tsDMARD						
Safety, of those with info. (%)	N/A	N/A	17%	18%	27%	22%
Inefficacy, of those with info. (%)	N/A	N/A	62%	47%	54%	49%
Non-medical switch, of those with info. (%)	N/A	N/A	0%	4%		2%
Other, of those with info. (%)	N/A	N/A	21%	31%	19%	27%
Missing, of total (%)	N/A	N/A	2%	2%	2%	1%

Notes: Procedures to treat CVD include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI).
Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire; DMARDS, disease modifying antirheumatic drugs; MI, myocardial infarction; NSAIDS, non-steroidal anti-inflammatory drugs; Hosp, hospitalization; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; MTX, methotrexate

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10.3. Outcome Data

Table 7 displays numbers of patients, numbers of events, crude and standardized incidence rates for all cohorts and outcomes. Table 8 displays hazard ratios (HRs) for each of the outcomes analyzed. Whereas HRa is only adjusted for age, sex, and year of start, HRb-d are models that include adjustment for additional covariates (see footnote in Table 8). HRc and HRd differ with respect to the method used for the handling of missing data, where missing values for covariates in HRd were included as separate categories. Due to the large amount of missing data on the DAS28 and HAQ covariates (around 50% of the b/tsDMARDs-exposed cohorts), the HRd estimates were included, to ensure that any differences between models 2 and 3 were not just due to loss of observations. Table 9 displays adjusted HRs, similar to Table 8, but is restricted to RA patients initiating tofacitinib or bDMARD treatment and is stratified by number of previous b/tsDMARDs, to evaluate potential confounding by indication as tofacitinib was mainly used in more experienced patients, while bDMARDs were mainly used as first line treatment.

10.4. Main Results

As shown previously in Table 5, there were non-negligible amounts of missing data for the DAS28 and HAQ covariates (51% and 55%, respectively, in the tofacitinib cohort), so to ensure that a difference between Model 2 and 3 was not due to loss of observations, we also fit an additional model, Model 4, where these covariates were modeled as categorical (split in quartiles), and with missing information coded as a separate category. Model 3 and 4 were only fitted for the tofacitinib and bDMARD cohorts, which are identified through ARTIS, since the RA-specific covariates are only available for patients registered in ARTIS.

10.4.1. Hospitalized Infections

During 1,477 person-years among the 557 tofacitinib initiations, 65 hospitalized infections occurred (IR: 44.01 per 1000 PYs). Compared with the bDMARD cohort, the incidence rate of hospitalized infections was slightly higher but not statistically significant (HRd = 1.14, 95% CI 0.88–1.48). Compared with the b/tsDMARD-naïve cohort, risk of hospitalized infections was elevated (HRb = 1.51, 95% CI 1.17-1.96), and higher relative to the general population (HRb = 2.97, 95% CI 2.28–3.85).

10.4.2. Opportunistic Infections

Across 1,585 person-years, 3 opportunistic infections occurred in the tofacitinib cohort (IR: 1.89 per 1000 PYs). This incidence rate of opportunistic infections was higher than the corresponding incidence rates in the bDMARD cohort (standardized IR: 0.97 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 0.38 per 1000 PYs) and in the general population cohort (standardized IR: 0.13 per 1000 PYs). Due the small number of events in the tofacitinib cohort, no comparative analyses were performed.

10.4.3. Herpes Zoster

During 1,587 person-years, 2 herpes zoster (HZ) events occurred in the tofacitinib cohort in which the patient was hospitalized (IR: 1.26 per 1000 PYs). This incidence rate was higher

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than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.47 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 0.20 per 1000 PYs) and in the general population cohort (standardized IR: 0.06 per 1000 PYs). Due to the small number of events in the tofacitinib cohort, no further analyses were performed.

10.4.4. Hepatitis

No hepatitis events were observed in the tofacitinib and bDMARD cohorts. A standardized incidence rate of 0.04 per 1000 PYs was observed in the b/tsDMARD-naïve cohort. A single hepatitis event was observed in the general population cohort, leading to a standardized incidence rate of 0.00.

10.4.5. Fractures

During 1,436 person-years contributed by the tofacitinib initiators, 57 fractures occurred (IR: 39.69 per 1000 PYs). Compared with bDMARD-treated patients, the incidence rate was lower but not statistically significant (HRd = 0.87, 95% CI 0.66–1.15). Relative to the b/tsDMARD-naïve cohort, incidence rate was comparable (HRb = 0.98, 95% CI 0.75–1.29). Compared with the general population, incidence rates were higher (HRb = 1.43, 95% CI 1.09–1.89).

10.4.6. Malignancies (Overall, Excluding NMSC)

10.4.6.1. Ever Exposed

Using an ever-exposed approach, 29 malignancies were observed among the tofacitinib cohort (IR: 13.21 per 1000 PYs). Cancer incidence was higher compared with bDMARD patients (HRd = 1.29, 95% CI 0.87–1.91), albeit not statistically significant. Rates were higher than in both the b/tsDMARD naïve cohort (HRb = 1.36, 95% CI 0.91–2.02) and the general population comparator (HRb = 1.48, 95% CI 0.99–2.19), albeit not statistically significant.

10.4.6.2. Treatment Switch

When censoring at treatment switch, 20 malignancies were observed over 1,253 person years among the tofacitinib cohort (IR: 15.96 per 1000 PYs). Rates were increased compared with bDMARD patients (HRd = 1.57, 95% CI 0.99–2.48), b/tsDMARD naïve patients (HRb = 1.62, 95% CI 1.02–2.58), and the general population (HRb = 1.76, 95% CI 1.10–2.80).

10.4.7. NMSC

10.4.7.1. Ever exposed

During 2,113 person years contributed among tofacitinib initiators, 53 NMSCs occurred (IR: 25.08 per 1000 PYs). The rate was higher than in the bDMARD cohort (HRd = 1.89, 95% CI

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1.41–2.53), the b/tsDMARD naïve cohort (HRb = 2.18, 95% CI 1.60–2.95) and than in the general population (HRb = 2.75, 95% CI 2.03–3.73). Results were similar across strata when stratification by previous numbers of bDMARD was performed.

10.4.7.2. Treatment switch

When censoring at treatment switch, 34 NMSC events occurred in the tofacitinib cohort during 1,211 person years (IR: 28.08 per 100 PYs). Incidence rates were increased compared with bDMARD patients (HRd = 2.23, 95% CI 1.56–3.20), b/tsDMARD naïve patients (HRb = 2.46, 95% CI 1.71–3.55), and the general population (HRb = 3.13, 95% CI 2.17–4.50).

10.4.8. Lung Cancer

10.4.8.1. Ever Exposed

During 2,229 person years among tofacitinib initiators, 5 lung cancer cases occurred in the tofacitinib cohort (IR: 2.24 per 1000 PYs). The incidence rate of lung cancer was higher than in the bDMARD cohort (HRd = 2.04, 95% CI 0.78–5.34), the b/tsDMARD naïve cohort (HRb = 1.92, 95% CI 0.72–5.12) and the general population (HRb = 3.21, 95% CI 1.20–8.56).

10.4.8.2. Treatment Switch

When censoring at treatment switch, 5 lung cancer cases occurred in the tofacitinib cohort (IR: 3.93 per 1000 PYs). Incidence rates of lung cancer were increased compared with bDMARD patients (HRd = 3.45, 95% CI 1.32–9.04), the b/tsDMARD naïve cohort (HRb = 3.45, 95% CI 1.31–9.10) and the general population (HRb = 5.70, 95% CI 2.15–15.09).

10.4.9. Lymphoma (Overall)

10.4.9.1. Ever Exposed

During 2,227 person years contributed among tofacitinib initiators, 3 lymphoma cases occurred (IR: 1.35 per 1000 PYs). This incidence rate was higher than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.65 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 1.13 per 1000 PYs) and in the general population cohort (standardized IR: 0.52 per 1000 PYs). Due to the small number of events in the tofacitinib cohort, no further analyses were performed.

10.4.9.2. Treatment Switch

When censoring at treatment switch, 3 lymphomas occurred during 1,272 person years contributed by the tofacitinib cohort (IR: 2.36 per 1000 PYs). This incidence rate was higher than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.67 per 1000 PYs). Due to the small number of events in the tofacitinib cohort, no further analyses were performed.

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10.4.10. Non-Hodgkin Lymphoma

10.4.10.1. Ever Exposed

During 2,227 person years, 3 non Hodgkin lymphoma cases occurred in the tofacitinib cohort (IR: 1.35 per 1000 PYs). This incidence rate was higher than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.53 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 0.94 per 1000 PYs) and in the general population cohort (standardized IR: 0.40 per 1000 PYs). Due to the small number of events in the tofacitinib cohort, no further analyses were performed.

10.4.10.2. Treatment Switch

When censoring at treatment switch, 3 non Hodgkin lymphoma cases were recorded during 1,272 person years contributed by the tofacitinib cohort (IR: 2.36 per 1000 PYs). This incidence rate was higher than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.54 per 1000 PYs).

10.4.11. Hodgkin Lymphoma

No Hodgkin lymphoma cases occurred among tofacitinib initiators. One case occurred in the bDMARD cohort (standardized IR: 0.02 per 1000 PYs), 16 in the b/tsDMARD-naïve cohort (standardized IR: 0.05 per 1000 PYs) and 8 in the general population (standardized IR: 0.03 per 1000 PYs).

10.4.12. Chronic lymphocytic leukemia (CLL)

No CLL cases occurred among tofacitinib initiators. Five cases occurred in the bDMARD cohort (standardized IR: 0.09 per 1000 PYs), 35 in the b/tsDMARD-naïve cohort (standardized IR: 0.11 per 1000 PYs) and 23 in the general population (standardized IR: 0.07 per 1000 PYs).

10.4.13. Major Cardiovascular Events (MACE)

During 1,561 person-years, 22 MACE events occurred among tofacitinib initiators (IR: 14.10 per 1000 PYs). The incidence rates were largely similar to the bDMARD cohort (HRd = 1.08, 95% CI 0.70–1.66) and the b/tsDMARD-naïve cohort (HRb = 0.99, 95% CI 0.64–1.55), and somewhat higher than in the general population (HRb = 1.36, 95% CI 0.87–2.11), albeit not statistically significant.

10.4.14. MI

During 1,580 person-years contributed by the tofacitinib cohort, 9 myocardial infarctions occurred (IR: 5.7 per 1000 PYs). Incidence rates were elevated but not statistically significantly different from the rates in both the bDMARD cohort (HRd = 1.23, 95% CI 0.62–

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2.44), and the b/tsDMARD-naïve cohort (HRb = 1.31, 95% CI 0.65–2.63), and were higher than in the general population (HRb = 1.96, 95% CI 0.98–3.95).

10.4.15. Venous Thromboembolism (VTE)

During 1,570 person-years contributed by the tofacitinib cohort, 13 VTE events occurred (IR: 8.28 per 1000 PYs). This incidence rate was comparable to that observed in the bDMARDs cohort (HRd = 1.07, 95% CI 0.60–1.89), and elevated (but non-statistically significant) compared to the incidence rate in b/tsDMARD-naïve cohort (HRb = 1.21, 95% CI 0.68–2.17). The incidence rate was also higher than in the general population (HRb = 1.94, 95% CI 1.08–3.47).

10.4.16. Deep Venous Thrombosis (DVT)

During 1,586 person-years contributed by the tofacitinib cohort, 4 DVT events occurred (IR: 2.52 per 1000 PYs). This incidence rate was lower than the corresponding incidence rates observed in the bDMARD cohort (standardized IR: 3.29 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 2.97 per 1000 PYs) but higher than the rate in the general population cohort (standardized IR: 1.70 per 1000 PYs). Due the small number of events, no further analyses were performed.

10.4.17. Pulmonary Embolisms (PEs)

During 1,580 person-years contributed by tofacitinib patients, 9 PE events occurred (IR: 5.69 per 1000 PYs). Incidence rates were elevated but not statistically significantly higher than the rates observed in both the bDMARD cohort (HRd = 1.33, 95% CI 0.67–2.67), and the b/tsDMARD-naïve cohort (HRb = 1.70, 95% CI 0.83–3.46), and were higher than the rate in the general population cohort (HRb = 2.63, 95% CI 1.29–5.37).

10.4.18. Congestive Heart Failure (CHF)

During 1,542 person-years contributed by tofacitinib patients, 18 CHF events occurred (IR: 11.67 per 1000 PYs). Compared with bDMARDs, incidence rate was higher (HRd = 1.62, 95% CI 0.99–2.63), but not statistically significant. When stratification by previous numbers of bDMARD was performed, the increased risk was restricted to those previously exposed to 1-2 bDMARDs (HRd = 2.68, 95% CI 1.37–5.24). Rates were higher than in the b/tsDMARD-naïve cohort (HRb = 1.86, 95% CI 1.13–3.06) and increased relative to the general population (HRb = 2.81, 95% CI 1.71–4.62).

10.4.19. Gastrointestinal (GI) Perforations

During 1,589 person-years contributed by tofacitinib patients, 6 GI perforations occurred (IR: 3.78 per 1000 PYs). Rates were higher but non-statistically significant when compared to both bDMARD patients (HRd = 1.44, 95% CI 0.61–3.39) and b/tsDMARD-naïve patients

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(HRb = 1.35, 95% CI 0.55–3.31), and higher than in the general population (HRb = 2.31, 95% CI 0.94–5.65).

10.4.20. PML

No PML cases occurred among tofacitinib initiators. Three cases occurred in the bDMARD cohort (standardized IR: 0.04 per 1000 PYs), two cases in the b/tsDMARD-naïve cohort (standardized IR: 0.01 per 1000 PYs) and no cases occurred in the general population.

10.4.21. Interstitial Lung Disease

No interstitial lung disease cases occurred among tofacitinib initiators. Twenty-three cases occurred in the bDMARD cohort (standardized IR: 0.44 per 1000 PYs), 174 in the b/tsDMARD-naïve cohort (standardized IR: 0.30 per 1000 PYs) and 73 in the general population (standardized IR: 0.17 per 1000 PYs).

10.4.22. All-cause Mortality

10.4.22.1. Ever Exposed

During 2,743 person years contributed by the tofacitinib cohort, 36 deaths occurred among tofacitinib initiators (IR: 13.13 per 1000 PYs). Mortality rates were comparable to bDMARDs (HRd = 0.96, 95% CI 0.68–1.36), lower (albeit not statistically significantly) than in the b/tsDMARD naïve cohort (HRb = 0.75, 95% CI 0.53–1.08), and comparable to the general population (HRb = 1.03, 95% CI 0.72–1.47).

10.4.22.2. Treatment Switch

When censoring at treatment switch, 20 deaths occurred among tofacitinib patients during 1,532 person years (IR: 13.05 per 1000 PYs). Mortality rates were similar to those in bDMARD patients (HRd = 1.03, 95% CI 0.65–1.61). Compared with the b/tsDMARD naïve cohort, rates were lower albeit not statistically significantly (HRb = 0.78, 95% CI 0.49–1.24), and similar to those in the general population cohort (HRb = 1.07, 95% CI 0.68–1.70).

10.4.22.3. Among Patients Receiving Combination Therapy with Methotrexate (MTX)

During 656 person years among 143 tofacitinib initiators receiving combination therapy with MTX, 6 deaths occurred (IR: 9.14 per 1000 PYs). Compared with bDMARD patients treated with MTX, rates were lower albeit not statistically significant (HRd = 0.62, 95% CI 0.27–1.44). No comparison was made with the other cohorts.

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
Hospitalized infections							
Tofacitinib	557	65	1477	44.01	(34.51-56.12)	44.01	2.65
0 previous b/tsDMARDs	80	4	282	14.19	(5.33-37.82)		3.52
1-2 previous b/tsDMARDs	206	20	549	36.45	(23.51-56.50)		2.66
3+ previous b/tsDMARDs	271	41	646	63.43	(46.71-86.15)		2.39
bDMARD	18201	1658	45466	36.47	(34.75-38.26)	32.24	2.50
0 previous b/tsDMARDs	9092	734	24013	30.57	(28.43-32.86)		2.64
1-2 previous b/tsDMARDs	6353	619	15539	39.83	(36.82-43.10)		2.45
3+ previous b/tsDMARDs	2756	305	5914	51.57	(46.10-57.70)		2.15
B/tsDMARD-naïve Patients	59969	10002	260684	38.37	(37.62-39.13)	22.09	4.35
General Population	93782	3661	345544	10.59	(10.26-10.94)	9.32	3.68
Opportunistic infections							
Tofacitinib	557	3	1585	1.89	(0.61-5.87)	1.89	2.85
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57
1-2 previous b/tsDMARDs	206	2	575	3.48	(0.87-13.92)		2.79
3+ previous b/tsDMARDs	271	1	725	1.38	(0.19-9.79)		2.68
bDMARD	18201	55	48447	1.14	(0.87-1.48)	0.97	2.66

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	9092	28	25321	1.11	(0.76-1.60)		2.79
1-2 previous b/tsDMARDs	6353	16	16698	0.96	(0.59-1.56)		2.63
3+ previous b/tsDMARDs	2756	11	6427	1.71	(0.95-3.09)		2.33
B/tsDMARD-naïve Patients	59969	213	284174	0.75	(0.66-0.86)	0.38	4.74
General Population	93782	54	352531	0.15	(0.12-0.20)	0.13	3.76
Herpes Zoster (hospitalized)							
Tofacitinib	557	2	1587	1.26	(0.32-5.04)	1.26	2.85
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57
1-2 previous b/tsDMARDs	206	2	575	3.48	(0.87-13.92)		2.79
3+ previous b/tsDMARDs	271	0	726	0.00	(.-.)		2.68
bDMARD	18201	26	48509	0.54	(0.36-0.79)	0.47	2.67
0 previous b/tsDMARDs	9092	9	25360	0.35	(0.18-0.68)		2.79
1-2 previous b/tsDMARDs	6353	11	16714	0.66	(0.36-1.19)		2.63
3+ previous b/tsDMARDs	2756	6	6434	0.93	(0.42-2.08)		2.33
B/tsDMARD-naïve Patients	59969	121	284377	0.43	(0.36-0.51)	0.20	4.74
General Population	93782	26	352591	0.07	(0.05-0.11)	0.06	3.76
Hepatitis							
Tofacitinib	557	0	1596	0.00	(.-.)	0.00	2.87

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57
1-2 previous b/tsDMARDs	206	0	584	0.00	(.-.)		2.84
3+ previous b/tsDMARDs	271	0	726	0.00	(.-.)		2.68
bDMARD	18201	0	48556	0.00	(.-.)	0.00	2.67
0 previous b/tsDMARDs	9092	0	25375	0.00	(.-.)		2.79
1-2 previous b/tsDMARDs	6353	0	16732	0.00	(.-.)		2.63
3+ previous b/tsDMARDs	2756	0	6449	0.00	(.-.)		2.34
B/tsDMARD-naïve Patients	59969	7	284697	0.02	(0.01-0.05)	0.04	4.75
General Population	93782	1	352641	0.00	(0.00-0.02)	0.00	3.76
Fractures							
Tofacitinib	557	57	1436	39.69	(30.61-51.45)	39.69	2.58
0 previous b/tsDMARDs	80	7	268	26.15	(12.47-54.85)		3.35
1-2 previous b/tsDMARDs	206	20	525	38.11	(24.58-59.07)		2.55
3+ previous b/tsDMARDs	271	30	644	46.60	(32.59-66.66)		2.38
bDMARD	18201	1852	44582	41.54	(39.69-43.48)	39.56	2.45
0 previous b/tsDMARDs	9092	856	23534	36.37	(34.02-38.89)		2.59
1-2 previous b/tsDMARDs	6353	676	15247	44.34	(41.12-47.81)		2.40

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
3+ previous b/tsDMARDs	2756	320	5800	55.17	(49.44-61.56)		2.10
B/tsDMARD-naïve Patients	59969	11305	250159	45.19	(44.37-46.03)	33.89	4.17
General Population	93782	7535	334450	22.53	(22.03-23.04)	21.83	3.57
Malignancies (overall, excluding NMSC), ever exposed*							
Tofacitinib	530	29	2195	13.21	(9.18-19.01)	13.21	4.14
0 previous b/tsDMARDs	77	7	311	22.54	(10.75-47.28)		4.03
1-2 previous b/tsDMARDs	190	8	764	10.47	(5.24-20.93)		4.02
3+ previous b/tsDMARDs	263	14	1120	12.50	(7.40-21.10)		4.26
bDMARD	15875	584	50107	11.65	(10.75-12.64)	10.75	3.16
0 previous b/tsDMARDs	7934	286	24137	11.85	(10.55-13.30)		3.04
1-2 previous b/tsDMARDs	5550	227	18429	12.32	(10.81-14.03)		3.32
3+ previous b/tsDMARDs	2391	71	7541	9.42	(7.46-11.88)		3.15
B/tsDMARD-naïve Patients	57416	3822	241200	15.85	(15.35-16.36)	11.51	4.20
General Population	82018	2827	263179	10.74	(10.35-11.15)	9.95	3.21
Malignancies (overall, excluding NMSC), treatment switch**							
Tofacitinib	508	20	1253	15.96	(10.30-24.74)	15.96	2.47

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	77	6	229	26.25	(11.79-58.44)		2.97
1-2 previous b/tsDMARDs	181	7	443	15.81	(7.54-33.15)		2.45
3+ previous b/tsDMARDs	250	7	582	12.03	(5.74-25.24)		2.33
bDMARD	15873	537	45221	11.87	(10.91-12.92)	10.85	2.85
0 previous b/tsDMARDs	7934	268	22587	11.87	(10.53-13.37)		2.85
1-2 previous b/tsDMARDs	5549	207	16311	12.69	(11.07-14.54)		2.94
3+ previous v	2390	62	6324	9.80	(7.64-12.57)		2.65
B/tsDMARD-naïve Patients	57416	3822	241200	15.85	(15.35-16.36)	11.60	4.20
General Population	82018	2827	263179	10.74	(10.35-11.15)	10.04	3.21
NMSC, ever exposed*							
Tofacitinib	530	53	2113	25.08	(19.16-32.82)	25.08	3.99
0 previous b/tsDMARDs	77	4	314	12.75	(4.78-33.96)		4.08
1-2 previous b/tsDMARDs	190	20	741	27.00	(17.42-41.84)		3.90
3+ previous b/tsDMARDs	263	29	1059	27.39	(19.03-39.41)		4.03
bDMARD	15875	751	49496	15.17	(14.13-16.30)	13.77	3.12
0 previous b/tsDMARDs	7934	327	23897	13.68	(12.28-15.25)		3.01
1-2 previous b/tsDMARDs	5550	306	18169	16.84	(15.06-18.84)		3.27

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
3+ previous b/tsDMARDs	2391	118	7430	15.88	(13.26-19.02)		3.11
B/tsDMARD-naïve Patients	57416	4295	236784	18.14	(17.60-18.69)	10.67	4.12
General Population	82018	2478	263055	9.42	(9.06-9.80)	8.43	3.21
NMSC, treatment switch**							
Tofacitinib	507	34	1211	28.08	(20.06-39.30)	28.08	2.39
0 previous b/tsDMARDs	77	3	231	13.01	(4.20-40.34)		2.99
1-2 previous v	180	13	428	30.37	(17.63-52.30)		2.38
3+ previous b/tsDMARDs	250	18	552	32.60	(20.54-51.74)		2.21
bDMARD	15873	667	44715	14.92	(13.83-16.09)	13.15	2.82
0 previous b/tsDMARDs	7934	300	22377	13.41	(11.97-15.01)		2.82
1-2 previous b/tsDMARDs	5549	264	16101	16.40	(14.53-18.50)		2.90
3+ previous b/tsDMARDs	2390	103	6237	16.51	(13.61-20.03)		2.61
B/tsDMARD-naïve Patients	57416	4295	236784	18.14	(17.60-18.69)	10.70	4.12
General Population	82018	2478	263055	9.42	(9.06-9.80)	8.41	3.21
Lung Cancer, ever exposed*							
Tofacitinib	530	5	2229	2.24	(0.93-5.39)	2.24	4.21
0 previous b/tsDMARDs	77	3	318	9.45	(3.05-29.29)		4.12
1-2 previous b/tsDMARDs	190	0	773	0.00	(.-.)		4.07

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
3+ previous b/tsDMARDs	263	2	1138	1.76	(0.44-7.03)		4.33
bDMARD	15875	77	51044	1.51	(1.21-1.89)	1.37	3.22
0 previous b/tsDMARDs	7934	39	24569	1.59	(1.16-2.17)		3.10
1-2 previous b/tsDMARDs	5550	28	18817	1.49	(1.03-2.16)		3.39
3+ previous b/tsDMARDs	2391	10	7659	1.31	(0.70-2.43)		3.20
B/tsDMARD-naïve Patients	57416	577	248785	2.32	(2.14-2.52)	1.72	4.33
General Population	82018	254	268056	0.95	(0.84-1.07)	0.87	3.27
Lung Cancer, treatment switch**							
Tofacitinib	508	5	1271	3.93	(1.64-9.45)	3.93	2.50
0 previous b/tsDMARDs	77	3	234	12.84	(4.14-39.83)		3.03
1-2 previous b/tsDMARDs	181	0	451	0.00	(.-.)		2.49
3+ previous b/tsDMARDs	250	2	586	3.41	(0.85-13.64)		2.35
bDMARD	15873	73	46066	1.58	(1.26-1.99)	1.40	2.90
0 previous b/tsDMARDs	7934	38	22989	1.65	(1.20-2.27)		2.90
1-2 previous b/tsDMARDs	5549	26	16657	1.56	(1.06-2.29)		3.00
3+ previous b/tsDMARDs	2390	9	6421	1.40	(0.73-2.69)		2.69
B/tsDMARD-naïve Patients	57416	577	248785	2.32	(2.14-2.52)	1.71	4.33

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
General Population	82018	254	268056	0.95	(0.84-1.07)	0.86	3.27
Lymphoma (overall), ever exposed*							
Tofacitinib	530	3	2227	1.35	(0.43-4.18)	1.35	4.20
0 previous b/tsDMARDs	77	1	317	3.15	(0.44-22.36)		4.12
1-2 previous b/tsDMARDs	190	1	773	1.29	(0.18-9.19)		4.07
3+ previous b/tsDMARDs	263	1	1137	0.88	(0.12-6.24)		4.32
bDMARD	15875	33	51060	0.65	(0.46-0.91)	0.63	3.22
0 previous b/tsDMARDs	7934	23	24561	0.94	(0.62-1.41)		3.10
1-2 previous b/tsDMARDs	5550	10	18827	0.53	(0.29-0.99)		3.39
3+ previous b/tsDMARDs	2391	0	7673	0.00	(.-.)		3.21
B/tsDMARD-naïve Patients	57416	282	248944	1.13	(1.01-1.27)	0.76	4.34
General Population	82018	139	268096	0.52	(0.44-0.61)	0.47	3.27
Lymphoma (overall), treatment switch **							
Tofacitinib	508	3	1272	2.36	(0.76-7.31)	2.36	2.50
0 previous b/tsDMARDs	77	1	233	4.28	(0.60-30.41)		3.03
1-2 previous b/tsDMARDs	181	1	451	2.22	(0.31-15.75)		2.49
3+ previous b/tsDMARDs	250	1	588	1.70	(0.24-12.08)		2.35
bDMARD	15873	31	46085	0.67	(0.47-0.96)	0.66	2.90

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	7934	22	22985	0.96	(0.63-1.45)		2.90
1-2 previous b/tsDMARDs	5549	9	16666	0.54	(0.28-1.04)		3.00
3+ previous b/tsDMARDs	2390	0	6435	0.00	(.-.)		2.69
B/tsDMARD-naïve Patients	57416	282	248944	1.13	(1.01-1.27)	0.77	4.34
General Population	82018	139	268096	0.52	(0.44-0.61)	0.48	3.27
Non-Hodgkin Lymphoma, ever exposed*							
Tofacitinib	530	3	2227	1.35	(0.43-4.18)	1.35	4.20
0 previous b/tsDMARDs	77	1	317	3.15	(0.44-22.36)		4.12
1-2 previous b/tsDMARDs	190	1	773	1.29	(0.18-9.19)		4.07
3+ previous b/tsDMARDs	263	1	1137	0.88	(0.12-6.24)		4.32
bDMARD	15875	27	51072	0.53	(0.36-0.77)	0.52	3.22
0 previous b/tsDMARDs	7934	18	24572	0.73	(0.46-1.16)		3.10
1-2 previous b/tsDMARDs	5550	9	18828	0.48	(0.25-0.92)		3.39
3+ previous b/tsDMARDs	2391	0	7673	0.00	(.-.)		3.21
B/tsDMARD-naïve Patients	57416	233	249062	0.94	(0.82-1.06)	0.60	4.34
General Population	82018	108	268179	0.40	(0.33-0.49)	0.37	3.27

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
Non-Hodgkin Lymphoma, treatment switch **							
Tofacitinib	508	3	1272	2.36	(0.76-7.31)	2.36	2.50
0 previous b/tsDMARDs	77	1	233	4.28	(0.60-30.41)		3.03
1-2 previous b/tsDMARDs	181	1	451	2.22	(0.31-15.75)		2.49
3+ previous b/tsDMARDs	250	1	588	1.70	(0.24-12.08)		2.35
bDMARD	15873	25	46094	0.54	(0.37-0.80)	0.54	2.90
0 previous b/tsDMARDs	7934	17	22992	0.74	(0.46-1.19)		2.90
1-2 previous b/tsDMARDs	5549	8	16667	0.48	(0.24-0.96)		3.00
3+ previous b/tsDMARDs	2390	0	6435	0.00	(.-.)		2.69
B/tsDMARD-naïve Patients	57416	233	249062	0.94	(0.82-1.06)	0.61	4.34
General Population	82018	108	268179	0.40	(0.33-0.49)	0.37	3.27
Hodgkin lymphoma, ever exposed*							
Tofacitinib	530	0	2234	0.00	(.-.)	0.00	4.21
0 previous b/tsDMARDs	77	0	320	0.00	(.-.)		4.16
1-2 previous b/tsDMARDs	190	0	773	0.00	(.-.)		4.07
3+ previous b/tsDMARDs	263	0	1140	0.00	(.-.)		4.34
bDMARD	15875	1	51121	0.02	(0.00-0.14)	0.02	3.22

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	7934	0	24602	0.00	(.-.)		3.10
1-2 previous b/tsDMARDs	5550	1	18847	0.05	(0.01-0.38)		3.40
3+ previous b/tsDMARDs	2391	0	7673	0.00	(.-.)		3.21
B/tsDMARD-naïve Patients	57416	16	249572	0.06	(0.04-0.10)	0.05	4.35
General Population	82018	8	268339	0.03	(0.01-0.06)	0.03	3.27
Hodgkin lymphoma, treatment switch**							
Tofacitinib	508	0	1276	0.00	(.-.)	0.00	2.51
0 previous b/tsDMARDs	77	0	236	0.00	(.-.)		3.07
1-2 previous b/tsDMARDs	181	0	451	0.00	(.-.)		2.49
3+ previous b/tsDMARDs	250	0	588	0.00	(.-.)		2.35
bDMARD	15873	1	46141	0.02	(0.00-0.15)	0.02	2.91
0 previous b/tsDMARDs	7934	0	23021	0.00	(.-.)		2.90
1-2 previous b/tsDMARDs	5549	1	16686	0.06	(0.01-0.43)		3.01
3+ previous b/tsDMARDs	2390	0	6435	0.00	(.-.)		2.69
B/tsDMARD-naïve Patients	57416	16	249572	0.06	(0.04-0.10)	0.05	4.35
General Population	82018	8	268339	0.03	(0.01-0.06)	0.03	3.27
Chronic Lymphatic Leukemia, ever exposed*							

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	530	0	2234	0.00	(.-.)	0.00	4.21
0 previous b/tsDMARDs	77	0	320	0.00	(.-.)		4.16
1-2 previous b/tsDMARDs	190	0	773	0.00	(.-.)		4.07
3+ previous b/tsDMARDs	263	0	1140	0.00	(.-.)		4.34
bDMARD	15875	5	51112	0.10	(0.04-0.24)	0.09	3.22
0 previous b/tsDMARDs	7934	5	24591	0.20	(0.08-0.49)		3.10
1-2 previous b/tsDMARDs	5550	0	18848	0.00	(.-.)		3.40
3+ previous b/tsDMARDs	2391	0	7673	0.00	(.-.)		3.21
B/tsDMARD-naïve Patients	57416	35	249519	0.14	(0.10-0.20)	0.11	4.35
General Population	82018	23	268293	0.09	(0.06-0.13)	0.07	3.27
Chronic Lymphatic Leukemia, treatment switch **							
Tofacitinib	508	0	1276	0.00	(.-.)	0.00	2.51
0 previous b/tsDMARDs	77	0	236	0.00	(.-.)		3.07
1-2 previous b/tsDMARDs	181	0	451	0.00	(.-.)		2.49
3+ previous b/tsDMARDs	250	0	588	0.00	(.-.)		2.35
bDMARD	15873	5	46135	0.11	(0.05-0.26)	0.10	2.91
0 previous b/tsDMARDs	7934	5	23013	0.22	(0.09-0.52)		2.90

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
1-2 previous b/tsDMARDs	5549	0	16687	0.00	(.-.)		3.01
3+ previous b/tsDMARDs	2390	0	6435	0.00	(.-.)		2.69
B/tsDMARD-naïve Patients	57416	35	249519	0.14	(0.10-0.20)	0.11	4.35
General Population	82018	23	268293	0.09	(0.06-0.13)	0.08	3.27
CV events (MACE)							
Tofacitinib	557	22	1561	14.10	(9.28-21.41)	14.10	2.80
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57
1-2 previous b/tsDMARDs	206	6	578	10.39	(4.67-23.12)		2.80
3+ previous b/tsDMARDs	271	16	697	22.95	(14.06-37.46)		2.57
bDMARD	18201	676	47470	14.24	(13.21-15.36)	11.79	2.61
0 previous b/tsDMARDs	9092	306	24892	12.29	(10.99-13.75)		2.74
1-2 previous b/tsDMARDs	6353	265	16287	16.27	(14.42-18.35)		2.56
3+ previous b/tsDMARDs	2756	105	6290	16.69	(13.79-20.21)		2.28
B/tsDMARD-naïve Patients	59969	7545	273093	27.63	(27.01-28.26)	13.12	4.55
General Population	93782	2961	347722	8.52	(8.21-8.83)	7.29	3.71
Myocardial infarction (MI)							
Tofacitinib	557	9	1580	5.70	(2.96-10.95)	5.70	2.84
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
1-2 previous b/tsDMARDs	206	3	578	5.19	(1.67-16.10)		2.80
3+ previous b/tsDMARDs	271	6	717	8.37	(3.76-18.64)		2.64
bDMARD	18201	236	48060	4.91	(4.32-5.58)	4.23	2.64
0 previous b/tsDMARDs	9092	118	25140	4.69	(3.92-5.62)		2.77
1-2 previous b/tsDMARDs	6353	85	16541	5.14	(4.15-6.36)		2.60
3+ previous b/tsDMARDs	2756	33	6379	5.17	(3.68-7.28)		2.31
B/tsDMARD-naïve Patients	59969	1921	279350	6.88	(6.58-7.19)	4.14	4.66
General Population	93782	874	350610	2.49	(2.33-2.66)	2.23	3.74
VTE (DVT and PE)							
Tofacitinib	557	13	1570	8.28	(4.81-14.26)	8.28	2.82
0 previous b/tsDMARDs	80	1	280	3.57	(0.50-25.35)		3.50
1-2 previous b/tsDMARDs	206	5	573	8.72	(3.63-20.95)		2.78
3+ previous b/tsDMARDs	271	7	717	9.77	(4.66-20.49)		2.64
bDMARD	18201	338	47988	7.04	(6.33-7.84)	6.50	2.64
0 previous b/tsDMARDs	9092	166	25090	6.62	(5.68-7.70)		2.76
1-2 previous b/tsDMARDs	6353	98	16578	5.91	(4.85-7.21)		2.61
3+ previous b/tsDMARDs	2756	74	6321	11.71	(9.32-14.70)		2.29

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
B/tsDMARD-naïve Patients	59969	2180	278914	7.82	(7.49-8.15)	5.62	4.65
General Population	93782	1208	350144	3.45	(3.26-3.65)	3.20	3.73
DVT							
Tofacitinib	557	4	1586	2.52	(0.95-6.72)	2.52	2.85
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57
1-2 previous b/tsDMARDs	206	3	576	5.21	(1.68-16.14)		2.80
3+ previous b/tsDMARDs	271	1	724	1.38	(0.19-9.81)		2.67
bDMARD	18201	166	48240	3.44	(2.96-4.01)	3.29	2.65
0 previous b/tsDMARDs	9092	80	25213	3.17	(2.55-3.95)		2.77
1-2 previous b/tsDMARDs	6353	57	16638	3.43	(2.64-4.44)		2.62
3+ previous b/tsDMARDs	2756	29	6389	4.54	(3.15-6.53)		2.32
B/tsDMARD-naïve Patients	59969	1102	281407	3.92	(3.69-4.15)	2.97	4.69
General Population	93782	631	351214	1.80	(1.66-1.94)	1.70	3.75
PE							
Tofacitinib	557	9	1580	5.69	(2.96-10.94)	5.69	2.84
0 previous b/tsDMARDs	80	1	280	3.57	(0.50-25.35)		3.50
1-2 previous b/tsDMARDs	206	2	581	3.44	(0.86-13.76)		2.82
3+ previous b/tsDMARDs	271	6	719	8.34	(3.75-18.57)		2.65
bDMARD	18201	179	48278	3.71	(3.20-4.29)	3.29	2.65

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	9092	90	25237	3.57	(2.90-4.38)		2.78
1-2 previous b/tsDMARDs	6353	45	16666	2.70	(2.02-3.62)		2.62
3+ previous b/tsDMARDs	2756	44	6374	6.90	(5.14-9.28)		2.31
B/tsDMARD-naïve Patients	59969	1116	281924	3.96	(3.73-4.20)	2.77	4.70
General Population	93782	611	351441	1.74	(1.61-1.88)	1.58	3.75
Congestive Heart Failure							
Tofacitinib	557	18	1542	11.67	(7.35-18.52)	11.67	2.77
0 previous b/tsDMARDs	80	2	280	7.15	(1.79-28.59)		3.50
1-2 previous b/tsDMARDs	206	10	556	17.99	(9.68-33.43)		2.70
3+ previous b/tsDMARDs	271	6	707	8.49	(3.81-18.90)		2.61
bDMARD	18201	440	47826	9.20	(8.38-10.10)	7.02	2.63
0 previous b/tsDMARDs	9092	225	25017	8.99	(7.89-10.25)		2.75
1-2 previous b/tsDMARDs	6353	150	16451	9.12	(7.77-10.70)		2.59
3+ previous b/tsDMARDs	2756	65	6358	10.22	(8.02-13.04)		2.31
B/tsDMARD-naïve Patients	59969	3779	276717	13.66	(13.23-14.10)	6.33	4.61
General Population	93782	1481	349782	4.23	(4.02-4.46)	3.39	3.73
GI perforations							
Tofacitinib	557	6	1589	3.78	(1.70-8.40)	3.78	2.85

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	80	1	284	3.52	(0.50-24.96)		3.55
1-2 previous b/tsDMARDs	206	2	582	3.44	(0.86-13.74)		2.82
3+ previous b/tsDMARDs	271	3	723	4.15	(1.34-12.86)		2.67
bDMARD	18201	101	48397	2.09	(1.72-2.54)	2.00	2.66
0 previous b/tsDMARDs	9092	37	25312	1.46	(1.06-2.02)		2.78
1-2 previous b/tsDMARDs	6353	41	16655	2.46	(1.81-3.34)		2.62
3+ previous b/tsDMARDs	2756	23	6431	3.58	(2.38-5.38)		2.33
B/tsDMARD-naïve Patients	59969	571	283323	2.02	(1.86-2.19)	1.51	4.72
General Population	93782	311	352028	0.88	(0.79-0.99)	0.86	3.75
PML, ever exposed*							
Tofacitinib	557	0	2743	0.00	(.-.)	0.00	4.92
0 previous b/tsDMARDs	80	0	393	0.00	(.-.)		4.91
1-2 previous b/tsDMARDs	206	0	964	0.00	(.-.)		4.68
3+ previous b/tsDMARDs	271	0	1385	0.00	(.-.)		5.11
bDMARD	18201	3	67431	0.04	(0.01-0.14)	0.04	3.70
0 previous b/tsDMARDs	9092	2	32825	0.06	(0.02-0.24)		3.61
1-2 previous b/tsDMARDs	6353	1	24525	0.04	(0.01-0.29)		3.86

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
3+ previous b/tsDMARDs	2756	0	10080	0.00	(.-.)		3.66
B/tsDMARD-naïve Patients	59969	2	284709	0.01	(0.00-0.03)	0.01	4.75
General Population	93782	0	353248	0.00	(.-.)	0.00	3.77
PML, treatment switch**							
Tofacitinib	537	0	1532	0.00	(.-.)	0.00	2.85
0 previous b/tsDMARDs	80	0	285	0.00	(.-.)		3.56
1-2 previous b/tsDMARDs	199	0	556	0.00	(.-.)		2.80
3+ previous b/tsDMARDs	258	0	691	0.00	(.-.)		2.68
bDMARD	18201	3	60811	0.05	(0.02-0.15)	0.05	3.34
0 previous b/tsDMARDs	9092	2	30657	0.07	(0.02-0.26)		3.37
1-2 previous b/tsDMARDs	6353	1	21687	0.05	(0.01-0.33)		3.41
3+ previous b/tsDMARDs	2756	0	8467	0.00	(.-.)		3.07
B/tsDMARD-naïve Patients	59969	2	284709	0.01	(0.00-0.03)	0.01	4.75
General Population	93782	0	353248	0.00	(.-.)	0.00	3.77
Interstitial lung disease***							
Tofacitinib	557	0	1596	0.00	(.-.)	0.00	2.87
0 previous b/tsDMARDs	80	0	286	0.00	(.-.)		3.57

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
1-2 previous b/tsDMARDs	206	0	584	0.00	(.-.)		2.84
3+ previous b/tsDMARDs	271	0	726	0.00	(.-.)		2.68
bDMARD	18201	23	48532	0.47	(0.31-0.71)	0.44	2.67
0 previous b/tsDMARDs	9092	6	25368	0.24	(0.11-0.53)		2.79
1-2 previous b/tsDMARDs	6353	11	16716	0.66	(0.36-1.19)		2.63
3+ previous b/tsDMARDs	2756	6	6448	0.93	(0.42-2.07)		2.34
B/tsDMARD-naïve Patients	59969	174	284506	0.61	(0.53-0.71)	0.30	4.74
General Population	93782	73	352562	0.21	(0.16-0.26)	0.17	3.76
All-cause mortality (overall), ever exposed*							
Tofacitinib	557	36	2743	13.13	(9.47-18.20)	13.13	4.92
0 previous b/tsDMARDs	80	5	393	12.73	(5.30-30.58)		4.91
1-2 previous b/tsDMARDs	206	9	964	9.33	(4.86-17.94)		4.68
3+ previous b/tsDMARDs	271	22	1385	15.88	(10.46-24.12)		5.11
bDMARD	18201	887	67431	13.15	(12.32-14.05)	10.54	3.70
0 previous b/tsDMARDs	9092	343	32826	10.45	(9.40-11.62)		3.61
1-2 previous b/tsDMARDs	6353	351	24525	14.31	(12.89-15.89)		3.86
3+ previous b/tsDMARDs	2756	193	10080	19.15	(16.63-22.05)		3.66

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
B/tsDMARD-naïve Patients	59969	11598	284717	40.74	(40.00-41.48)	15.77	4.75
General Population	93782	3107	353248	8.80	(8.49-9.11)	6.76	3.77
All-cause mortality, treatment switch **							
Tofacitinib	537	20	1532	13.05	(8.42-20.23)	13.05	2.85
0 previous b/tsDMARDs	80	4	285	14.04	(5.27-37.41)		3.56
1-2 previous b/tsDMARDs	199	6	556	10.79	(4.85-24.01)		2.80
3+ previous b/tsDMARDs	258	10	691	14.47	(7.78-26.89)		2.68
bDMARD	18201	815	60811	13.40	(12.51-14.35)	10.69	3.34
0 previous b/tsDMARDs	9092	320	30657	10.44	(9.35-11.65)		3.37
1-2 previous b/tsDMARDs	6353	326	21687	15.03	(13.49-16.76)		3.41
3+ previous b/tsDMARDs	2756	169	8467	19.96	(17.17-23.21)		3.07
B/tsDMARD-naïve Patients	59969	11598	284717	40.74	(40.00-41.48)	16.32	4.75
General Population	93782	3107	353248	8.80	(8.49-9.11)	7.00	3.77
All-cause mortality (among patients with a combination therapy with MTX) ***							
Tofacitinib	143	6	656	9.14	(4.11-20.35)	9.14	4.59
0 previous b/tsDMARDs	19	0	98	0.00	(.-.)		5.16

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Table 7. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
1-2 previous b/tsDMARDs	58	1	220	4.54	(0.64-32.20)		3.80
3+ previous b/tsDMARDs	66	5	338	14.80	(6.16-35.57)		5.12
bDMARD	6465	254	23626	10.75	(9.51-12.16)	8.69	3.65
0 previous b/tsDMARDs	3778	104	13159	7.90	(6.52-9.58)		3.48
1-2 previous b/tsDMARDs	1994	102	7865	12.97	(10.68-15.75)		3.94
3+ previous b/tsDMARDs	693	48	2602	18.45	(13.90-24.48)		3.75

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; CV, cardiovascular; DVT, deep venous thrombosis; GI, gastrointestinal infection; MACE, major adverse cardiovascular event; MI: myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PML, progressive multifocal leukoencephalopathy; VTE, venous thromboembolism.
IR Incidence Rate; 95% CI 95% confidence interval; Std IR standardised to the age/sex distribution in the tofacitinib cohort.
*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. A 90-day risk window will be applied to the censoring at switch approach

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	bDMARD	1.23	(0.96-1.58)	1.26	(0.98-1.62)	1.03	(0.67-1.56)	1.14	(0.88-1.48)
	b/tsDMARD naïve	1.49	(1.15-1.93)	1.51	(1.17-1.96)	n/r	n/r	n/r	n/r
	General population	3.58	(2.76-4.64)	2.97	(2.28-3.85)	n/r	n/r	n/r	n/r
Opportunistic infections	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/a	n/r	n/r	n/r
Herpes Zoster (hospitalized)	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Hepatitis	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Fractures	bDMARD	0.93	(0.71-1.21)	0.93	(0.71-1.22)	0.90	(0.59-1.37)	0.87	(0.66-1.15)
	b/tsDMARD naïve	0.98	(0.74-1.29)	0.98	(0.75-1.29)	n/r	n/r	n/r	n/r
	General population	1.55	(1.18-2.04)	1.43	(1.09-1.89)	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Malignancies (overall, excluding NMSC), ever exposed	bDMARD	1.32	(0.90-1.94)	1.32	(0.90-1.93)	1.40	(0.76-2.57)	1.29	(0.87-1.91)
	b/tsDMARD naïve	1.36	(0.92-2.02)	1.36	(0.91-2.02)	n/a	n/a	n/a	n/a
	General population	1.50	(1.01-2.23)	1.48	(0.99-2.19)	n/r	n/r	n/r	n/r
Malignancies (overall, excluding NMSC), treatment switch	bDMARD	1.58	(1.01-2.49)	1.59	(1.01-2.50)	2.13	(1.10-4.10)	1.57	(0.99-2.48)
	b/tsDMARD naïve	1.61	(1.02-2.56)	1.62	(1.02-2.58)	n/a	n/a	n/a	n/a
	General population	1.78	(1.12-2.83)	1.76	(1.10-2.80)	n/r	n/r	n/r	n/r
NMSC, ever exposed	bDMARD	1.80	(1.35-2.39)	1.81	(1.36-2.41)	2.70	(1.75-4.16)	1.89	(1.41-2.53)
	b/tsDMARD naïve	2.13	(1.57-2.89)	2.18	(1.60-2.95)	n/a	n/a	n/a	n/a
	General population	2.71	(2.00-3.67)	2.75	(2.03-3.73)	n/r	n/r	n/r	n/r
NMSC, treatment switch	bDMARD	2.11	(1.48-2.99)	2.13	(1.50-3.02)	3.31	(1.98-5.54)	2.23	(1.56-3.20)
	b/tsDMARD naïve	2.40	(1.67-3.46)	2.46	(1.71-3.55)	n/a	n/a	n/a	n/a
	General population	3.07	(2.13-4.42)	3.13	(2.17-4.50)	n/r	n/r	n/r	n/r
Lung Cancer, ever exposed	bDMARD	1.80	(0.70-4.62)	1.83	(0.71-4.70)	n/a	n/a	2.04	(0.78-5.34)
	b/tsDMARD naïve	1.87	(0.71-4.98)	1.92	(0.72-5.12)	n/a	n/a	n/a	n/a
	General population	3.35	(1.26-8.90)	3.21	(1.20-8.56)	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Lung Cancer, treatment switch	bDMARD	3.05	(1.20-7.79)	3.18	(1.24-8.13)	n/a	n/a	3.45	(1.32-9.04)
	b/tsDMARD naïve	3.28	(1.25-8.63)	3.45	(1.31-9.10)	n/a	n/a	n/a	n/a
	General population	5.81	(2.20-15.31)	5.70	(2.15-15.09)	n/r	n/r	n/r	n/r
Lymphoma (overall), ever exposed	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/a	n/r	n/r	n/r
Lymphoma (overall), treatment switch	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/a	n/r	n/r	n/r
Non-Hodgkin Lymphoma, ever exposed	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/a	n/r	n/r	n/r
Non-Hodgkin Lymphoma, treatment switch	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/a	n/r	n/r	n/r
Hodgkin Lymphoma, ever exposed	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Hodgkin Lymphoma, treatment switch	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Chronic Lymphatic Leukemia, ever exposed	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Chronic Lymphatic Leukemia, treatment switch	bDMARD	n/a	n/a	0.00	(.-.)	n/a	n/a	0.00	(.-.)
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
CV events (MACE)	bDMARD	1.10	(0.71-1.68)	1.09	(0.71-1.68)	0.80	(0.38-1.64)	1.08	(0.70-1.66)
	b/tsDMARD naïve	1.00	(0.64-1.56)	0.99	(0.64-1.55)	n/r	n/r	n/r	n/r
	General population	1.58	(1.02-2.46)	1.36	(0.87-2.11)	n/r	n/r	n/r	n/r
Myocardial infarction (MI)	bDMARD	1.24	(0.63-2.44)	1.21	(0.61-2.38)	1.47	(0.62-3.52)	1.23	(0.62-2.44)
	b/tsDMARD naïve	1.36	(0.68-2.73)	1.31	(0.65-2.63)	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population	2.29	(1.14-4.59)	1.96	(0.98-3.95)	n/r	n/r	n/r	n/r
VTE	bDMARD	1.09	(0.62-1.91)	1.10	(0.63-1.94)	1.59	(0.75-3.35)	1.07	(0.60-1.89)
	b/tsDMARD naïve	1.19	(0.66-2.12)	1.21	(0.68-2.17)	n/r	n/r	n/r	n/r
	General population	2.09	(1.17-3.74)	1.94	(1.08-3.47)	n/r	n/r	n/r	n/r
DVT	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
PE	bDMARD	1.40	(0.71-2.78)	1.43	(0.72-2.84)	n/a	n/a	1.33	(0.67-2.67)
	b/tsDMARD naïve	1.65	(0.81-3.37)	1.70	(0.83-3.46)	n/r	n/r	n/r	n/r
	General population	2.89	(1.42-5.88)	2.63	(1.29-5.37)	n/r	n/r	n/r	n/r
Congestive heart failure	bDMARD	1.75	(1.08-2.82)	1.69	(1.05-2.75)	1.25	(0.57-2.74)	1.62	(0.99-2.63)
	b/tsDMARD naïve	1.93	(1.18-3.15)	1.86	(1.13-3.06)	n/r	n/r	n/r	n/r
	General population	3.63	(2.22-5.93)	2.81	(1.71-4.62)	n/r	n/r	n/r	n/r
GI perforations	bDMARD	1.57	(0.68-3.63)	1.58	(0.68-3.66)	n/a	n/a	1.44	(0.61-3.39)
	b/tsDMARD naïve	1.34	(0.55-3.28)	1.35	(0.55-3.31)	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population	2.65	(1.08-6.48)	2.31	(0.94-5.65)	n/r	n/r	n/r	n/r
PML, ever exposed	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
PML, treatment switch	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
Interstitial lung disease	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
All-cause mortality (overall), ever exposed	bDMARD	0.98	(0.70-1.38)	1.00	(0.71-1.40)	0.60	(0.32-1.11)	0.96	(0.68-1.36)
	b/tsDMARD naïve	0.74	(0.52-1.06)	0.75	(0.53-1.08)	n/a	n/a	n/a	n/a
	General population	1.26	(0.88-1.79)	1.03	(0.72-1.47)	n/r	n/r	n/r	n/r
All-cause mortality (overall), treatment switch	bDMARD	1.03	(0.66-1.61)	1.06	(0.68-1.66)	n/a	n/a	1.03	(0.65-1.61)
	b/tsDMARD naïve	0.76	(0.48-1.21)	0.78	(0.49-1.24)	n/a	n/a	n/a	n/a
	General population	1.29	(0.82-2.04)	1.07	(0.68-1.70)	n/r	n/r	n/r	n/r

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Table 8. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
All-cause mortality (among patients with a combination therapy with MTX)	bDMARD	0.72	(0.31-1.64)	0.65	(0.28-1.49)	0.65	(0.25-1.68)	0.62	(0.27-1.44)
	b/tsDMARD naïve	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
	General population	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DAS28, disease activity score 28; DVT, deep venous thrombosis; GI, gastrointestinal infection; HAQ, health assessment questionnaire; MACE, major adverse cardiovascular event; MI: myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PML, progressive multifocal leukoencephalopathy; RF, rheumatoid factor; VTE, venous thromboembolism, HR: Hazard Ratio. CI: Confidence Interval. .
Notes: 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, 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.
n/a: not available (number of events <5)
n/r: not relevant
*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. A 90-day risk window will be applied to the censoring at switch approach

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Table 9. Adjusted Hazard Ratios (HRs) Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the number of previous biologic drugs

Outcome	Number of previous b/tsDMARDs	HR a	95% CI	HR b	95% CI	HR c	95% CI	HR d	95% CI
Hospitalized infections	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	0.96	(0.61-1.50)	1.04	(0.67-1.64)	1.04	(0.48-2.23)	1.14	(0.73-1.79)
	3+	0.73	(0.53-1.03)	1.41	(1.01-1.97)	1.07	(0.60-1.90)	1.25	(0.88-1.77)
	Aggregate estimate	0.87	(0.68-1.12)	1.18	(0.92-1.52)	n/a	n/a	1.15	(0.89-1.49)
Fractures	0	1.27	(0.60-2.67)	0.84	(0.40-1.78)	n/a	n/a	0.74	(0.33-1.66)
	1-2	1.03	(0.66-1.61)	0.97	(0.62-1.52)	0.97	(0.45-2.08)	0.98	(0.62-1.56)
	3+	1.10	(0.75-1.61)	0.91	(0.62-1.33)	1.02	(0.59-1.77)	0.85	(0.58-1.25)
	Aggregate estimate	1.11	(0.85-1.46)	0.91	(0.69-1.19)	n/a	n/a	0.88	(0.66-1.15)
Malignancies (overall, excluding NMSC), ever exposed	0	0.47	(0.22-0.99)	2.32	(1.09-4.94)	n/a	n/a	2.35	(1.10-5.02)
	1-2	1.01	(0.50-2.05)	0.92	(0.45-1.87)	1.60	(0.63-4.07)	0.81	(0.38-1.73)
	3+	0.72	(0.40-1.30)	1.35	(0.75-2.41)	n/a	n/a	1.40	(0.77-2.54)
	Aggregate estimate	0.75	(0.51-1.11)	1.31	(0.89-1.92)	n/a	n/a	1.29	(0.87-1.91)
Malignancies (overall, excluding NMSC), treatment switch	0	0.42	(0.19-0.95)	2.53	(1.12-5.73)	n/a	n/a	2.52	(1.11-5.71)
	1-2	0.67	(0.32-1.43)	1.42	(0.67-3.04)	2.56	(1.00-6.52)	1.39	(0.65-2.99)

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Table 9. Adjusted Hazard Ratios (HRs) Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the number of previous biologic drugs

Outcome	Number of previous b/tsDMARDs	HR a	95% CI	HR b	95% CI	HR c	95% CI	HR d	95% CI
	3+	0.76	(0.35-1.69)	1.23	(0.56-2.72)	n/a	n/a	1.23	(0.55-2.76)
	Aggregate estimate	0.63	(0.40-1.00)	1.57	(0.99-2.47)	n/a	n/a	1.57	(0.99-2.48)
NMSC, ever exposed	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	0.53	(0.34-0.84)	1.89	(1.20-2.98)	2.21	(1.05-4.64)	2.00	(1.25-3.20)
	3+	0.51	(0.33-0.77)	2.03	(1.33-3.09)	3.57	(1.80-7.11)	2.15	(1.38-3.32)
	Aggregate estimate	0.55	(0.42-0.74)	1.83	(1.37-2.44)	n/a	n/a	1.88	(1.40-2.53)
NMSC, treatment switch	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	0.44	(0.25-0.77)	2.27	(1.30-3.98)	2.73	(1.15-6.47)	2.29	(1.27-4.14)
	3+	0.40	(0.24-0.67)	2.57	(1.53-4.32)	4.75	(1.96-11.55)	2.71	(1.58-4.62)
	Aggregate estimate	0.47	(0.33-0.66)	2.17	(1.52-3.09)	n/a	n/a	2.23	(1.55-3.20)
Lung Cancer, ever exposed	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Aggregate estimate	0.53	(0.20-1.36)	1.94	(0.75-5.01)	n/a	n/a	2.04	(0.78-5.36)
Lung Cancer, treatment switch	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

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Table 9. Adjusted Hazard Ratios (HRs) Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the number of previous biologic drugs

Outcome	Number of previous b/tsDMARDs	HR a	95% CI	HR b	95% CI	HR c	95% CI	HR d	95% CI
	Aggregate estimate	0.32	(0.12-0.81)	3.31	(1.29-8.54)	n/a	n/a	3.48	(1.33-9.10)
CV events (MACE)	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	1.35	(0.60-3.03)	0.72	(0.32-1.62)	n/a	n/a	0.74	(0.32-1.67)
	3+	0.61	(0.36-1.06)	1.57	(0.91-2.73)	1.39	(0.59-3.25)	1.72	(0.98-3.02)
	Aggregate estimate	0.97	(0.63-1.49)	1.04	(0.68-1.61)	n/a	n/a	1.08	(0.70-1.67)
Myocardial infarction	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	0.53	(0.22-1.31)	1.76	(0.71-4.36)	2.54	(0.81-7.98)	1.93	(0.75-4.99)
	Aggregate estimate	0.81	(0.41-1.60)	1.20	(0.61-2.37)	n/a	n/a	1.23	(0.62-2.45)
VTE	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	0.66	(0.27-1.63)	1.56	(0.63-3.87)	n/a	n/a	1.55	(0.62-3.89)
	3+	1.04	(0.47-2.31)	1.00	(0.45-2.20)	1.47	(0.53-4.10)	0.99	(0.44-2.20)
	Aggregate estimate	0.93	(0.53-1.65)	1.09	(0.62-1.92)	n/a	n/a	1.07	(0.60-1.89)
PE	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	0.74	(0.30-1.78)	1.47	(0.61-3.56)	n/a	n/a	1.58	(0.64-3.88)

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Table 9. Adjusted Hazard Ratios (HRs) Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the number of previous biologic drugs

Outcome	Number of previous b/tsDMARDs	HR a	95% CI	HR b	95% CI	HR c	95% CI	HR d	95% CI
	Aggregate estimate	0.73	(0.37-1.46)	1.40	(0.70-2.78)	n/a	n/a	1.33	(0.66-2.67)
Heart failure	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	0.36	(0.19-0.69)	2.75	(1.43-5.28)	n/a	n/a	2.68	(1.37-5.24)
	3+	0.77	(0.33-1.82)	1.33	(0.56-3.17)	n/a	n/a	1.08	(0.44-2.63)
	Aggregate estimate	0.59	(0.36-0.95)	1.72	(1.06-2.79)	n/a	n/a	1.62	(1.00-2.64)
GI perforations	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Aggregate estimate	0.63	(0.27-1.47)	1.61	(0.69-3.76)	n/a	n/a	1.46	(0.62-3.43)
All-cause mortality (overall), ever exposed	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	1.06	(0.67-1.66)	0.89	(0.57-1.40)	n/a	n/a	0.94	(0.59-1.48)
	Aggregate estimate	1.07	(0.76-1.51)	0.92	(0.65-1.30)	n/a	n/a	0.96	(0.68-1.35)
All-cause mortality (overall), treatment switch	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	1.10	(0.49-2.47)	0.88	(0.39-1.98)	n/a	n/a	0.93	(0.41-2.11)
	3+	1.10	(0.58-2.10)	0.83	(0.43-1.58)	n/a	n/a	0.87	(0.45-1.67)

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Table 9. Adjusted Hazard Ratios (HRs) Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the number of previous biologic drugs

Outcome	Number of previous b/tsDMARDs	HR a	95% CI	HR b	95% CI	HR c	95% CI	HR d	95% CI
	Aggregate estimate	1.02	(0.65-1.60)	0.98	(0.62-1.54)	n/a	n/a	1.02	(0.65-1.61)
All-cause mortality (among patients with a combination therapy with MTX)	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	1-2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	3+	1.23	(0.48-3.12)	0.74	(0.28-1.93)	n/a	n/a	0.70	(0.26-1.86)
	Aggregate estimate	1.40	(0.61-3.21)	0.65	(0.28-1.49)	n/a	n/a	0.62	(0.27-1.44)

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DAS28, disease activity score 28; GI, gastrointestinal infection; HAQ, health assessment questionnaire; MACE, major adverse cardiovascular event; MI: myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; RF, rheumatoid factor; VTE, venous thromboembolism, HR: Hazard Ratio. CI: Confidence Interval.
Notes:
The following outcomes were excluded from the analyses due to a lower number of events: opportunistic infections, Herpes Zoster (hospitalized), hepatitis, lymphoma (overall), non-Hodgkin lymphoma, Hodgkin lymphoma, CLL, and DVT, congestive heart failure, PML, interstitial lung disease.
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, 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.
n/a: not available (number of events <5)
n/r: not relevant
*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. A 90-day risk window will be applied to the censoring at switch approach

10.5. Other Analyses

10.5.1. Subgroup Analyses by Age at Treatment Initiation

Table 10 presents the numbers of patients, numbers of events, crude and standardized incidence rates by age subgroups. Between 01-JAN-2017 and 31-DEC-2024, there were 375 tofacitinib initiations and 10,925 bDMARD initiations among subjects younger than 65 years old at cohort entry, and 182 tofacitinib treatment initiations and 7,276 bDMARD treatment initiations among those older than 65 years at cohort entry.

10.5.1.1. Hospitalized Infections

During 1040 person-years (PYs) of follow-up among 375 RA patients aged less than 65 years at tofacitinib initiation between 01-JAN-2017 and 31-DEC-2024, we observed 31 individuals who were hospitalized with a discharge diagnosis listing an infection, resulting in an IR of 29.80/1000 PYs. For those 65 years and older at tofacitinib initiation, the IR was higher at 77.89/1000 PYs (34 events in 437 person-years).

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 21.03 per 1000 PYs (570 events) and 58.21 per 1000 PYs (1088 events) for patients younger than 65 years and aged 65 years and older, respectively. In the b/tsDMARD-naïve cohort, the rates were 12.41 per 1000 PYs (1349 events) and 44.06 per 1000 PYs (8653 events), and in the general population, 5.56 per 1000 PYs (1187 events) and 18.06 per 1000 PYs (2474 events), respectively.

10.5.1.2. Fractures

During 994 PYs among 375 tofacitinib-treated RA patients under age 65 years, 31 fractures were recorded, corresponding to an IR of 31.18 per 1000 PYs. In contrast, 26 fractures occurred during 442 PYs among 182 patients aged 65 years or above, giving an IR of 58.83 per 1000 PYs.

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 29.79 per 1000 PYs (777 events) and 61.35 per 1000 PYs (1075 events), in the b/tsDMARD-naïve cohort 24.69 per 1000 PYs (2438 events) and 53.67 per 1000 PYs (8867 events), and in the general population 16.55 per 1000 PYs (3313 events) and 33.51 per 1000 PYs (4222 events), respectively.

10.5.1.3. Malignancies (Overall, Excluding NMSC)

Among the 356 tofacitinib-treated RA patients younger than 65, we observed 13 cancer events during 1515 PYs, for an IR of 8.58 per 1000 PYs. For 174 patients aged 65 years and older, 16 events occurred over 680 PYs, corresponding to an IR of 23.54 per 1000 PYs.

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 6.61 per 1000 PYs (201 events) and 19.64 per 1000 PYs (383 events), in the b/tsDMARD-naïve cohort 7.55 per 1000 PYs (746 events) and 19.82 per 1000 PYs (3076 events), and in the general population 5.87 per 1000 PYs (928 events) and 18.80 per 1000 PYs (1899 events), respectively.

10.5.1.4. Non-Melanoma Skin Cancer

Among the 356 tofacitinib initiators aged younger than 65, 21 NMSC events occurred during 1474 PYs, yielding an incidence rate of 14.24 per 1000 PYs. For 174 patients aged ≥65, 32

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NMSC events occurred during 639 PYs, corresponding to a higher incidence rate of 50.06 per 1000 PYs.

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 7.04 per 1000 PYs (206 events) and 29.16 per 1000 PYs (545 events), in the b/tsDMARD-naïve cohort 5.37 per 1000 PYs (523 events) and 22.23 per 1000 PYs (3772 events), and in the general population 4.23 per 1000 PYs (662 events) and 17.85 per 1000 PYs (1816 events), respectively.

10.5.1.5. MACE

In the 375 tofacitinib-treated patients under 65 years, 8 MACE events occurred during 1073 PYs, an IR of 7.46 per 1000 PYs. Among 182 patients aged 65 years or above, 14 MACE events occurred over 488 PYs, corresponding to 28.70 per 1000 PYs.

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 5.73 per 1000 PYs (154 events) and 24.66 per 1000 PYs (522 events), in the b/tsDMARD-naïve cohort 5.63 per 1000 PYs (678 events) and 28.72 per 1000 PYs (6867 events), and in the general population 3.23 per 1000 PYs (658 events) and 16.06 per 1000 PYs (2303 events), respectively.

10.5.1.6. Congestive heart failure

Among the 375 tofacitinib users younger than 65 years at treatment initiation, 6 congestive heart failure events occurred during 1071 PYs, giving an IR of 5.60 per 1000 PYs. In 182 older (≥65) patients, 12 events during 472 PYs resulted in an IR of 25.43 per 1000 PYs.

The corresponding standardized incidence rates and number of events in the bDMARD cohort were 2.79 per 1000 PYs (79 events) and 16.39 per 1000 PYs (361 events), in the b/tsDMARD-naïve cohort 2.45 per 1000 PYs (299 events) and 14.72 per 1000 PYs (3480 events), and in the general population 1.15 per 1000 PYs (244 events) and 8.39 per 1000 PYs (1237 events), respectively.

10.5.1.7. All-cause mortality

In the 375 tofacitinib-treated patients under the age of 65 years at treatment start, 6 deaths were observed during 1894 PYs, corresponding to an IR of 3.17 per 1000 PYs. Among 182 patients aged 65 years or older at treatment initiation 30 deaths occurred throughout 849 PYs, resulting in an IR of 35.35 per 1000 PYs.

The corresponding standardized mortality rates and number of events in the bDMARD cohort were 4.08 per 1000 PYs (162 events) and 24.66 per 1000 PYs (725 events), in the b/tsDMARD-naïve cohort 5.15 per 1000 PYs (628 events) and 38.59 per 1000 PYs (10970 events), and in the general population 2.13 per 1000 PYs (451 events) and 16.86 per 1000 PYs (2656 events), respectively.

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Younger than 65								
Hospitalized infections								
Tofacitinib	Overall	375	31	1040	29.80	(20.96-42.37)	29.80	2.77
Tofacitinib	0	58	4	204	19.56	(7.34-52.12)		3.53
Tofacitinib	1–2	146	9	400	22.51	(11.71-43.26)		2.74
Tofacitinib	3+	171	18	436	41.28	(26.01-65.53)		2.55
bDMARD	Overall	10925	570	27899	20.43	(18.82-22.18)	21.03	2.55
bDMARD	0	5648	247	15370	16.07	(14.19-18.20)		2.72
bDMARD	1–2	3629	206	9017	22.85	(19.93-26.19)		2.48
bDMARD	3+	1648	117	3512	33.32	(27.79-39.93)		2.13
b/tsDMARD-naïve		23388	1349	104820	12.87	(12.20-13.58)	12.41	4.48
General population		56471	1187	216852	5.47	(5.17-5.79)	5.56	3.84
Fractures								
Tofacitinib	Overall	375	31	994	31.18	(21.93-44.33)	31.18	2.65
Tofacitinib	0	58	4	196	20.38	(7.65-54.31)		3.38
Tofacitinib	1–2	146	11	378	29.13	(16.13-52.59)		2.59

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	3+	171	16	420	38.06	(23.32-62.13)		2.46
bDMARD	Overall	10925	777	27389	28.37	(26.44-30.44)	29.79	2.51
bDMARD	0	5648	382	15024	25.43	(23.00-28.11)		2.66
bDMARD	1–2	3629	266	8883	29.94	(26.55-33.77)		2.45
bDMARD	3+	1648	129	3482	37.05	(31.18-44.03)		2.11
b/tsDMARD-naïve		23388	2438	100706	24.21	(23.27-25.19)	24.69	4.31
General population		56471	3313	210894	15.71	(15.18-16.25)	16.55	3.73
Malignancies (overall, excluding NMSC), ever exposed								
Tofacitinib	Overall	356	13	1515	8.58	(4.98-14.78)	8.58	4.26
Tofacitinib	0	56	3	230	13.05	(4.21-40.45)		4.11
Tofacitinib	1–2	132	5	540	9.26	(3.85-22.25)		4.09
Tofacitinib	3+	168	5	745	6.71	(2.79-16.12)		4.44
bDMARD	Overall	9574	201	31606	6.36	(5.54-7.30)	6.61	3.3
bDMARD	0	4953	110	15617	7.04	(5.84-8.49)		3.15
bDMARD	1–2	3192	62	11247	5.51	(4.30-7.07)		3.52
bDMARD	3+	1429	29	4741	6.12	(4.25-8.80)		3.32
b/tsDMARD-naïve		22255	746	92746	8.04	(7.49-8.64)	7.55	4.17

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
General population		49619	928	165488	5.61	(5.26-5.98)	5.87	3.34
Malignancies (overall, excluding NMSC), treatment switch								
Tofacitinib	Overall	343	11	862	12.77	(7.07-23.05)	12.77	2.51
Tofacitinib	0	56	3	165	18.15	(5.86-56.29)		2.95
Tofacitinib	1–2	126	5	310	16.15	(6.72-38.81)		2.46
Tofacitinib	3+	161	3	387	7.75	(2.50-24.04)		2.4
bDMARD	Overall	9572	178	28003	6.36	(5.49-7.36)	6.63	2.93
bDMARD	0	4953	100	14440	6.93	(5.69-8.42)		2.92
bDMARD	1–2	3191	53	9723	5.45	(4.16-7.14)		3.05
bDMARD	3+	1428	25	3840	6.51	(4.40-9.64)		2.69
b/tsDMARD-naïve		22255	746	92746	8.04	(7.49-8.64)	7.62	4.17
General population		49619	928	165488	5.61	(5.26-5.98)	5.94	3.34
NMSC, ever exposed								
Tofacitinib	Overall	356	21	1474	14.24	(9.29-21.85)	14.24	4.14
Tofacitinib	0	56	3	229	13.07	(4.22-40.53)		4.1
Tofacitinib	1–2	132	6	533	11.25	(5.06-25.05)		4.04
Tofacitinib	3+	168	12	712	16.86	(9.58-29.69)		4.24
bDMARD	Overall	9574	206	31583	6.52	(5.69-7.48)	7.04	3.3
bDMARD	0	4953	97	15632	6.21	(5.09-7.57)		3.16

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
bDMARD	1–2	3192	73	11219	6.51	(5.17-8.18)		3.51
bDMARD	3+	1429	36	4732	7.61	(5.49-10.55)		3.31
b/tsDMARD-naïve		22255	523	93086	5.62	(5.16-6.12)	5.37	4.18
General population		49619	662	165866	3.99	(3.70-4.31)	4.23	3.34
NMSC, treatment switch								
Tofacitinib	Overall	343	13	848	15.33	(8.90-26.40)	15.33	2.47
Tofacitinib	0	56	3	165	18.21	(5.87-56.46)		2.94
Tofacitinib	1–2	126	3	308	9.72	(3.14-30.15)		2.45
Tofacitinib	3+	161	7	375	18.67	(8.90-39.16)		2.33
bDMARD	Overall	9572	173	28009	6.18	(5.32-7.17)	6.71	2.93
bDMARD	0	4953	85	14461	5.88	(4.75-7.27)		2.92
bDMARD	1–2	3191	58	9708	5.97	(4.62-7.73)		3.04
bDMARD	3+	1428	30	3840	7.81	(5.46-11.17)		2.69
b/tsDMARD-naïve		22255	523	93086	5.62	(5.16-6.12)	5.39	4.18
General population		49619	662	165866	3.99	(3.70-4.31)	4.24	3.34
CV events (MACE)								
Tofacitinib	Overall	375	8	1073	7.46	(3.73-14.91)	7.46	2.86
Tofacitinib	0	58	0	208	0.00	(.-.)		3.59
Tofacitinib	1–2	146	1	411	2.43	(0.34-17.26)		2.82

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	3+	171	7	453	15.45	(7.37-32.42)		2.65
bDMARD	Overall	10925	154	28740	5.36	(4.58-6.28)	5.73	2.63
bDMARD	0	5648	72	15725	4.58	(3.63-5.77)		2.78
bDMARD	1–2	3629	62	9324	6.65	(5.18-8.53)		2.57
bDMARD	3+	1648	20	3692	5.42	(3.49-8.40)		2.24
b/tsDMARD-naïve		23388	678	107169	6.33	(5.87-6.82)	5.63	4.58
General population		56471	658	218091	3.02	(2.80-3.26)	3.23	3.86
Congestive heart failure								
Tofacitinib	Overall	375	6	1071	5.60	(2.52-12.48)	5.60	2.85
Tofacitinib	0	58	2	202	9.88	(2.47-39.52)		3.49
Tofacitinib	1–2	146	2	403	4.97	(1.24-19.86)		2.76
Tofacitinib	3+	171	2	465	4.30	(1.07-17.18)		2.72
bDMARD	Overall	10925	79	28943	2.73	(2.19-3.40)	2.79	2.65
bDMARD	0	5648	39	15801	2.47	(1.80-3.38)		2.8
bDMARD	1–2	3629	30	9410	3.19	(2.23-4.56)		2.59
bDMARD	3+	1648	10	3731	2.68	(1.44-4.98)		2.26
b/tsDMARD-naïve		23388	299	108093	2.77	(2.47-3.10)	2.45	4.62
General population		56471	244	218856	1.11	(0.98-1.26)	1.15	3.88
All-cause mortality, ever exposed								
Tofacitinib	Overall	375	6	1894	3.17	(1.42-7.05)	3.17	5.05
Tofacitinib	0	58	1	290	3.45	(0.49-24.47)		5

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	146	2	685	2.92	(0.73-11.67)		4.69
Tofacitinib	3+	171	3	918	3.27	(1.05-10.13)		5.37
bDMARD	Overall	10925	162	42198	3.84	(3.29-4.48)	4.08	3.86
bDMARD	0	5648	49	21126	2.32	(1.75-3.07)		3.74
bDMARD	1–2	3629	71	14755	4.81	(3.81-6.07)		4.07
bDMARD	3+	1648	42	6317	6.65	(4.91-9.00)		3.83
b/tsDMARD-naïve		23388	628	108958	5.76	(5.33-6.23)	5.15	4.66
General population		56471	451	219712	2.05	(1.87-2.25)	2.13	3.89
65 years and above								
Hospitalized infections								
Tofacitinib	Overall	182	34	437	77.89	(55.65-109.00)	77.89	2.4
Tofacitinib	0	22	0	77	0.00	(.-.)		3.52
Tofacitinib	1–2	60	11	149	73.89	(40.92-133.43)		2.48
Tofacitinib	3+	100	23	210	109.35	(72.67-164.56)		2.1
bDMARD	Overall	7276	1088	17567	61.93	(58.36-65.73)	58.21	2.41
bDMARD	0	3444	487	8642	56.35	(51.56-61.58)		2.51
bDMARD	1–2	2724	413	6523	63.32	(57.50-69.73)		2.39
bDMARD	3+	1108	188	2402	78.27	(67.84-90.29)		2.17

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
b/tsDMARD-naïve		36581	8653	155864	55.52	(54.36-56.70)	44.06	4.26
General population		37311	2474	128692	19.22	(18.48-20.00)	18.06	3.45
Fractures								
Tofacitinib	Overall	182	26	442	58.83	(40.05-86.40)	58.83	2.43
Tofacitinib	0	22	3	71	41.99	(13.54-130.20)		3.25
Tofacitinib	1–2	60	9	147	61.15	(31.82-117.53)		2.45
Tofacitinib	3+	100	14	223	62.68	(37.12-105.83)		2.23
bDMARD	Overall	7276	1075	17192	62.53	(58.90-66.38)	61.35	2.36
bDMARD	0	3444	474	8510	55.70	(50.90-60.95)		2.47
bDMARD	1–2	2724	410	6364	64.43	(58.48-70.98)		2.34
bDMARD	3+	1108	191	2319	82.37	(71.48-94.93)		2.09
b/tsDMARD-naïve		36581	8867	149453	59.33	(58.11-60.58)	53.67	4.09
General population		37311	4222	123556	34.17	(33.16-35.22)	33.51	3.31
Malignancies (overall, excluding NMSC), ever exposed								
Tofacitinib	Overall	174	16	680	23.54	(14.42-38.42)	23.54	3.91

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	0	21	4	81	49.65	(18.63-132.28)		3.84
Tofacitinib	1–2	58	3	224	13.38	(4.31-41.48)		3.87
Tofacitinib	3+	95	9	375	24.00	(12.49-46.13)		3.95
bDMARD	Overall	6301	383	18502	20.70	(18.73-22.88)	19.64	2.94
bDMARD	0	2981	176	8520	20.66	(17.82-23.95)		2.86
bDMARD	1–2	2358	165	7182	22.97	(19.72-26.76)		3.05
bDMARD	3+	962	42	2800	15.00	(11.09-20.30)		2.91
b/tsDMARD-naïve		35161	3076	148453	20.72	(20.00-21.47)	19.82	4.22
General population		32399	1899	97691	19.44	(18.58-20.33)	18.80	3.02
Malignancies (overall, excluding NMSC), treatment switch								
Tofacitinib	Overall	165	9	391	22.99	(11.96-44.18)	22.99	2.37
Tofacitinib	0	21	3	63	47.40	(15.29-146.96)		3.01
Tofacitinib	1–2	55	2	133	15.00	(3.75-59.99)		2.42
Tofacitinib	3+	89	4	195	20.52	(7.70-54.69)		2.19

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
bDMARD	Overall	6301	359	17219	20.85	(18.80-23.12)	19.84	2.73
bDMARD	0	2981	168	8146	20.62	(17.73-23.99)		2.73
bDMARD	1–2	2358	154	6588	23.37	(19.96-27.37)		2.79
bDMARD	3+	962	37	2484	14.89	(10.79-20.56)		2.58
b/tsDMARD-naïve		35161	3076	148453	20.72	(20.00-21.47)	19.87	4.22
General population		32399	1899	97691	19.44	(18.58-20.33)	18.87	3.02
NMSC, ever exposed								
Tofacitinib	Overall	174	32	639	50.06	(35.40-70.79)	50.06	3.67
Tofacitinib	0	21	1	84	11.86	(1.67-84.18)		4.02
Tofacitinib	1–2	58	14	208	67.42	(39.93-113.83)		3.58
Tofacitinib	3+	95	17	347	48.96	(30.44-78.76)		3.65
bDMARD	Overall	6301	545	17914	30.42	(27.97-33.09)	29.16	2.84
bDMARD	0	2981	230	8265	27.83	(24.45-31.67)		2.77
bDMARD	1–2	2358	233	6950	33.53	(29.49-38.12)		2.95
bDMARD	3+	962	82	2699	30.38	(24.47-37.73)		2.81

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
b/tsDMARD-naïve		35161	3772	143698	26.25	(25.43-27.10)	22.23	4.09
General population		32399	1816	97189	18.69	(17.85-19.56)	17.85	3
NMSC, treatment switch								
Tofacitinib	Overall	164	21	363	57.90	(37.75-88.81)	57.90	2.21
Tofacitinib	0	21	0	66	0.00	(.-.)		3.13
Tofacitinib	1–2	54	10	120	83.63	(44.99-155.42)		2.21
Tofacitinib	3+	89	11	177	62.05	(34.36-112.05)		1.99
bDMARD	Overall	6301	494	16706	29.57	(27.07-32.30)	28.01	2.65
bDMARD	0	2981	215	7916	27.16	(23.76-31.04)		2.66
bDMARD	1–2	2358	206	6393	32.22	(28.11-36.94)		2.71
bDMARD	3+	962	73	2397	30.45	(24.21-38.31)		2.49
b/tsDMARD-naïve		35161	3772	143698	26.25	(25.43-27.10)	22.42	4.09
General population		32399	1816	97189	18.69	(17.85-19.56)	17.92	3
CV events (MACE)								
Tofacitinib	Overall	182	14	488	28.70	(17.00-48.45)	28.70	2.68
Tofacitinib	0	22	0	77	0.00	(.-.)		3.52

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	60	5	166	30.06	(12.51-72.23)		2.77
Tofacitinib	3+	100	9	244	36.85	(19.18-70.83)		2.44
bDMARD	Overall	7276	522	18730	27.87	(25.58-30.37)	24.66	2.57
bDMARD	0	3444	234	9168	25.52	(22.46-29.01)		2.66
bDMARD	1–2	2724	203	6964	29.15	(25.40-33.45)		2.56
bDMARD	3+	1108	85	2598	32.71	(26.45-40.46)		2.35
b/tsDMARD-naïve		36581	6867	165925	41.39	(40.42-42.38)	28.72	4.54
General population		37311	2303	129631	17.77	(17.05-18.51)	16.06	3.47
Congestive heart failure								
Tofacitinib	Overall	182	12	472	25.43	(14.44-44.77)	25.43	2.59
Tofacitinib	0	22	0	77	0.00	(.-.)		3.52
Tofacitinib	1–2	60	8	153	52.17	(26.09-104.31)		2.56
Tofacitinib	3+	100	4	241	16.58	(6.22-44.17)		2.41
bDMARD	Overall	7276	361	18884	19.12	(17.24-21.19)	16.39	2.6
bDMARD	0	3444	186	9216	20.18	(17.48-23.30)		2.68

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years
bDMARD	1–2	2724	120	7042	17.04	(14.25-20.38)		2.59
bDMARD	3+	1108	55	2627	20.94	(16.08-27.27)		2.37
b/tsDMARD-naïve		36581	3480	168624	20.64	(19.96-21.33)	14.72	4.61
General population		37311	1237	130927	9.45	(8.94-9.99)	8.39	3.51
All-cause mortality, ever exposed								
Tofacitinib	Overall	182	30	849	35.35	(24.72-50.56)	35.35	4.66
Tofacitinib	0	22	4	103	38.97	(14.62-103.83)		4.67
Tofacitinib	1–2	60	7	279	25.09	(11.96-52.63)		4.65
Tofacitinib	3+	100	19	467	40.68	(25.95-63.78)		4.67
bDMARD	Overall	7276	725	25233	28.73	(26.71-30.90)	24.66	3.47
bDMARD	0	3444	294	11700	25.13	(22.41-28.17)		3.4
bDMARD	1–2	2724	280	9770	28.66	(25.49-32.22)		3.59
bDMARD	3+	1108	151	3764	40.12	(34.21-47.06)		3.4
b/tsDMARD-naïve		36581	10970	175759	62.42	(61.26-63.59)	38.59	4.8
General population		37311	2656	133536	19.89	(19.15-20.66)	16.86	3.58

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Patients Aged Less Than 65 Years vs 65 Years and Older at Cohort Entry

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-years	IR	95% CI	Std IR	Mean follow-up, years

Notes: Analysis was only made for comparisons where both cohorts had at least 5 observed events. Some rows were intentionally deleted.
IR Incidence Rate; 95% CI 95% confidence interval; Std IR standardized to the age/sex distribution in the tofacitinib cohort.
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. A 90-day risk window will be applied to the censoring at switch approach.
Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; CV, cardiovascular; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer

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10.5.2. Sensitivity Analysis – Characteristics by previous Tofacitinib usage

To assess potential confounding by previous tofacitinib usage, Table 11 describes the demographic and clinical characteristics of the bDMARD cohort by previous tofacitinib use. Out of 18,201 patient initiations of a bDMARD between 2017 and 2024, 377 occurred after a previous tofacitinib exposure. The patients with previous tofacitinib usage tended to be more often female (86% vs. 77%), have a longer disease duration (median 17.5 years vs 9.6 years), have a higher number of previous b/tsDMARDs recorded (84% having 3 or more previous b/ts-DMARDs, compared to 14% among patients with no previous tofacitinib exposure), and generally have more comorbidities than those patients who had not previously been treated with tofacitinib.

Table 11. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
N observations	17824	377
N patients	13399	211
Demographics		
Age (median, IQR)	61 (50-71)	59 (50-67)
Sex (% females)	77%	86%
Disease-related characteristics		
Rheumatoid factor positive (%)	74%	71%
Rheumatoid factor positive missing (%)	2%	4%
Disease duration (median, IQR)	9.6 (3.4-18.9)	17.5 (10.2-26.5)
Disease duration missing (%)	0%	2%

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Table 11. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
Calendar year of dx (median)	2021	2021
DAS28 (median, IQR)	4.5 (3.6-5.4)	4.9 (3.9-5.8)
DAS28 missing (%)	55%	59%
HAQ (median, IQR)	1.0 (0.5-1.5)	1.4 (0.9-1.9)
HAQ missing (%)	51%	58%
Concomitant DMARDs (%)	63%	47%
Concomitant DMARDs missing (%)	34%	38%
Oral steroids (%)	38%	58%
Oral steroids missing (%)	34%	38%
Combination therapy with MTX (%)	54%	37%
NSAIDs (%)	18%	31%
NSAIDs missing (%)	34%	38%
Smoking		
Ever	56%	47%
Number of previous b/tsDMARDs		
0	51%	
0-2	35%	16%
3+	14%	84%
Disease history		
Serious infection (%)	22.5%	37.1%
Opportunistic infection (%)	0.2%	0%
Herpes zoster (%)	0.1%	0%
Fracture (%)	12.6%	17.8%
Malignancies, excl. NMSC (%)	9.1%	7.2%
NMSC (%)	7%	6.4%
Lymphoma (%)	0.6%	0.8%
Lung cancer (%)	0.3%	0.3%
Joint replacement surgery (%)	12.8%	19.4%
COPD (%)	3.6%	4.2%
Diabetes mellitus (%)	8.3%	10.1%

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Table 11. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
MI (%)	1.7%	2.1%
Hypertension (%)	20.2%	23.9%
Statin use (%)	18.8%	23.6%
CHD (%)	3.5%	3.7%
CKD (%)	2%	1.6%
Stable angina pectoris (%)	1.9%	2.4%
Procedures to treat CVD (%)	2.8%	2.7%
VTE	2.8%	6.6%
Undergoing major surgery from date of hospital admission to one month after date of discharge (%)	2.9%	5.6%
Heart failure (%)	1.6%	1.3%
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)	8.3%	9%
Inpatient care because of RA (%)	20.2%	44.6%
Total days in hosp (median, IQR)	0 (0-4)	3 (0-8)
Reason for discontinuing previous b/tsDMARD		
Safety, of those with info. (%)	19%	24%
Inefficacy, of those with info. (%)	47%	57%
Non-medical switch, of those with info. (%)	4%	1%
Other, of those with info. (%)	30%	18%
Missing, of total (%)	2%	1%

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DMARDS, disease modifying antirheumatic drugs; Hosp, hospitalization; MI, myocardial infarction; MTX, methotrexate; NSAIDS, non-steroidal anti-inflammatory drugs; VTE, venous thromboembolism

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10.5.3. Sensitivity Analysis – Stratification by VTE Risk Factors

To assess potential confounding by VTE risk factors, Table 12 presents the numbers of patients, numbers of events, crude and standardized incidence rates of VTE by presence of VTE risk factors. Among patients without VTE risk factors, there were 188 initiations of Tofacitinib which resulted in no cases of VTE. Among patients with at least 1 VTE risk factor, there were 369 treatment initiations of Tofacitinib and 13 VTE events, resulting in an incidence rate of 12.74 per 1000 PYs.

For the bDMARD cohort, the corresponding standardized incidence rate was 2.87 (51 events) for patients without VTE risk factors and 8.77 (287 events) for patients with at least 1 VTE risk factor. For the b/ts-DMARD naïve cohort, the corresponding standardized incidence rate was 2.50 (200 events) for patients without VTE risk factors and 7.86 (1980 events) for patients with at least 1 VTE risk factor. Finally, for the general population cohort, the corresponding standardized incidence rate was 1.52 (270 events) for subjects without VTE risk factors and 4.87 (938 events) for subjects with at least 1 VTE risk factor.

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Table 12. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by VTE Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
No VTE risk factors								
VTE								
Tofacitinib	Overall	188	0	550	0.00	(.-.)	0.00	2.93
Tofacitinib	0	39	0	145	0.00	(.-.)		3.71
Tofacitinib	1–2	83	0	240	0.00	(.-.)		2.90
Tofacitinib	3+	66	0	165	0.00	(.-.)		2.50
bDMARD	Overall	6910	51	18478	2.76	(2.10-3.63)	2.87	2.67
bDMARD	0	4042	34	11335	3.00	(2.14-4.20)		2.80
bDMARD	1–2	2180	11	5578	1.97	(1.09-3.56)		2.56
bDMARD	3+	688	6	1565	3.83	(1.72-8.53)		2.27
b/tsDMARD-naïve		16650	200	75317	2.66	(2.31-3.05)	2.50	4.52
General population		46385	270	180766	1.49	(1.33-1.68)	1.52	3.90
At least 1 VTE risk factor								
VTE								
Tofacitinib	Overall	369	13	1020	12.74	(7.40-21.95)	12.74	2.76
Tofacitinib	0	41	1	135	7.38	(1.04-52.40)		3.30
Tofacitinib	1–2	123	5	333	15.02	(6.25-36.08)		2.71

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Table 12. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by VTE Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	3+	205	7	552	12.69	(6.05-26.62)		2.69
bDMARD	Overall	11291	287	29510	9.73	(8.66-10.92)	8.77	2.61
bDMARD	0	5050	132	13755	9.60	(8.09-11.38)		2.72
bDMARD	1–2	4173	87	11000	7.91	(6.41-9.76)		2.64
bDMARD	3+	2068	68	4756	14.30	(11.27-18.14)		2.30
b/tsDMARD-naïve		43319	1980	203596	9.73	(9.31-10.16)	7.86	4.70
General population		47397	938	169378	5.54	(5.19-5.90)	4.87	3.57

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; IR, Incidence Rate; 95% CI, 95% confidence interval; Std IR, standardized to the age/sex distribution in the tofacitinib cohort; VTE, venous thromboembolism

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10.5.4. Sensitivity Analysis – Stratification by CV Risk Factors

To assess potential confounding by CV risk factors, Table 13 presents the number of patients, number of events, as well as crude and standardized IRs of cardiovascular events by presence of CV risk factors. Among 282 tofacitinib initiators without CV risk factors, we saw 3 MACE events and 0 MI events, leading to an incidence rate of 3.75 per 1000 PYs for MACE and 0 for MI. In the 275 tofacitinib initiators with at least one CV risk factor, there were 19 MACE events and 9 MI events, leading to an incidence rate of MACE at 24.98 per 1000 person-years and an incidence rate of 11.65 per 1000 person-years for MI.

For the bDMARD cohort, the corresponding standardized incidence rate was 3.80 (83 events) for MACE and 1.65 (36 events) for MI, among patients without VTE risk factors. Among patients with at least 1 CV risk factor the standardized incidence rates were and 20.51 (593 events) for MACE and 7.14 (200 events) for MI.

For the b/ts-DMARD naïve cohort, the corresponding standardized incidence rate was 3.50 (351 events) for MACE and 1.41 (36 events) for MI, among patients without VTE risk factors. Among patients with at least 1 CV risk factor the standardized incidence rates were and 23.61 (7,194 events) for MACE and 7.24 (1,771 events) for MI.

For the general population cohort, the corresponding standardized incidence rate was 2.25 (431 events) for MACE and 0.85 (164 events) for MI, among subjects without VTE risk factors. Among subjects with at least 1 CV risk factor the standardized incidence rates were and 13.17 (2530 events) for MACE and 3.89 (710 events) for MI.

Table 13. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by CV Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
No CV risk factors								
MACE								
Tofacitinib	Overall	282	3	800	3.75	(1.21-11.63)	3.75	2.84
Tofacitinib	0	47	0	172	0.00	(.-.)		3.66
Tofacitinib	1–2	118	0	323	0.00	(.-.)		2.74

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Table 13. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by CV Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	3+	117	3	305	9.83	(3.17-30.49)		2.61
bDMARD	Overall	8792	83	23311	3.56	(2.87-4.42)	3.80	2.65
bDMARD	0	4674	42	13132	3.20	(2.36-4.33)		2.81
bDMARD	1–2	2885	31	7421	4.18	(2.94-5.94)		2.57
bDMARD	3+	1233	10	2759	3.62	(1.95-6.74)		2.24
b/tsDMARD-naïve		19040	351	87289	4.02	(3.62-4.46)	3.50	4.58
General population		49924	431	194239	2.22	(2.02-2.44)	2.25	3.89
At least 1 CV risk factor								
MACE								
Tofacitinib	Overall	275	19	761	24.98	(15.93-39.16)	24.98	2.77
Tofacitinib	0	33	0	114	0.00	(.-.)		3.45
Tofacitinib	1–2	88	6	255	23.54	(10.58-52.41)		2.90
Tofacitinib	3+	154	13	392	33.16	(19.25-57.10)		2.55
bDMARD	Overall	9409	593	24159	24.55	(22.65-26.60)	20.51	2.57
bDMARD	0	4418	264	11760	22.45	(19.90-25.33)		2.66
bDMARD	1–2	3468	234	8867	26.39	(23.22-30.00)		2.56

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Table 13. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by CV Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
bDMARD	3+	1523	95	3531	26.90	(22.00-32.89)		2.32
b/tsDMARD-naïve		40929	7194	185804	38.72	(37.83-39.62)	23.61	4.54
General population		43858	2530	153483	16.48	(15.85-17.14)	13.17	3.50
No CV risk factors								
MI								
Tofacitinib	Overall	282	0	807	0.00	(.-.)	0.00	2.86
Tofacitinib	0	47	0	172	0.00	(.-.)		3.66
Tofacitinib	1–2	118	0	323	0.00	(.-.)		2.74
Tofacitinib	3+	117	0	313	0.00	(.-.)		2.67
bDMARD	Overall	8792	36	23398	1.54	(1.11-2.13)	1.65	2.66
bDMARD	0	4674	21	13166	1.59	(1.04-2.45)		2.82
bDMARD	1–2	2885	12	7460	1.61	(0.91-2.83)		2.59
bDMARD	3+	1233	3	2771	1.08	(0.35-3.36)		2.25
b/tsDMARD-naïve		19040	150	87684	1.71	(1.46-2.01)	1.41	4.61
General population		49924	164	194705	0.84	(0.72-0.98)	0.85	3.90
At least 1 CV risk factor								
MI								

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Table 13. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by CV Risk Factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	Crude IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	Overall	275	9	773	11.65	(6.06-22.39)	11.65	2.81
Tofacitinib	0	33	0	114	0.00	(.-.)		3.45
Tofacitinib	1–2	88	3	255	11.77	(3.79-36.48)		2.90
Tofacitinib	3+	154	6	404	14.85	(6.67-33.07)		2.62
bDMARD	Overall	9409	200	24662	8.11	(7.06-9.32)	7.14	2.62
bDMARD	0	4418	97	11974	8.10	(6.64-9.89)		2.71
bDMARD	1–2	3468	73	9081	8.04	(6.39-10.11)		2.62
bDMARD	3+	1523	30	3608	8.31	(5.81-11.89)		2.37
b/tsDMARD-naïve		40929	1771	191666	9.24	(8.82-9.68)	7.24	4.68
General population		43858	710	155904	4.55	(4.23-4.90)	3.89	3.55

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; 95% CI, 95% confidence interval; CV, cardiovascular; IR, Incidence Rate; MI, myocardial infarction; Std IR, standardized to the age/sex distribution in the tofacitinib cohort; VTE, venous thromboembolism.

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10.5.5. Stratification by Time Periods Defined by Changes in the Summary of Product Characteristics (SmPC) for Tofacitinib

Table 14 presents the number of patients, number of events, as well as crude and standardized IRs stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors. Among the 344 RA patients who initiated tofacitinib in the time period prior to 31-JAN-2020, we saw 11 VTE events resulting in an IR of 9.80/1000 PYs. Among the 213 tofacitinib initiators in the time period after 31-JAN-2020, 2 VTE events occurred, leading to an IR of 4.47/1000 person-years. Turning to NMSC, 27 events occurred among those who started tofacitinib in the time period prior to 31-JAN-2020 and 8 events among those who started tofacitinib after 31-JAN-2020, leading to incidence rates of 25.23 and 18.52 per 1000 PYs, respectively.

Table 15 presents the number of patients, number of events, as well as crude and standardized IRs stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors. Among the 447 RA patients who started tofacitinib prior to June 2021, we saw 32 NMSC events, leading to an IR of 23.85/1000 PYs. For the 110 tofacitinib initiations after June 2021, there were 3 NMSC events, leading to an IR of 18.70. For lung cancer, there were 5 events among those who initiated tofacitinib before June 2021, leading to an IR of 3.51 per 1000 PYs, while no events among those who started tofacitinib occurred after June 2021. For lymphoma, there were 3 events, with an IR of 2.11 events per 1000 PYs, for those who started tofacitinib treatment prior to June 2021, with no events among those who started after June 2021. For major adverse cardiovascular events (MACE), the corresponding number of events was 22, with an IR of 15.78 events per 1000 person-years among those who initiated tofacitinib treatment prior to June 2021, with no events observed among those who started treatment after June 2021. For myocardial infarction, there were 9 events, with an IR of 6.37 events per 1000 PYs for individuals who began tofacitinib treatment before June 2021, and no events were reported among those who initiated treatment after June 2021.

Table 14. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Time period prior to 31 January 2020								
VTE								
Tofacitinib	Overall	344	11	1123	9.80	(5.43-17.69)	9.80	3.26
Tofacitinib	0	50	1	210	4.77	(0.67-33.87)		4.19

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Table 14. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	114	4	374	10.71	(4.02-28.53)		3.28
Tofacitinib	3+	180	6	539	11.12	(5.00-24.76)		3.00
bDMARD	Overall	6406	161	24993	6.44	(5.52-7.52)	5.99	3.90
bDMARD	0	2999	81	12555	6.45	(5.19-8.02)		4.19
bDMARD	1–2	2440	51	9206	5.54	(4.21-7.29)		3.77
bDMARD	3+	967	29	3232	8.97	(6.24-12.91)		3.34
b/tsDMARD-naïve		45825	1942	252528	7.69	(7.36-8.04)	5.65	5.51
General population		33747	715	204656	3.49	(3.25-3.76)	3.35	6.06
Time period after 31 January 2020								
VTE								
Tofacitinib	Overall	213	2	447	4.47	(1.12-17.87)	4.47	2.10
Tofacitinib	0	30	0	70	0.00	(.-.)		2.35
Tofacitinib	1–2	92	1	200	5.00	(0.70-35.53)		2.17
Tofacitinib	3+	91	1	177	5.64	(0.79-40.06)		1.95
bDMARD	Overall	11795	177	22996	7.70	(6.64-8.92)	6.94	1.95
bDMARD	0	6093	85	12535	6.78	(5.48-8.39)		2.06
bDMARD	1–2	3913	47	7372	6.38	(4.79-8.49)		1.88
bDMARD	3+	1789	45	3089	14.57	(10.88-19.51)		1.73

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Table 14. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
b/tsDMARD-naïve		14144	238	26386	9.02	(7.94-10.24)	5.94	1.87
General population		60035	493	145488	3.39	(3.10-3.70)	2.99	2.42
Time period prior to 31 January 2020								
NMSC								
Tofacitinib	Overall	344	27	1070	25.23	(17.30-36.79)	25.23	3.11
Tofacitinib	0	50	3	207	14.51	(4.68-44.98)		4.14
Tofacitinib	1–2	114	11	351	31.33	(17.35-56.58)		3.08
Tofacitinib	3+	180	13	512	25.38	(14.73-43.70)		2.85
bDMARD	Overall	6406	310	24359	12.73	(11.39-14.23)	11.31	3.80
bDMARD	0	2999	137	12289	11.15	(9.43-13.18)		4.10
bDMARD	1–2	2440	125	8907	14.03	(11.78-16.72)		3.65
bDMARD	3+	967	48	3163	15.18	(11.44-20.14)		3.27
b/tsDMARD-naïve		45825	3983	242751	16.41	(15.91-16.93)	9.82	5.30
General population		33747	1545	200887	7.69	(7.32-8.08)	7.12	5.95
Time period after 31 January 2020								
NMSC								
Tofacitinib	Overall	213	8	432	18.52	(9.26-37.03)	18.52	2.03

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Table 14. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	0	30	0	70	0.00	(.-.)		2.35
Tofacitinib	1–2	92	3	196	15.30	(4.93-47.44)		2.13
Tofacitinib	3+	91	5	165	30.21	(12.58-72.59)		1.82
bDMARD	Overall	11795	237	22730	10.43	(9.18-11.84)	7.96	1.93
bDMARD	0	6093	105	12405	8.46	(6.99-10.25)		2.04
bDMARD	1–2	3913	94	7241	12.98	(10.61-15.89)		1.85
bDMARD	3+	1789	38	3084	12.32	(8.97-16.94)		1.72
b/tsDMARD-naïve		14144	312	26080	11.96	(10.71-13.37)	6.47	1.84
General population		60035	927	144119	6.43	(6.03-6.86)	5.11	2.40

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; 95% CI, 95% confidence interval; CV, cardiovascular; IR, Incidence Rate; MI, myocardial infarction; NMSC, non-melanoma skin cancer; Std IR, standardized to the age/sex distribution in the tofacitinib cohort; VTE, venous thromboembolism.

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Time period prior to June 2021								
NMSC, ever exposed								
Tofacitinib	Overall	447	32	1342	23.85	(16.87-33.73)	23.85	3.00
Tofacitinib	0	65	3	256	11.72	(3.78-36.33)		3.94
Tofacitinib	1–2	155	13	470	27.68	(16.08-47.68)		3.03
Tofacitinib	3+	227	16	616	25.97	(15.91-42.39)		2.71
bDMARD	Overall	9522	415	33773	12.29	(11.16-13.53)	10.77	3.55
bDMARD	0	4610	187	17492	10.69	(9.26-12.34)		3.79
bDMARD	1–2	3492	166	11925	13.92	(11.96-16.21)		3.41
bDMARD	3+	1420	62	4356	14.23	(11.10-18.26)		3.07
b/tsDMARD-naïve		49789	4144	254353	16.29	(15.80-16.80)	9.65	5.11
General population		49842	2019	265957	7.59	(7.27-7.93)	6.98	5.34
Time period after June 2021								
NMSC, ever exposed								
Tofacitinib	Overall	110	3	160	18.70	(6.03-57.98)	18.70	1.46
Tofacitinib	0	15	0	21	0.00	(.-.)		1.42
Tofacitinib	1–2	51	1	78	12.89	(1.82-91.53)		1.52
Tofacitinib	3+	44	2	62	32.45	(8.11-129.74)		1.40
bDMARD	Overall	8679	132	13316	9.91	(8.36-11.76)	6.65	1.53
bDMARD	0	4482	55	7202	7.64	(5.86-9.95)		1.61
bDMARD	1–2	2861	53	4223	12.55	(9.59-16.43)		1.48
bDMARD	3+	1336	24	1891	12.69	(8.51-18.94)		1.42

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
b/tsDMARD-naïve		10180	151	14479	10.43	(8.89-12.23)	5.06	1.42
General population		43940	453	79049	5.73	(5.23-6.28)	4.11	1.80
Time period prior to June 2021								
Lung cancer, ever exposed								
Tofacitinib	Overall	447	5	1424	3.51	(1.46-8.44)	3.51	3.19
Tofacitinib	0	65	3	262	11.45	(3.69-35.50)		4.03
Tofacitinib	1–2	155	0	504	0.00	(.-.)		3.25
Tofacitinib	3+	227	2	657	3.04	(0.76-12.16)		2.90
bDMARD	Overall	9522	50	34949	1.43	(1.08-1.89)	1.29	3.67
bDMARD	0	4610	28	18044	1.55	(1.07-2.25)		3.91
bDMARD	1–2	3492	20	12388	1.61	(1.04-2.50)		3.55
bDMARD	3+	1420	2	4518	0.44	(0.11-1.77)		3.18
b/tsDMARD-naïve		49789	557	269010	2.07	(1.91-2.25)	1.54	5.40
General population		49842	219	272354	0.80	(0.70-0.92)	0.76	5.46
Time period after June 2021								
Lung cancer, ever exposed								
Tofacitinib	Overall	110	0	167	0.00	(.-.)	0.00	1.51
Tofacitinib	0	15	0	21	0.00	(.-.)		1.42
Tofacitinib	1–2	51	0	80	0.00	(.-.)		1.56
Tofacitinib	3+	44	0	66	0.00	(.-.)		1.49
bDMARD	Overall	8679	12	13520	0.89	(0.50-1.56)	0.51	1.56

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
bDMARD	0	4482	6	7292	0.82	(0.37-1.83)		1.63
bDMARD	1–2	2861	2	4305	0.46	(0.12-1.86)		1.50
bDMARD	3+	1336	4	1923	2.08	(0.78-5.54)		1.44
b/tsDMARD-naïve		10180	20	14704	1.36	(0.88-2.11)	0.79	1.44
General population		43940	34	79861	0.43	(0.30-0.60)	0.26	1.82
Time period prior to June 2021								
Lymphoma, ever exposed								
Tofacitinib	Overall	447	3	1424	2.11	(0.68-6.53)	2.11	3.19
Tofacitinib	0	65	1	261	3.83	(0.54-27.21)		4.01
Tofacitinib	1–2	155	1	503	1.99	(0.28-14.12)		3.24
Tofacitinib	3+	227	1	660	1.51	(0.21-10.75)		2.91
bDMARD	Overall	9522	18	34985	0.51	(0.32-0.82)	0.49	3.67
bDMARD	0	4610	14	18048	0.78	(0.46-1.31)		3.92
bDMARD	1–2	3492	4	12416	0.32	(0.12-0.86)		3.56
bDMARD	3+	1420	0	4521	0.00	(.-.)		3.18
b/tsDMARD-naïve		49789	273	269159	1.01	(0.90-1.14)	0.69	5.41
General population		49842	111	272418	0.41	(0.34-0.49)	0.39	5.47
Time period after June 2021								
Lymphoma, ever exposed								
Tofacitinib	Overall	110	0	167	0.00	(.-.)	0.00	1.51
Tofacitinib	0	15	0	21	0.00	(.-.)		1.42

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	51	0	80	0.00	(.-.)		1.56
Tofacitinib	3+	44	0	66	0.00	(.-.)		1.49
bDMARD	Overall	8679	7	13523	0.52	(0.25-1.09)	0.46	1.56
bDMARD	0	4482	3	7293	0.41	(0.13-1.28)		1.63
bDMARD	1–2	2861	4	4303	0.93	(0.35-2.48)		1.50
bDMARD	3+	1336	0	1928	0.00	(.-.)		1.44
b/tsDMARD-naïve		10180	9	14719	0.61	(0.32-1.18)	0.35	1.45
General population		43940	26	79862	0.33	(0.22-0.48)	0.25	1.82
Time period prior to June 2021								
MACE								
Tofacitinib	Overall	447	22	1394	15.78	(10.39-23.97)	15.78	3.12
Tofacitinib	0	65	0	265	0.00	(.-.)		4.07
Tofacitinib	1–2	155	6	498	12.05	(5.41-26.81)		3.21
Tofacitinib	3+	227	16	631	25.34	(15.52-41.36)		2.78
bDMARD	Overall	9522	499	34084	14.64	(13.41-15.98)	12.50	3.58
bDMARD	0	4610	223	17662	12.63	(11.07-14.40)		3.83
bDMARD	1–2	3492	197	12039	16.36	(14.23-18.82)		3.45
bDMARD	3+	1420	79	4383	18.03	(14.46-22.47)		3.09
b/tsDMARD-naïve		49789	7229	258590	27.96	(27.32-28.61)	13.41	5.19
General population		49842	2255	268453	8.40	(8.06-8.75)	7.54	5.39
Time period after June 2021								
MACE								
Tofacitinib	Overall	110	0	167	0.00	(.-.)	0.00	1.51
Tofacitinib	0	15	0	21	0.00	(.-.)		1.42

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	51	0	80	0.00	(.-.)		1.56
Tofacitinib	3+	44	0	66	0.00	(.-.)		1.49
bDMARD	Overall	8679	177	13386	13.22	(11.41-15.32)	9.21	1.54
bDMARD	0	4482	83	7230	11.48	(9.26-14.24)		1.61
bDMARD	1–2	2861	68	4249	16.00	(12.62-20.30)		1.49
bDMARD	3+	1336	26	1908	13.63	(9.28-20.02)		1.43
b/tsDMARD-naïve		10180	316	14503	21.79	(19.51-24.33)	9.26	1.42
General population		43940	706	79269	8.91	(8.27-9.59)	6.47	1.80
Time period prior to June 2021								
MI								
Tofacitinib	Overall	447	9	1413	6.37	(3.31-12.24)	6.37	3.16
Tofacitinib	0	65	0	265	0.00	(.-.)		4.07
Tofacitinib	1–2	155	3	498	6.02	(1.94-18.67)		3.21
Tofacitinib	3+	227	6	651	9.22	(4.14-20.52)		2.87
bDMARD	Overall	9522	172	34590	4.97	(4.28-5.77)	4.48	3.63
bDMARD	0	4610	82	17874	4.59	(3.69-5.70)		3.88
bDMARD	1–2	3492	65	12254	5.30	(4.16-6.76)		3.51
bDMARD	3+	1420	25	4462	5.60	(3.79-8.29)		3.14
b/tsDMARD-naïve		49789	1850	26468	6.99	(6.68-7.32)	4.22	5.32
General population		49842	660	270978	2.44	(2.26-2.63)	2.25	5.44
Time period after June 2021								
MI								
Tofacitinib	Overall	110	0	167	0.00	(.-.)	0.00	1.51
Tofacitinib	0	15	0	21	0.00	(.-.)		1.42

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Table 15. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	1–2	51	0	80	0.00	(.-.)		1.56
Tofacitinib	3+	44	0	66	0.00	(.-.)		1.49
bDMARD	Overall	8679	64	13471	4.75	(3.72-6.07)	3.38	1.55
bDMARD	0	4482	36	7266	4.95	(3.57-6.87)		1.62
bDMARD	1–2	2861	20	4287	4.67	(3.01-7.23)		1.50
bDMARD	3+	1336	8	1918	4.17	(2.09-8.34)		1.44
b/tsDMARD-naïve		10180	71	14666	4.84	(3.84-6.11)	2.79	1.44
General population		43940	214	79632	2.69	(2.35-3.07)	2.20	1.81

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; 95% CI, 95% confidence interval; CV, cardiovascular; IR, Incidence Rate; MACE, major adverse cardiovascular event; MI, myocardial infarction; NMSC, non-melanoma skin cancer; Std IR, standardized to the age/sex distribution in the tofacitinib cohort; VTE, venous thromboembolism.

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10.5.6. Analysis Restricted to Patients Without Prior History of Malignancy

Table 16 presents the number of patients, number of events, as well as crude and standardized IRs for malignancy outcomes among patients without prior history of malignancy. Among 494 tofacitinib users, 26 malignancy events (overall, excluding NMSC) occurred during 2,058 person-years, giving an IR of 12.64 per 1000 PYs. In the same cohort, 46 NMSC events occurred during 1,991 PYs, resulting in an IR of 23.10 per 1000 PYs. Among the 494 tofacitinib users, 5 lung cancer events occurred during 2,091 person-years, giving an IR of 2.39 per 1000 PYs. Additionally, 3 lymphoma events occurred during 2,089 PYs, resulting in an IR of 1.44 per 1000 PYs. Three non-Hodgkin lymphoma events were observed during 2,089 person-years, corresponding to an IR of 1.44 per 1000 person-years. No Hodgkin lymphoma events were observed among tofacitinib users over 2,096 person-years, resulting in an incidence rate of 0 per 1000 PYs. Similarly, no CLL events occurred during 2096 PYs, giving an IR of 0 per 1000 PYs.

Among 14,448 bDMARD users, 487 malignancy events (overall, excluding NMSC) occurred during 45,956 PYs, giving a standardized IR of 9.69 per 1000 PYs. In the same cohort, 603 NMSC events occurred during 45,523 PYs, resulting in a standardized IR of 12.25 per 1000 PYs. Among the 14,448 bDMARD users, 55 lung cancer events occurred during 46,757 PYs, giving a standardized IR of 1.06 per 1000 PYs. Additionally, 26 lymphoma events occurred during 46,758 PYs, resulting in a standardized IR of 0.55 per 1000 PYs. Twenty-two non-Hodgkin lymphoma events were observed during 46,768 PYs, corresponding to a standardized IR of 0.46 per 1000 PYs. One Hodgkin lymphoma event was observed over 46,813 PYs, resulting in a standardized IR of 0.02 per 1000 PYs. Similarly, 3 CLL events occurred during 46,806 PYs, giving a standardized IR of 0.07 per 1000 PYs.

Among 49,136 b/ts-DMARD naïve patients, 3,091 malignancy events (overall, excluding NMSC) occurred during 208,582 PYs, giving a standardized IR of 10.58 per 1000 PYs. In the same cohort, 3,180 NMSC events occurred during 206,013 PYs, resulting in a standardized IR of 9.34 per 1000 PYs. Among the 49,136 patients, 442 lung cancer events occurred during 214,817 PYs, giving a standardized IR of 1.52 per 1000 PYs. Additionally, 227 lymphoma events occurred during 214,932 PYs, resulting in a standardized IR of 0.71 per 1000 PYs. One hundred eighty-seven non-Hodgkin lymphoma events were observed during 215,031 PYs, corresponding to a standardized IR of 0.56 per 1000 PYs. Fifteen Hodgkin lymphoma events were observed over 215,435 PYs, resulting in a standardized IR of 0.06 per 1000 PYs. Similarly, 27 CLL events occurred during 215,400 PYs, giving a standardized IR of 0.10 per 1000 PYs.

Among 73,897 subjects in the general population, 2,342 malignancy events (overall, excluding NMSC) occurred during 239,741 PYs, giving a standardized IR of 9.13 per 1000 PYs. In the same cohort, 1,904 NMSC events occurred during 240,000 PYs, resulting in a standardized IR of 7.26 per 1000 PYs. Among the 73,897 individuals, 200 lung cancer events occurred during 243,845 PYs, giving a standardized IR of 0.75 per 1000 PYs. Additionally, 119 lymphoma events occurred during 243,840 PYs, resulting in a standardized IR of 0.44 per 1000 PYs. Eighty-eight non-Hodgkin lymphoma events were observed during 243,923 PYs, corresponding to a

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standardized IR of 0.33 per 1000 PYs. Eight Hodgkin lymphoma events were observed over 244,058 PYs, resulting in a standardized IR of 0.03 per 1000 PYs. Similarly, 23 CLL events occurred during 244,012 PYs, giving a standardized IR of 0.08 per 1000 PYs.

Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Malignancy, excl. NMSC, ever exposed								
Tofacitinib	Overall	494	26	2058	12.64	(8.60-18.56)	12.64	4.17
Tofacitinib	0	76	7	306	22.89	(10.91-48.01)		4.02
Tofacitinib	1-2	176	8	709	11.28	(5.64-22.56)		4.03
Tofacitinib	3+	242	11	1043	10.55	(5.84-19.05)		4.31
bDMARD	Overall	14448	487	45957	10.60	(9.70-11.58)	9.69	3.18
bDMARD	0	7281	249	22275	11.18	(9.87-12.66)		3.06
bDMARD	1-2	5004	182	16821	10.82	(9.36-12.51)		3.36
bDMARD	3+	2163	56	6860	8.16	(6.28-10.61)		3.17
b/tsDMARD-naïve		49136	3091	208582	14.82	(14.31-15.35)	10.58	4.24
General population		73897	2342	239741	9.77	(9.38-10.17)	9.13	3.24

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Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
NMSC, ever exposed								
Tofacitinib	Overall	494	46	1991	23.10	(17.30-30.84)	23.10	4.03
Tofacitinib	0	76	4	309	12.94	(4.86-34.48)		4.07
Tofacitinib	1-2	176	18	687	26.20	(16.51-41.58)		3.90
Tofacitinib	3+	242	24	995	24.12	(16.17-35.99)		4.11
bDMARD	Overall	14448	603	45523	13.25	(12.23-14.35)	12.25	3.15
bDMARD	0	7281	269	22106	12.17	(10.80-13.71)		3.04
bDMARD	1-2	5004	242	16630	14.55	(12.83-16.51)		3.32
bDMARD	3+	2163	92	6787	13.56	(11.05-16.63)		3.14
b/tsDMARD-naïve		49136	3180	206013	15.44	(14.91-15.98)	9.34	4.19
General population		73897	1904	240000	7.93	(7.58-8.30)	7.26	3.25
Lung Cancer, ever exposed								
Tofacitinib	Overall	494	5	2091	2.39	(1.00-5.74)	2.39	4.23
Tofacitinib	0	76	3	313	9.59	(3.09-29.73)		4.12
Tofacitinib	1-2	176	0	718	0.00	(.-.)		4.08

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Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	3+	242	2	1060	1.89	(0.47-7.54)		4.38
bDMARD	Overall	14448	55	46757	1.18	(0.90-1.53)	1.06	3.24
bDMARD	0	7281	28	22661	1.24	(0.85-1.79)		3.11
bDMARD	1-2	5004	20	17140	1.17	(0.75-1.81)		3.43
bDMARD	3+	2163	7	6955	1.01	(0.48-2.11)		3.22
b/tsDMARD-naïve		49136	442	214817	2.06	(1.87-2.26)	1.52	4.37
General population		73897	200	243845	0.82	(0.71-0.94)	0.75	3.30
Lymphoma, ever exposed								
Tofacitinib	Overall	494	3	2089	1.44	(0.46-4.45)	1.44	4.23
Tofacitinib	0	76	1	313	3.20	(0.45-22.70)		4.12
Tofacitinib	1-2	176	1	718	1.39	(0.20-9.89)		4.08
Tofacitinib	3+	242	1	1059	0.94	(0.13-6.70)		4.38
bDMARD	Overall	14448	26	46758	0.56	(0.38-0.82)	0.55	3.24
bDMARD	0	7281	19	22648	0.84	(0.54-1.32)		3.11

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Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
bDMARD	1-2	5004	7	17142	0.41	(0.19-0.86)		3.43
bDMARD	3+	2163	0	6969	0.00	(.-.)		3.22
b/tsDMARD-naïve		49136	227	214932	1.06	(0.93-1.20)	0.71	4.37
General population		73897	119	243840	0.49	(0.41-0.58)	0.44	3.30
Non-Hodgkin Lymphoma, ever exposed								
Tofacitinib	Overall	494	3	2089	1.44	(0.46-4.45)	1.44	4.23
Tofacitinib	0	76	1	313	3.20	(0.45-22.70)		4.12
Tofacitinib	1-2	176	1	718	1.39	(0.20-9.89)		4.08
Tofacitinib	3+	242	1	1059	0.94	(0.13-6.70)		4.38
bDMARD	Overall	14448	22	46768	0.47	(0.31-0.71)	0.46	3.24
bDMARD	0	7281	16	22656	0.71	(0.43-1.15)		3.11
bDMARD	1-2	5004	6	17143	0.35	(0.16-0.78)		3.43
bDMARD	3+	2163	0	6969	0.00	(.-.)		3.22
b/tsDMARD-naïve		49136	187	215031	0.87	(0.75-1.00)	0.56	4.38
General population		73897	88	243923	0.36	(0.29-0.44)	0.33	3.30
Hodgkin Lymphoma, ever exposed								

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Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Tofacitinib	Overall	494	0	2096	0.00	(.-.)	0.00	4.24
Tofacitinib	0	76	0	315	0.00	(.-.)		4.15
Tofacitinib	1-2	176	0	718	0.00	(.-.)		4.08
Tofacitinib	3+	242	0	1062	0.00	(.-.)		4.39
bDMARD	Overall	14448	1	46813	0.02	(0.00-0.15)	0.02	3.24
bDMARD	0	7281	0	22685	0.00	(.-.)		3.12
bDMARD	1-2	5004	1	17159	0.06	(0.01-0.41)		3.43
bDMARD	3+	2163	0	6969	0.00	(.-.)		3.22
b/tsDMARD-naïve		49136	15	215435	0.07	(0.04-0.12)	0.06	4.38
General population		73897	8	244058	0.03	(0.02-0.07)	0.03	3.30
Chronic Lymphocytic Leukemia, ever exposed								
Tofacitinib	Overall	494	0	2096	0.00	(.-.)	0.00	4.24
Tofacitinib	0	76	0	315	0.00	(.-.)		4.15
Tofacitinib	1-2	176	0	718	0.00	(.-.)		4.08
Tofacitinib	3+	242	0	1062	0.00	(.-.)		4.39
bDMARD	Overall	14448	3	46806	0.06	(0.02-0.20)	0.07	3.24
bDMARD	0	7281	3	22677	0.13	(0.04-0.41)		3.11
bDMARD	1-2	5004	0	17160	0.00	(.-.)		3.43
bDMARD	3+	2163	0	6969	0.00	(.-.)		3.22

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Table 16. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Restricted to Patients without prior history of malignancy

Cohort	Number of previous b/tsDMARDs	N subjects	N events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
b/tsDMARD-naïve		49136	27	215400	0.13	(0.09-0.18)	0.10	4.38
General population		73897	23	244012	0.09	(0.06-0.14)	0.08	3.30

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; 95% CI, 95% confidence interval; IR, Incidence Rate; NMSC, non-melanoma skin cancer; Std IR, standardized to the age/sex distribution in the tofacitinib cohort.

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10.5.7. Sensitivity Analysis with Censoring at Time of New Treatment Start

Table 17 and Table 18 presents the number of patients, number of events, as well as crude and standardized IRs and HRs for MACE, MI, serious infection, VTE, herpes zoster, PML and gastrointestinal perforations in the case when, 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 was assigned to the discontinued medication.

During 1,364 person-years, 57 hospitalized infections occurred (IR: 41.79 per 1000 PYs). Compared with the bDMARD cohort, the incidence rate of hospitalized infections was slightly higher but not statistically significant (HRd = 1.12, 95% CI 0.85–1.47). Compared with the b/tsDMARD-naïve cohort, risk of hospitalized infections was elevated (HRb = 1.47, 95% CI 1.11-1.94), and higher relative to the general population (HRb = 2.88, 95% CI 2.19–3.80).

During 1,470 person-years, 2 herpes zoster (HZ) events occurred in the tofacitinib cohort in which the patient was hospitalized (IR: 1.36 per 1000 PYs). This incidence rate was higher than the corresponding incidence rates of HZ events in the bDMARD cohort (standardized IR: 0.54 per 1000 PYs), in the b/tsDMARD-naïve cohort (standardized IR: 0.43 per 1000 PYs) and in the general population cohort (standardized IR: 0.07 per 1000 PYs). Due to the small number of events in the tofacitinib cohort, no further analyses were performed.

During 1,445 person-years, 20 MACE events occurred among tofacitinib initiators (IR: 13.84 per 1000 PYs). The incidence rates were largely similar to the bDMARD cohort (HRd = 1.05, 95% CI 0.67–1.66) and the b/tsDMARD-naïve cohort (HRb = 0.98, 95% CI 0.62–1.55), and somewhat higher than in the general population (HRb = 1.34, 95% CI 0.84–2.12), albeit not statistically significant.

During 1,464 person-years contributed by the tofacitinib cohort, 8 myocardial infarctions occurred (IR: 5.46 per 1000 PYs). Incidence rates were elevated but not statistically significantly different from the rates in both the bDMARD cohort (HRd = 1.18, 95% CI 0.57–2.43), and the b/tsDMARD-naïve cohort (HRb = 1.26, 95% CI 0.60–2.62), and were higher than in the general population (HRb = 1.89, 95% CI 0.91–3.94).

During 1,455 person-years contributed by the tofacitinib cohort, 11 VTE events occurred (IR: 7.56 per 1000 PYs). This incidence rate was comparable to that observed in the bDMARDs cohort (HRd = 1.00, 95% CI 0.54–1.86), and elevated (but non-statistically significant) compared to the incidence rate in b/tsDMARD-naïve cohort (HRb = 1.13, 95% CI 0.60–2.11). The incidence rate was also higher than in the general population (HRb = 1.80, 95% CI 0.96–3.37).

During 1,474 person-years contributed by tofacitinib patients, 6 GI perforations occurred (IR: 4.07 per 1000 PYs). Rates were higher but non-statistically significant when compared to both bDMARD patients (HRd = 1.56, 95% CI 0.66–3.67) and b/tsDMARD-naïve patients (HRb = 1.46, 95% CI 0.60–3.57), and higher than in the general population (HRb = 2.49, 95% CI 1.02–6.09).

No PML cases occurred among tofacitinib initiators.

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Table 17. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Censoring at start of next treatment (if within 90 days of stop of treatment)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
Hospitalized infections							
Tofacitinib	530	57	1364	41.79	(32.24-54.18)	41.79	2.57
0 previous b/tsDMARDs	80	4	277	14.43	(5.42-38.46)		3.46
1-2 previous b/tsDMARDs	199	18	506	35.60	(22.43-56.50)		2.54
3+ previous b/tsDMARDs	251	35	581	60.22	(43.24-83.88)		2.32
bDMARD	18199	1636	45132	36.25	(34.53-38.05)	31.94	2.48
0 previous b/tsDMARDs	9092	729	23914	30.48	(28.35-32.78)		2.63
1-2 previous b/tsDMARDs	6352	611	15399	39.68	(36.65-42.95)		2.42
3+ previous b/tsDMARDs	2755	296	5818	50.88	(45.40-57.02)		2.11
B/tsDMARD-naïve Patients	59969	10002	260684	38.37	(37.62-39.13)	22.04	4.35
General Population	93782	3661	345544	10.59	(10.26-10.94)	9.30	3.68
Herpes Zoster (hospitalized)							
Tofacitinib	536	2	1470	1.36	(0.34-5.44)	1.36	2.74
0 previous b/tsDMARDs	80	0	281	0.00	(.-.)		3.51
1-2 previous b/tsDMARDs	199	2	531	3.77	(0.94-15.06)		2.67
3+ previous b/tsDMARDs	257	0	658	0.00	(.-.)		2.56
bDMARD	18201	26	48161	0.54	(0.37-0.79)	0.47	2.65

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Table 17. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Censoring at start of next treatment (if within 90 days of stop of treatment)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	9092	9	25258	0.36	(0.19-0.68)		2.78
1-2 previous b/tsDMARDs	6353	11	16569	0.66	(0.37-1.20)		2.61
3+ previous b/tsDMARDs	2756	6	6334	0.95	(0.43-2.11)		2.30
B/tsDMARD-naïve Patients	59969	121	284377	0.43	(0.36-0.51)	0.20	4.74
General Population	93782	26	352591	0.07	(0.05-0.11)	0.06	3.76
CV events (MACE)							
Tofacitinib	534	20	1445	13.84	(8.93-21.45)	13.84	2.71
0 previous b/tsDMARDs	80	0	281	0.00	(.-.)		3.51
1-2 previous b/tsDMARDs	199	6	534	11.23	(5.05-25.01)		2.68
3+ previous b/tsDMARDs	255	14	630	22.22	(13.16-37.52)		2.47
bDMARD	18201	676	47125	14.34	(13.30-15.47)	11.85	2.59
0 previous b/tsDMARDs	9092	306	24791	12.34	(11.03-13.81)		2.73
1-2 previous b/tsDMARDs	6353	265	16143	16.42	(14.55-18.52)		2.54
3+ previous b/tsDMARDs	2756	105	6191	16.96	(14.01-20.54)		2.25
B/tsDMARD-naïve Patients	59969	7545	273093	27.63	(27.01-28.26)	13.12	4.55
General Population	93782	2961	347722	8.52	(8.21-8.83)	7.29	3.71

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Table 17. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Censoring at start of next treatment (if within 90 days of stop of treatment)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
Myocardial infarction (MI)							
Tofacitinib	535	8	1464	5.46	(2.73-10.92)	5.46	2.74
0 previous b/tsDMARDs	80	0	281	0.00	(.-.)		3.51
1-2 previous b/tsDMARDs	199	3	534	5.62	(1.81-17.41)		2.68
3+ previous b/tsDMARDs	256	5	649	7.70	(3.21-18.51)		2.54
bDMARD	18201	236	47714	4.95	(4.35-5.62)	4.26	2.62
0 previous b/tsDMARDs	9092	118	25038	4.71	(3.93-5.64)		2.75
1-2 previous b/tsDMARDs	6353	85	16397	5.18	(4.19-6.41)		2.58
3+ previous b/tsDMARDs	2756	33	6280	5.26	(3.74-7.39)		2.28
B/tsDMARD-naïve Patients	59969	1921	279350	6.88	(6.58-7.19)	4.15	4.66
General Population	93782	874	350610	2.49	(2.33-2.66)	2.24	3.74
VTE (DVT and PE)							
Tofacitinib	535	11	1455	7.56	(4.19-13.65)	7.56	2.72
0 previous b/tsDMARDs	80	1	275	3.63	(0.51-25.78)		3.44
1-2 previous b/tsDMARDs	199	5	530	9.43	(3.93-22.67)		2.66
3+ previous b/tsDMARDs	256	5	649	7.70	(3.21-18.50)		2.54
bDMARD	18200	335	47642	7.03	(6.32-7.83)	6.47	2.62

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Table 17. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Censoring at start of next treatment (if within 90 days of stop of treatment)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	9092	165	24988	6.60	(5.67-7.69)		2.75
1-2 previous b/tsDMARDs	6353	98	16433	5.96	(4.89-7.27)		2.59
3+ previous b/tsDMARDs	2755	72	6221	11.57	(9.19-14.58)		2.26
B/tsDMARD-naïve Patients	59969	2180	278914	7.82	(7.49-8.15)	5.62	4.65
General Population	93782	1208	350144	3.45	(3.26-3.65)	3.20	3.73
GI perforations							
Tofacitinib	536	6	1474	4.07	(1.83-9.06)	4.07	2.75
0 previous b/tsDMARDs	80	1	280	3.57	(0.50-25.38)		3.50
1-2 previous b/tsDMARDs	199	2	538	3.72	(0.93-14.86)		2.70
3+ previous b/tsDMARDs	257	3	656	4.58	(1.48-14.19)		2.55
bDMARD	18201	101	48050	2.10	(1.73-2.55)	2.02	2.64
0 previous b/tsDMARDs	9092	37	25210	1.47	(1.06-2.03)		2.77
1-2 previous b/tsDMARDs	6353	41	16509	2.48	(1.83-3.37)		2.60
3+ previous b/tsDMARDs	2756	23	6330	3.63	(2.41-5.47)		2.30
B/tsDMARD-naïve Patients	59969	571	283323	2.02	(1.86-2.19)	1.51	4.72
General Population	93782	311	352028	0.88	(0.79-0.99)	0.86	3.75
PML							
Tofacitinib	537	0	1532	0.00	(.-.)	0.00	2.85

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Table 17. Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person Years) – Censoring at start of next treatment (if within 90 days of stop of treatment)

	Observations	Events	Person-years	Crude IR	95% CI	Std IR	Mean follow-up, years
0 previous b/tsDMARDs	80	0	285	0.00	(.-.)		3.56
1-2 previous b/tsDMARDs	199	0	556	0.00	(.-.)		2.80
3+ previous b/tsDMARDs	258	0	691	0.00	(.-.)		2.68
bDMARD	18201	3	60811	0.05	(0.02-0.15)	0.05	3.34
0 previous b/tsDMARDs	9092	2	30657	0.07	(0.02-0.26)		3.37
1-2 previous b/tsDMARDs	6353	1	21687	0.05	(0.01-0.33)		3.41
3+ previous b/tsDMARDs	2756	0	8467	0.00	(.-.)		3.07
B/tsDMARD-naïve Patients	59969	2	284709	0.01	(0.00-0.03)	0.01	4.75
General Population	93782	0	353248	0.00	(.-.)	0.00	3.77

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; 95% CI, 95% confidence interval; IR, Incidence Rate; NMSC, non-melanoma skin cancer; Std IR, standardized to the age/sex distribution in the tofacitinib cohort.

Table 18. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts – Censoring at start of next treatment (if within 90 days of stop of treatment)

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	bDMARD	1.19	(0.91-1.56)	1.23	(0.94-1.60)	1.03	(0.67-1.60)	1.12	(0.85-1.47)
	b/tsDMARD naïve	1.44	(1.09-1.90)	1.47	(1.11-1.94)	n/r	n/r	n/r	n/r

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Table 18. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts – Censoring at start of next treatment (if within 90 days of stop of treatment)

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population	3.46	(2.62-4.56)	2.88	(2.19-3.80)	n/r	n/r	n/r	n/r
Herpes Zoster (hospitalized)	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
CV events (MACE)	bDMARD	1.07	(0.68-1.68)	1.07	(0.68-1.69)	0.75	(0.35-1.62)	1.05	(0.67-1.66)
	b/tsDMARD naïve	0.99	(0.62-1.56)	0.98	(0.62-1.55)	n/r	n/r	n/r	n/r
	General population	1.56	(0.98-2.46)	1.34	(0.84-2.12)	n/r	n/r	n/r	n/r
Myocardial infarction (MI)	bDMARD	1.19	(0.58-2.43)	1.16	(0.57-2.37)	1.33	(0.52-3.41)	1.18	(0.57-2.43)
	b/tsDMARD naïve	1.31	(0.63-2.72)	1.26	(0.60-2.62)	n/r	n/r	n/r	n/r
	General population	2.20	(1.06-4.57)	1.89	(0.91-3.94)	n/r	n/r	n/r	n/r
VTE	bDMARD	1.01	(0.55-1.86)	1.03	(0.56-1.89)	1.52	(0.69-3.37)	1.00	(0.54-1.86)
	b/tsDMARD naïve	1.10	(0.59-2.06)	1.13	(0.60-2.11)	n/a	n/a	n/a	n/a
	General population	1.94	(1.04-3.62)	1.80	(0.96-3.37)	n/r	n/r	n/r	n/r
GI perforations	bDMARD	1.68	(0.72-3.90)	1.70	(0.73-3.93)	1.45	(0.33-6.36)	1.56	(0.66-3.67)
	b/tsDMARD naïve	1.44	(0.59-3.52)	1.46	(0.60-3.57)	n/r	n/r	n/r	n/r

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Table 18. Adjusted Hazard Ratios (HRs) Comparing Main Cohort (Tofacitinib) to Comparator Cohorts – Censoring at start of next treatment (if within 90 days of stop of treatment)

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population	2.85	(1.17-6.96)	2.49	(1.02-6.09)	n/r	n/r	n/r	n/r
PML	bDMARD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	b/tsDMARD naïve	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r
	General population	n/a	n/a	n/a	n/a	n/r	n/r	n/r	n/r

Abbreviations: b/tsDMARD, biological or targeted synthetic disease modifying anti-rheumatic drug; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DAS28, disease activity score 28; DVT, deep venous thrombosis; GI, gastrointestinal infection; HAQ, health assessment questionnaire; MACE, major adverse cardiovascular event; MI: myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PML, progressive multifocal leukoencephalopathy; RF, rheumatoid factor; VTE, venous thromboembolism, HR: Hazard Ratio. CI: Confidence Interval. .
Notes: 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, 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.
n/a: not available (number of events <5)
n/r: not relevant
*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. A 90-day risk window will be applied to the censoring at switch approach

10.6. Adverse Events/Adverse Reactions

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

In these data sources, individual patient data were 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) were not met.

11. DISCUSSION

11.1. Key Results

This final study report describes the relative uptake of tofacitinib in the treatment of RA in Sweden since market approval, and presents a coherent analysis of key safety outcomes. A number of important observations were made:

(i) There were few events in the tofacitinib group overall, despite the longer follow-up compared to the previously submitted interim reports. Therefore, it is difficult to draw firm conclusions from such data.

(ii) Some of the key results are as follows:

- The incidence rate for hospitalized infection was high in those treated with tofacitinib, but comparable to that observed in those treated with other bDMARDs, with no statistically significant difference between the groups.
- There was an increased incidence rate of NMSC in those treated with tofacitinib and a consistent, and statistically significant, increased risk for NMSC in those patients initiating tofacitinib in comparison to bDMARDs.
- There was a high rate of PE in those treated with tofacitinib and a consistent, but non-statistically significant, increased risk for PE in those patients initiating tofacitinib in comparison to bDMARDs. This was in contrast to VTE overall, where there was no increased risk in those initiating tofacitinib relative to bDMARDs, which may suggest that any potential safety concerns for VTE are limited to PE.
- There was a high incidence rate of CHF in patients treated with tofacitinib and a consistent, though not statistically significant in the fully adjusted model, increased risk for this outcome in those patients initiating tofacitinib compared with bDMARDs.
- There was a high incidence rate of GI perforation in patients treated with tofacitinib and a consistent, but non-statistically significant, increased risk for GI perforation in those patients initiating tofacitinib in comparison to bDMARDs.
- Furthermore, there was an increased risk of lung cancer in the tofacitinib cohort when compared with the bDMARD cohort, although the estimates were statistically significant only in the censor at treatment switch analyses and not in the ever-

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exposed approach. This is due to an overall shorter time on treatment for the tofacitinib cohort as compared to the bDMARD cohort.

- Future surveillance is necessary for these potential safety concerns, which should be interpreted in light of the few recorded events. Overall, this study did not identify new or unexpected safety concerns associated with tofacitinib use, and findings are consistent with the SmPC.[35]

(iii) The absolute rates for opportunistic infections and herpes zoster outcomes, and to a lesser extent lymphoma and non-Hodgkin lymphoma, for patients initiating tofacitinib were elevated compared with the other RA cohorts, including both bDMARD-treated and b/tsDMARD-naïve patients, but the numbers of events were too low to perform further comparative analyses. It is, however, an important observation to monitor given that these outcomes are events of special safety interest for tofacitinib.

(iv) For the cohorts defined by initiation of a b/tsDMARD treatment, start of follow-up corresponded to a clinical event at which the treated patient was deemed fit enough to tolerate the intended b/tsDMARD treatment, and likely to remain alive so that the response to treatment could be evaluated. For the b/tsDMARD-naïve cohort, no such assumptions on survival were made, and start of follow-up corresponded to an arbitrary date. Thus, the initial mortality in the b/tsDMARD-initiator cohorts is likely to be affected by depletion of individuals with poor short-term survival relative to the b/tsDMARD-naïve cohort.

11.2. Sensitivity Analyses

A number of sensitivity analyses were conducted to assess the robustness of the main findings and to explore the potential impact of confounding.

Analyses considering previous tofacitinib use showed that patients who contributed to the bDMARD cohort after prior exposure to tofacitinib differed from those without such exposure. These patients were more often female, had longer disease duration, had been treated with a greater number of previous b/tsDMARDs, and had a higher burden of comorbidities. This suggests that confounding by indication cannot be excluded.

Stratification by VTE risk factors showed that VTE events in the tofacitinib cohort occurred exclusively among patients with at least one baseline risk factor, whereas no events were observed among those without such risk factors. A similar pattern was seen across the comparator cohorts, with substantially higher incidence rates in patients with risk factors than in those without.

Stratification by cardiovascular risk factors showed a consistent pattern across all cohorts, with markedly higher rates of MACE and myocardial infarction among patients with baseline CV risk factors compared with those without. Among tofacitinib initiators, event rates were low in the absence of CV risk factors and higher among those with such risk factors, in line with what was observed for the comparator cohorts. These findings suggest that the elevated absolute rates of cardiovascular outcomes are strongly influenced by baseline risk profiles rather than treatment alone.

Analyses stratified by calendar periods defined by changes to the SmPC suggested lower incidence rates for several outcomes, including VTE and NMSC, among patients initiating tofacitinib in the later time periods. For some outcomes, including malignancies and

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cardiovascular events, no events were observed after the most recent label change. However, these findings should be interpreted cautiously given the limited follow-up time and small number of events in the later periods.

Restriction to patients without a prior history of malignancy showed that incidence rates for malignancy outcomes, including NMSC, lung cancer and lymphoma, remained higher in the tofacitinib cohort than in the comparator cohorts. However, the number of events was low, and the estimates should be interpreted with caution.

Finally, sensitivity analyses with censoring at switch to next treatment showed no marked difference with the main analyses.

Overall, the sensitivity analyses were consistent with the main findings. They do, however, highlight the importance of baseline patient characteristics, including comorbidities and established risk factors, when interpreting the observed associations.

11.3. Limitations

- The consistent format of the analyses provided an easy overview across all analyses but represented a “best compromise” between feasibility and readability on the one hand and the optimal design and analytic approach for each of the outcomes under study.

- While the study design, comparators, and multitude of data allowed for alternative comparisons and for adjustment for known or tentative confounders for the hospitalized infection events, it is likely that residual confounding and channeling effects remain. This is especially true since the clinical decision-making process, the components of which our multivariable analyses seek to unpick, is multifactorial and based on – in addition to more easily estimable factors related to indication (e.g., DAS28) – an elusive mix of personal preferences, subjective estimates of frailty and perceived prognosis.

- Most outcomes had relatively small numbers of events and hence there was limited statistical precision.

- For some variables (i.e., DAS28 and HAQ) there was a non-negligible amount of missingness among patients in the b/tsDMARDs-exposed cohorts. To address this, in addition to the complete case analysis, an additional model was fit where these covariates were modeled as categorical (split in quartiles), and with missing information coded as a separate category. However, this approach may also be subject to bias.

This approach also has a number of strengths:

- A nationwide approach together with the high coverage of ARTIS.

- The population-based setting in a public healthcare system acted to increase generalizability, although we acknowledge that baseline risks for the outcomes under study, the set-up of other risk factors, as well as the penetration of

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b/tsDMARD therapies may vary across countries, and thus that the generalizability to other settings (particularly outside of western Europe and the US) may be limited.

- The prospectively collected longitudinal data on covariates and outcomes ascertained from linkages with external registers independently of disease- or treatment- status clearly reduced the risk of selective outcome ascertainment. At the same time, we cannot rule out surveillance bias which may lead to an increased number of detected events in patient cohorts compared to non-patient cohorts. This bias should be of lesser magnitude the "harder" the outcome under study, and virtually non-existent for mortality.

- The register linkages allowed for information on covariates including several important potential confounders.

Inclusion of several different comparators as defined by alternative treatments, alternative positioning of treatments, arthritis disease but no b/tsDMARD treatment, and the Swedish general population provided a powerful means of estimating risks or hazard ratios that varied with the treated context rather than with the exact treatment, and also the marginal increase in risk with different treatment options compared to risks associated with the treated disease per se.

11.4. Interpretation

After adjusting for measured potential confounders, a statistically significantly increased risk of NMSC and lung cancer was observed among tofacitinib initiators versus bDMARDs, under the treatment switch approach. However, under the ever-exposed approach, only the HR for NMSC was statistically significant. These results are consistent with the known safety profile of tofacitinib, as NMSC and lung cancer are important identified risks in the EU RMP, and no new safety signals were identified from this study. The meta-analysis of the four tofacitinib PASS (Appendix 8) demonstrated statistically significant increased risk of NMSC compared to bDMARDs in the pooled estimates: HR: 2.08 (1.55, 2.79) using the 90-Day-Window "Censor-at-switch" approach (details provided in Appendix 8 in the meta-analysis SAP). Future surveillance is necessary for these potential safety concerns, which should be interpreted in light of the few recorded events despite the follow-up of 7.5 years.

Any crude comparisons of incidence rates for the tofacitinib and the comparison cohorts should be interpreted with caution, as comparisons may be confounded by small sample size in the tofacitinib cohort and baseline differences between cohorts, such as disease duration, comorbidities, and medication use. Further study would be required to draw any final conclusions, especially for outcomes with long latency.

11.5. Generalizability

This study utilized data from the Swedish national registers which collects data from all residents in Sweden. Therefore, the study findings are likely to be generalizable to all tofacitinib treated patients in Sweden and in similar settings.

12. OTHER INFORMATION

Not applicable.

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13. CONCLUSIONS

In summary, this report describes the relative occurrence of a series of pre-defined safety events of interest in Swedish patients with RA treated with tofacitinib or with other anti-rheumatic treatments, from marketing of tofacitinib until end of 2024 (end of 2023 for malignancy outcomes). Crude differences in the incidence rates for the tofacitinib and the comparison cohorts were observed for hospitalized infections, NMSC, PE, congestive heart failure, and GI perforations, however only NMSC risk was statistically significant after considering several confounders (using both the ever-exposed and on-drug approaches). We also found statistically significant adjusted hazard ratios when comparing the risk of lung cancer, only under the on-drug approach. Overall, the findings presented should be interpreted with caution considering the limitations of the study and the limited power for some of the outcome.

No new safety signals identified from this study. These results are consistent with the known safety profile of tofacitinib, as NMSC and lung cancer are important identified risks in the EU RMP.

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35. SUMMARY OF PRODUCT CHARACTERISTICS, XELJANZ
https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf Accessed July 25 2026

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

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Document Approval Record

Document Name:	A3921314 Non-Interventional-Low-Interventional Study Type 1 Study Report
Document 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

Signed By:	Date(GMT)	Signing Capacity
Koram, Nana	30-Jul-2026 16:25:00	Manager Approval
De Bernardi, Barbara	30-Jul-2026 20:42:12	EUQPPV Approval

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APPENDIX 1. SIGNATURES

PROTOCOL NUMBER:	A3921314
TITLE OF STUDY:	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
FINAL STUDY REPORT VERSION:	1.0 Date: 28-Jul-2026

Confirmation: I confirm that this study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study. This signature page does not pertain to the conduct of the meta-analysis.

Pfizer NI study lead/LIS1 study lead
Shahar Shmuel, PhD

Signature: **Date:** 28-Jul-2026

Principal Investigator, the Anti Rheumatic Treatment in Sweden (ARTIS) Register; Professor of Rheumatology / Rheumatic Disease Epidemiology; Senior Consultant Rheumatologist
Johan Askling, MD, PhD

Signature: **Date: 2026-July-28**

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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
Protocol Number	A3921314
Protocol Version Identifier	v 6.0
Date	06 July 2025
EU Post Authorisation Study (PAS) Register Number	EUPAS31157
Active Substance	L04AA29 Tofacitinib
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?

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	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.
Country of Study	Sweden
Author	Shahar Shmuel, PhD Pfizer, Inc. 219 East 42nd St New York, New York 10017 USA

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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

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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

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3. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable.

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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.

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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.

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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.

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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

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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

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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

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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

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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

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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

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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

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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

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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]

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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.

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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.

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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]

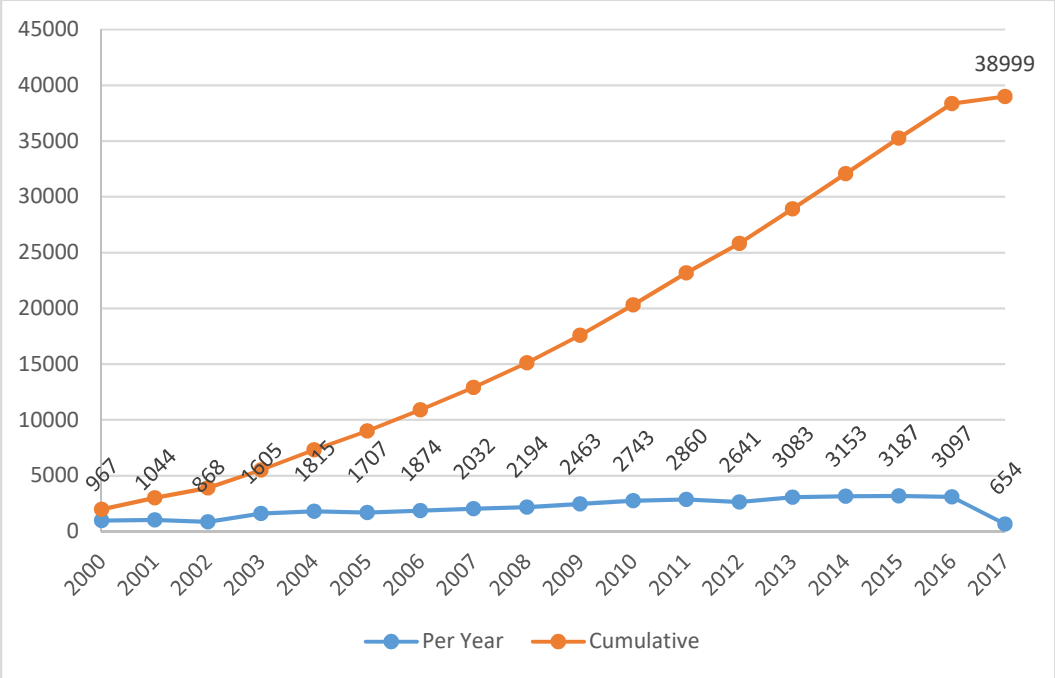
To maintain this high amount of data capture, and to improve the completeness further, the Swedish Society for Rheumatology regularly holds scientific meetings during which the surveillance data is presented. The managers and research nurses of ARTIS regularly visit participating centers to support the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

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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.

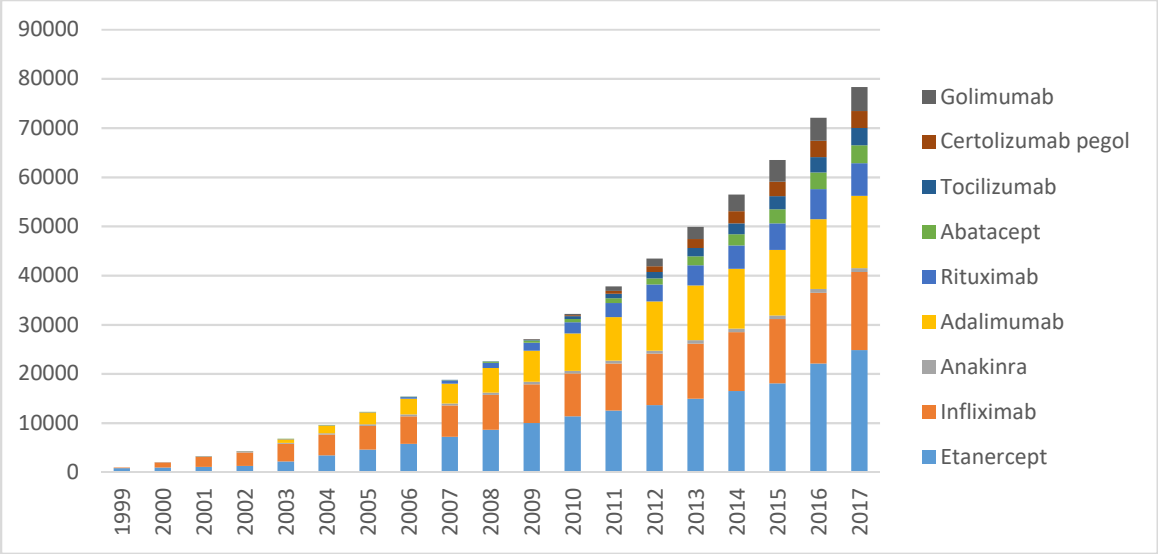
Figure 1. Accumulated Number of First Ever Biologics Starts Across All Rheumatology Indications Registered in the Swedish Rheumatology Quality Register (SRQ) and Amenable for Monitoring in the ARTIS Programme.



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.

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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.

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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 tofacitinib 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.

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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.

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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

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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.

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	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).

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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

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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.

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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

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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.

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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

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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.

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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

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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).

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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.

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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

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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

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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.

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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.

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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?	☐	☐	☒	

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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)	☐	☒	☐	

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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

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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

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Comments:

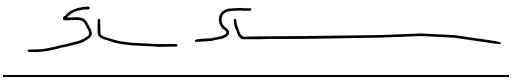
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Shahar Shmuel

Date: 06 July 2025

Signature:



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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.

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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		

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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		

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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		

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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

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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 (%)				

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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 (%)				

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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

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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 (%)						

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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 (%)						

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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

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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.

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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.

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	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;

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	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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	ARTIS		BIOBADASER, BSRBR, RABBIT
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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	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
			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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	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
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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	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
			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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	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
			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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	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints).
	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.

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Non-Interventional Study Protocol
A3921314

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

Statistical Analysis Plan
(SAP)

Version: 1

Author: Hannah Bower, Johan Askling, Shahar Shmuel

Date: 24-JUN-2025

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Figure 1. Accumulated number of first ever biologics starts registered in the Swedish Rheumatology Quality Register (SRQ), specifically in its biologics module (ARTIS). Dashed grey line = across all Rheumatology indications, solid orange line = RA and polyarthritis (PA), solid blue line = annual number of new starts, any indication. Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is higher than the number of first ever biologics that is presented in the figure (>80,000 treatment starts). 6

Figure 2. Schematic illustrating how different types of Swedish data may be linked to the data collected in the SRQ. 'Rheum register' here stands for SRQ/ARTIS. 7

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable

2. INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is **italicised**.

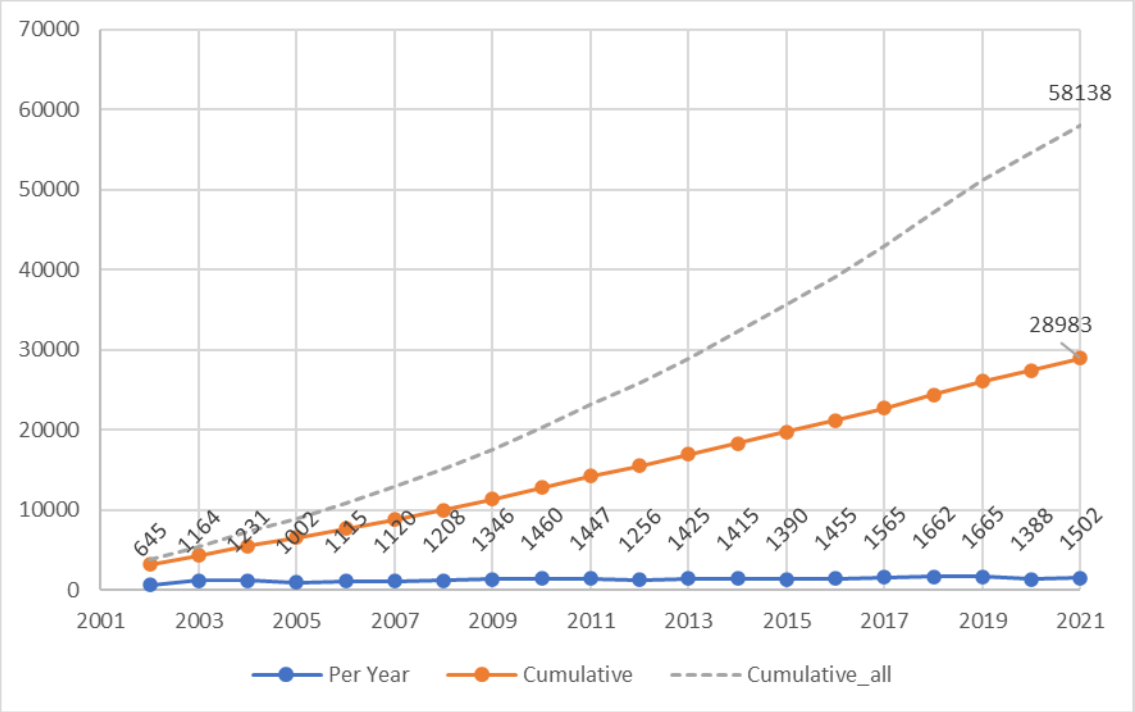
RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[1] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently 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 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). Tofacitinib citrate is also approved in more than 80 additional countries as of August 2017, including the United States, Canada, Australia, Switzerland, and Japan.

From its launch in Sweden for the treatment of RA, XELJANZ® has been monitored by the Swedish Biologics Register ARTIS (Anti-Rheumatic Treatment in Sweden). Built on the already existing Swedish Rheumatology Quality register (SRQ, see below), ARTIS was initiated in 1999, and serves as a national surveillance program for investigation of safety and effectiveness of new anti-rheumatic drugs as used in clinical practice. below depicts the accumulated number of patients initiating such therapies.

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Figure 1. Accumulated number of first ever biologics starts registered in the Swedish Rheumatology Quality Register (SRQ), specifically in its biologics module (ARTIS). Dashed grey line = across all Rheumatology indications, solid orange line = RA and polyarthritis (PA), solid blue line = annual number of new starts, any indication. Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is higher than the number of first ever biologics that is presented in the figure (>80,000 treatment starts).



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 special interest including rare events and endpoints with long latency periods, Pfizer implemented a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data included in the ARTIS register. Long term follow up of morbidity- and mortality-events following exposure to tofacitinib over 7 years is an appropriate method for evaluating the risk associated with tofacitinib.

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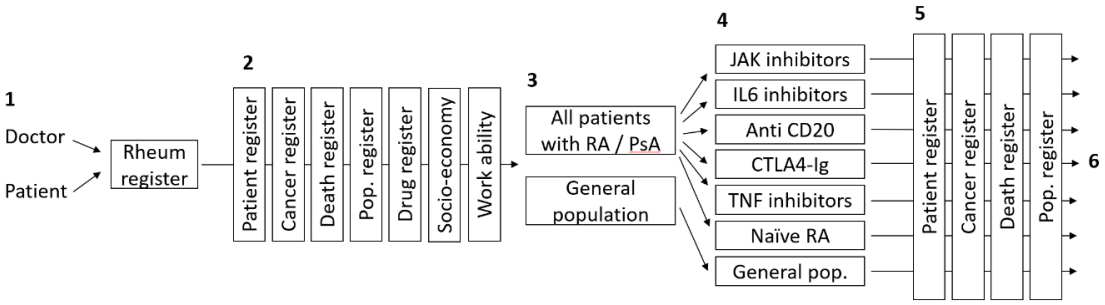
Since XELJANZ® entered the Swedish market, Pfizer has had agreements with ARTIS via Karolinska Institutet regarding the safety monitoring of Xeljanz as used in rheumatology in Sweden. In these agreements, safety data from the ARTIS program come from two sources:

(i) Spontaneous adverse drug reaction reporting to the Medical Products Agency. ARTIS has a reporting module that greatly facilitates this type of reporting. Once adjudicated and categorized, reported events are fed into the usual adverse drug reaction reporting system (Eudravigilance). The same adjudicated events also make up the biannual reports sent from ARTIS to Samsung, which has adhered to a pre-defined format ("the Manchester template").

(ii) Data from SRQ/ARTIS are (on a regular basis) linked to data from other national Swedish registers, as depicted in Figure 2 below. This analysis plan pertains entirely to events detected through this second route, i.e., register linkages.

The resulting linkage database is used for all scientific safety reports from ARTIS.

Figure 2. Schematic illustrating how different types of Swedish data may be linked to the data collected in the SRQ. 'Rheum register' here stands for SRQ/ARTIS.



1 Clinical data entry into the Rheumatology register, by the patient and by the rheumatologist
2 Linkage of the rheumatology registers to a series of other national population-based registers
3 Processing of the linked data to create a cohort of all patients with the rheum diagnosis in the country
4 Use of the data in **4** to define treatment-specific new-user cohorts, internal and external comparators, and covariates
5 Follow-up for defined or undefined safety outcomes through linkage to national population-based registers
6 Statistical analysis (pooling of data or results)

2.1. Study Design

2.1.1. Primary objectives:

a. To estimate the rates of serious infections, malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, cardiovascular (CV) events, major adverse cardiovascular events (MACE) and 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.

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b. To estimate the rates of the same events of interest among the comparator groups:

Patients with RA who have not been treated with bDMARD or tsDMARD

Patients with RA who initiate bDMARDs

The general population to provide context for rates observed on tofacitinib.

2.1.2. Secondary objectives:

To compare the rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE MI, VTE, and other event rates, including fractures between tofacitinib-treated RA patients and other comparator cohorts, if feasible.

Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated stratified by age (in patients younger than 65 years and in older adult patients aged 65 years and older)

2.1.3. Study population

The active surveillance study population will comprise all patients with RA enrolled within the ARTIS register who receive tofacitinib following EU approval and marketing (May 1, 2017), through the end of the study period (December 31, 2024 for all outcomes). In addition, three comparator cohorts will be assembled during the same study period 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.

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.

Inclusion Criteria:

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

RA patient Treated with Tofacitinib

- Initiation of tofacitinib as captured in SRQ.

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- Age 18 years and older
- Diagnosis of rheumatoid arthritis by a consulting rheumatologist.

RA patient Treated with bDMARD

- Initiation of a bDMARD as captured in SRQ.
- Diagnosis of rheumatoid arthritis by a consulting rheumatologist.
- Age 18 years and older

Ts/bDMARD-naïve RA Cohort

- 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.
- Patients are censored from this cohort when they start tofacitinib or a b/tsDMARD, but are eligible for subsequent inclusion into the respective drug-based cohorts defined above.
- Age 18 years and older

General Population Cohort

- Randomly selected from general population and region- (i.e., county), age-, vital status-, and sex-matched to RA patient cohorts, up to 5 population controls per patient on a b/tsDMARD (i.e., the combined population of the bDMARD and tofacitinib cohorts).
- Age 18 years and older

2.1.4. Data source

Swedish healthcare 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 recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible.[3] 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.

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Patients treated with tofacitinib will be identified through the Swedish Rheuatmology Quality Register (SRQ) (www.srq.nu), with comparator cohorts identified through a combination of SRQ, the Swedish Patient Register, and the Total Population register. Baseline comorbidities and outcomes during follow-up will be identified by linking individuals in these cohorts to the Swedish Patient Register, the Swedish Cancer Register, and the Cause of Death Register.

The Swedish Rheumatology Quality Register (SRQ) and ARTIS

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Rheumatology Society to improve the healthcare and treatment for patients with RA. SRQ followed on regional registry initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national registry. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis, myositis, systemic lupus erythematosus and additional conditions. SRQ covers around 90% of all biologic initiations in in Swedish Rheumatology after 1999.[4,5] Currently, some 25,000 patients with RA initiating over 75,000 biological treatments have been enrolled in ARTIS. The SRQ also contains early RA patients, and increasingly, RA patients are followed from their first RA diagnosis and onwards. In conjunction with each patient visit, the treating rheumatologist enters data on disease activity and anti-rheumatic treatment.

The Swedish 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 (ICD-10) since 1997.

The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. Validation against medical files have found an overall error rate in the main diagnoses of 4% at the ICD chapter level, and 12% at the three digit level, suggesting that the positive predictive values for most reported diagnoses are high.[6] The outpatient component of the Patient register was initiated with nationwide coverage in 2001. Overall, 13% of outpatient visits lack records, but coverage is higher for somatic public care (including most rheumatology care). Chart reviews and validation of the RA diagnosis based on different algorithms applied to the register data indicate a positive predictive value for a register-based diagnosis of RA around 90%.

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.

The Swedish Cancer Register

The Swedish Cancer Register was established in 1958, and contains information on date of cancer (and some selected pre-cancers) onset and type of cancer, according to the ICD

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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%.

The Swedish Basal Cell Cancer Register

The Swedish Basal Cell Cancer Register was established in 2004, and is linked to the Swedish Cancer Regsiter.[7] Approximately 50,000 individuals are diagnosed with basal cell carcinoma each year in Sweden.

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.[8] 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.

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. The register was started in 1952, and the data is considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three digit level of the ICD-coded underlying cause of death.

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 residing in Sweden since 1961. This register will be used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

This study analyzes data existing with the ongoing ARTIS register. The ARTIS researchers are responsible for the data collection, management and analysis 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.[2] 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.

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2.1.5. Treatment/cohort labels

2.1.5.1. Main Cohort (Patients with RA who initiate Tofacitinib)

This cohort will be defined as all patients in ARTIS who met the study eligibility criteria and started tofacitinib as their first or later biological treatment in 2017-2025. Entry will be defined as date of treatment start from 01 May 2017 through 31 December 2024 for all outcomes. Patients with prior use of bDMARDs or other therarpies (e.g., other JAK inhibitors) during the baseline period will not be excluded.

2.1.5.2. Comparator Cohorts

For the comparator cohorts, treatments with one and the same biologic (i.e., the originator biologic and its biosimilar not being distinguished from each other) will be counted as separate biological treatments if the previous treatment is registered as discontinued, and more than 90 days (183 days for rituximab) has passed between the discontinuation and the next initiation. If there are two records of the same treatment where the gap in between the discontinuation of the first, and the start date of the second is less than 90 days, then they will be treated as one treatment episode. If there is a gap of over 90 days then these will be treated as separate treatment episodes, and thus can one individual contribute more than once to the treatment cohort. The end date/censoring depends on the approach taken (e.g., for an ever-exposed approach they will not be censored). Entry will be defined as date of treatment start.

2.1.5.2.1. RA patients treated with a bDMARD

This cohort will be defined as all eligible patients with RA as recorded in the SRQ with an initiation of a bDMARD therapy in the SRQ. bDMARD therapies are defined in Table 1. Entry will be defined as the first date when all inclusion criteria are fulfilled 2017-2025. There are no exclusions based on previous tofacitinib use. No matching is performed between the tofacitinib and bDMARD cohort. Note that the general population cohort is matched to patients with b/tsDMARDs overall.

2.1.5.2.2. ts/bDMARD-naïve RA cohort

This cohort will contain all eligible patients with RA, defined as those with at least two diagnoses of RA (ICD-10: M05, M060, M062, M063, M068, M069, M123) recorded in the Swedish Patient Register with at least one being recorded in a unit of rheumatology or internal medicine; this definition has been used in previous ARTIS reports. This definition is specific to the ts/bDMARD-näive cohort. The other cohorts will be selected from the SRQ. The SRQ contains patients initiating b/tsDMARD with RA as treated by a rheumatologist. It does not (sufficiently) contain those RA patients who are not treated with a b/tsDMARD, thus we use instead diagnosis codes in the National Patient Register to identify this population.

Patients will be followed from the date when all inclusion and exclusion criteria were met from 2017-2025. These patients will be censored on the date of initiation of tofacitinib or

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another ts/bDMARD. The Prescribed Drug Register will be used to supplement the SRQ and further ensure that the b/tsDMARD-naïve cohort was b/tsDMARD-naïve (i.e., also tofacitinib-naïve) prior to cohort entry (data is available back to 2005 in the prescribed drug register), and to quality control the date of start of the first ever b/tsDMARD.

2.1.5.2.3. The General Swedish population

The collective study population in the b/tsDMARD-treated cohorts will be matched (1:5, by year of birth, sex, county of residence, and vital status at the date of first identification of rheumatoid arthritis from 2001 onwards) to the Swedish Population Register. Date of entry in the general population comparators will be set to date of entry of their corresponding RA patient. Patients in the general Swedish population cohort are RA-free at the time of study entry (i.e., no record of RA ever).

Table 1. Classification of Medications (ATC Codes) for the Treatment of RA

BDMARD		TSDMARD (JAKI)
Abatacept (L04AA24)	Anakinra (L04AC03)	Tofacitinib (Xeljanz, L04AA29)
Adalimumab (L04AB04)	Certolizumab pegol (L04AB05)	Baricitinib (L04AA37)
Etanercept (L04AB01)	Golimumab (L04AB06)	Upadacitinib (L04AA44)
Infliximab (L04AB02)	Rituximab (L01XC02)	
Sarilumab (L04AC14)	Tocilizumab (L04AC07)	

2.2. Study Objectives

2.2.1. Primary objectives:

- To estimate the rates of serious infections, malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, cardiovascular (CV) events, major adverse cardiovascular events (MACE) and 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.

- To estimate the rates of the same events of interest among the comparator groups:

    - Patients with RA who have not been treated with bDMARD or tsDMARD

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- Patients with RA who initiate bDMARDs
- The general population to provide context for rates observed on tofacitinib.

2.2.2. Secondary objectives:

- To compare the rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE MI, VTE, and other event rates, including fractures between tofacitinib-treated RA patients and other comparator cohorts, if feasible.

- Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated stratified by age (in patients younger than 65 years and in older adult patients aged 65 years and older)

3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

No a priori hypotheses will be specified for the interim analyses. While the primary objective of the protocols is active surveillance, conducting quantitative, confounding controlled comparisons will depend on having a sufficient sample.

3.2. Statistical decision rules

For all comparisons, the alpha level will be 0.05, 2-sided. No adjustments for multiple comparisons will be made.

4. ANALYSIS SETS/POPULATIONS

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.

4.1. Full analysis set

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

RA patient Treated with Tofacitinib

- Initiation of tofacitinib as captured in SRQ.
- Age 18 years and older

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- Diagnosis of rheumatoid arthritis by a consulting rheumatologist.

RA patient Treated with bDMARD

- Initiation of a bDMARD as captured in SRQ.
- Diagnosis of rheumatoid arthritis by a consulting rheumatologist.
- Age 18 years and older

Ts/bDMARD-naïve RA Cohort

- 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.
- Patients are censored from this cohort when they start tofacitinib or a b/tsDMARD, but are eligible for subsequent inclusion into the respective drug-based cohorts defined above.
- Age 18 years and older

General Population Cohort

- Randomly selected from general population and region- (i.e., county), age-, vital status-, and sex-matched to RA patient cohorts, up to 5 population controls per tofacitinib exposed patient.
- Age 18 years and older

Follow-up time and risk windows

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, or study end treated as censoring events.

The **index date** was defined as:

- **Tofacitinib cohort:** Date of first pharmacy dispensation of tofacitinib
- **bDMARD exposed comparator cohort:** Date of the first dose of bDMARD therapy, whichever therapy was taken first
- **ts/bDMARD naïve cohort:** Date of start of study period (among patients with an RA diagnosis at the start of the study period and no sign of previous or on-going treatment with b/tsDMARD therapy)
- **General population cohort:** Date determined by match to tofacitinib cohort entry

(1) Primary Analysis for Non-malignancy and Non-mortality outcomes. Non-malignancy outcomes (see below for outcome definitions) and non-mortality outcomes were followed up until the first of the following time points:

- Event of interest
- First date of emigration from Sweden,
- Date of death,

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- End of data collection
- End of treatment* +90 days

*End of treatment was defined as the end of treatment date recorded by the treating rheumatologist in the SRQ. When a patient initiated a new therapy within the 90 day extention, the follow-up time and events during the overlapping period was assigned to both treatments.

(2) Analysis for Malignancy and All-Cause Mortality outcomes. Malignancy outcomes (including non-melanoma skin cancer) were evaluated using two approaches: an 'ever exposed' analysis as per the primary analysis, and a censor at switch approach as the secondary analysis.

For the ever exposed approach end of follow-up was defined as the first of the following:
- Event of interest
- First date of emigration from Sweden,
- Date of death,
- End of data collection

For the censor at switch approach end of follow-up was defined as the first of the following dates:
- Event of interest
- First date of emigration from Sweden,
- Date of death,
- End of data collection
- Date of switch to a tsDMARD (in the non-tofacitinib cohorts), or date of switch to a non-tsDMARD (in the tofacitinib cohort), or discontinuation.

Switch is defined differently in each cohort:

1. **Tofacitinib cohort:** switch to another JAK inhibitor, or switch to a non-JAK-inhibitor based advanced systemic therapy
2. **bDMARD cohort:** switch to tofacitinib or other non-biological advanced systemic therapy
3. **ts/bDMARD naïve cohort:** switch to a b/tsDMARD therapy

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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).

(3) Additional Sensitivity analyses

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 in the SRQ. These sensitivity analysis results will be presented as summary statistics of those with and without previous tofacitinib use.

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

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

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.[10-13]

Exclusion criteria:

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

Patients can request to be removed from the national rheumatology database. If patients make such a request, they will be excluded from the current study. Note that the remaining national registries that are to be used in the study include anonymized, nationally collected data for which individual patient consent is not required.

4.2. Safety analysis set

The safety analysis set is the same as the full analysis set.

4.3. Other analysis set

Not applicable

4.4. Subgroups

Given the age-dependent rate events of interest, we will stratify by age (aged ≥65 years vs. <65 years) for all safety outcomes.

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

The final analysis of endpoints will provide the rates of events overall and in subgroups defined by baseline characteristics as defined below:

For the outcome of **VTE incidence rates** for the tofacitinib cohort will be estimated overall and stratified by the following:

Patients with ≥1 VTE risk factors vs. no VTE risk factors. VTE risk factors (evaluated at baseline) are defined as: 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).

For the outcomes of **MACE and MI**, incidence rates for the tofacitinib cohort will also be estimated overall and stratified by the following:

Patients with ≥1 CV risk factors vs. no CV risk factors. Where CV risk factors (evaluated at baseline) are defined as: 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)).

For the outcome of lymphoma, incidence rates for the tofacitinib cohort will be estimated overall and reported for by the following lymphoma subtypes:

Non-Hodgkin lymphoma (NHL)

Hodgkin lymphoma

Chronic lymphocytic leukemia (CLL)

In addition, the final report will include the number of tofacitinib-exposed births or pregnancies surviving up to 25 weeks of gestation.

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).

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5. ENDPOINTS AND COVARIATES

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).

5.1. Efficacy/Effectiveness Endpoint(s)

Not applicable

5.2. Safety Endpoints

The following are pre-specified safety endpoints of interest that will be reported in the final report. These are defined in Table 2.

Hospitalizaed infections overall
Opportunistic infections
Herpes zoster (hospitalized)
Hepatitis
Fractures
NMSC
Malignancies (overall, excluding NMSC)
Lung Cancer
Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia)
CV events (defined as Major Adverse Cardiovascular Events (MACE))
Deep vein thrombosis (DVT)
Pulmonary embolism (PE)
Venous Thromboembolism (VTE (DVT/PE))
Myocardial infarction (MI)
Gastrointestinal (GI) perforations
Progressive multifocal leukoencephalopathy (PML)
Interstitial lung disease, pending feasibility
All-cause mortality

The first event during follow-up will be recorded. Individuals with a history of the event (including prior malignancy) at start of follow-up will not be excluded. Note that follow-up data is expected to be available until 31 December 2024.

Table 2. Outcome Definitions

Variable	Role	Data source(s)	Operational definition (ICD10 codes)
Hospitalized Infections overall	Outcome (primary endpoint)	Main diagnosis in inpatient component of Patient	A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2,

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Table 2. Outcome Definitions

Variable	Role	Data source(s)	Operational definition (ICD10 codes)
		Register. If the main diagnosis was RA then contributory diagnoses will also be allowed.	G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J38.3, 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, N10, N11, N12, 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
Opportunistic infections	Outcome (secondary endpoint)	Main diagnosis in inpatient component of Patient Register. If the main diagnosis was RA then contributory diagnoses will also be allowed.	A02, A15, A16, A17, A18, A19, A31, A32, A43, A481, B02, B38, B39, B40, B44, B45, B58, B69
Herpes zoster (hospitalized)	Outcome (secondary endpoint)	Main diagnosis in inpatient component of Patient Register. If the main diagnosis was RA then contributory diagnoses will also beallowed.	B02
Hepatitis	Outcome (secondary endpoint)	Main diagnosis in inpatient component of Patient Register. If the main diagnosis was RA then contributory diagnoses will also be allowed.	B15-B19
Fractures	Outcome (secondary endpoint)	Identified in patient register, in- or outpatient component.	Skull/face: S02 Neck: S12 Ribs/chest: S22 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,

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Table 2. Outcome Definitions

Variable	Role	Data source(s)	Operational definition (ICD10 codes)
			T12, T14.2. M48.5, M80, M84
Non-melanoma skin cancers (NMSC), including basal cell cancer	Outcome (secondary endpoint)	The Cancer Register. Basal cell cancers will be identified using The Swedish Basal Cell Cancer Register.	C44 and D04
All primary invasive cancers excluding non-melanoma skin cancers (NMSC)	Outcome (secondary endpoint)	The Cancer Register, invasive cancers only.	All non-benign tumors, excluding C44 and D04
Lung cancer	Outcome (secondary endpoint)	Identified through the Cancer Register	ICD-7: 162.1
Lymphoma (overall)	Outcome (secondary endpoint)	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
Non-Hodgkin lymphoma	Outcome (secondary endpoint)	Identified through the Cancer Register	ICD-7: 200,202
Hodgkin lymphoma	Outcome (secondary endpoint)	Identified through the Cancer Register	ICD-7: 201
Chronic lymphatic leukemia	Outcome (secondary endpoint)	Identified through the Cancer Register	ICD-7: 204.1
Cardiovascular (CV) events (defined as MACE)	Outcome (secondary endpoint)	Main diagnosis in the Patient register, in- or outpatient component. The underlying (main) cause recorded in the Cause of Death Register	I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis (combines MI, stroke and fatal CV events)
Myocardial infartction (MI)	Outcome (secondary endpoint)	Main diagnosis in the Patient register, in-patient component	I20.0, I21
VTE (DVT/PE)	Outcome (secondary endpoint)	Main diagnosis in the Patient Register (in- or out-patient component), plus I26.0 as main cause of death in the Cause of Death Register. Anti-coagulants identified using the prescribed drug register.	ICD10 I26, I80-I82 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the VTE ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.
DVT	Outcome (secondary endpoint)	Main diagnosis in the Patient Register (in- or out-patient component), Anti-coagulants identified using the prescribed drug register.	ICD10 I80-I82 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02),

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Table 2. Outcome Definitions

Variable	Role	Data source(s)	Operational definition (ICD10 codes)
			B01AE, B01AF, B01AX) within 30 days after the DVT ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.
PE	Outcome (secondary endpoint)	Main diagnosis in the Patient Register (in- or out-patient component), plus I26.0 as main cause of death in the Cause of Death Register. Anti-coagulants identified using the prescribed drug register.	ICD10 I26 with a filled prescription of an anticoagulant (ATC = B01AA, B01AB (excluding B01AB01 and B01AB02), B01AE, B01AF, B01AX) within 30 days after the VTE ICD10 code record in the National patient register, unless any death from any cause occurred within 30 days.
Gastrointestinal (GI) perforations	Outcome (secondary endpoint)	Main or secondary diagnoses in the Patient register, in- or outpatient component.	K223, K251, K252, K255, K256, K261, K262, K265, K266, K271, K272, K275, K276, K281, K282, K285, K286, K316, K570, K572 K574, K578, K630, K631, K632
Progressive multifocal leukoencephalopathy (PML)	Outcome (secondary endpoint)	Main or secondary diagnoses in the Patient register, in- or outpatient component.	A81.2
Interstitial lung disease, pending feasibility	Outcome (secondary endpoint)	Main diagnoses in the Patient register, in- or outpatient component.	J80-I84
All-cause mortality	Outcome (secondary endpoint)	The Cause of Death Register	-

In addition, the final safety reports will include the number of tofacitinib-exposed births or pregnancies surviving up to 25 weeks of gestation.

5.3. Other endpoints

Not applicable

5.4. Covariates

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

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malignancy excluding NMSC, and specifically history of NMSC, history of lymphoma and history of lung cancer), and history of therapeutic procedures.

Table 3. Definitions of baseline patient characteristics

Variable	Data source(s)	Operational definition
Age at start of of follow-up	SRQ	Value at treatment start as recorded in the SRQ
Sex (M/F)	SRQ	Value at treatment start as recorded in the SRQ
Smoking (ever/never)*	SRQ	Most recent value recorded in the SRQ prior to treatment start, but within the previous 5 years.
Rheumatoid factor positive (RF+/RF-)*	SRQ	Value recorded in SRQ
RA disease duration at start of of follow-up (<5, 5+ years)*	SRQ	Value at treatment start as recorded in the SRQ
Calendar year at start of follow-up	SRQ	Value at treatment start as recorded in the SRQ
DAS28 at start of follow-up (continuous)*	SRQ	Most recent value recorded in a rheumatology visit recorded in the SRQ within 30 days of treatment start

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Table 3. Definitions of baseline patient characteristics

Variable	Data source(s)	Operational definition
HAQ at start of follow-up (continuous)*	SRQ	Most recent value recorded in a rheumatology visit recorded in the SRQ within 30 days of treatment start
Concomittant csDMARDs at start of follow-up (Y/N)*	SRQ	Value at treatment start as recorded in the SRQ
Oral steroids at start of follow-up (Y/N)*	SRQ	Value at treatment start as recorded in the SRQ
NSAIDs at start of follow-up (Y/N)*	SRQ	Value at treatment start as recorded in the SRQ
Number of previous b/tsDMARDs (0, 1-2, 3+)*	SRQ	Value at treatment start as recorded in the SRQ
Total days in hospital (in last 5 years) (continuous)	National Patient Register	Value at treatment start
(Where applicable) Reason for discontinuing previous biologic (safety, inefficacy, non-medical switch, other, missing)	SRQ	Value at treatment start as recorded in the SRQ
History of statin use (as a proxy for history of hypercholesterolemia) (last 1 years) (Y/N)	Dispensation recorded in the prescribed drug register	ATC=C10AA
History of coronary heart disease (CHD) (last 5 years) (Y/N)	Main or secondary diagnoses from the Inpatient and Outpatient components of the	I20-I25

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Table 3. Definitions of baseline patient characteristics

Variable	Data source(s)	Operational definition
	Patient Register.	
History of chronic kidney failure (last 5 years) (Y/N)	Main or secondary diagnoses from the Inpatient and Outpatient components of the Patient Register.	N17-N19
History of stable angina pectoris (last 5 years) (Y/N)	Main or secondary diagnoses from the Inpatient and Outpatient components of the Patient Register.	I20 (minus I20.0)
History of therapeutic procedures to treat cardiovascular disease (e.g., coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI))	Surgical intervention codes recorded in the National Patient Register	FN* (Swedish surgical intervention codes)

* Clinical variables that will only be available for the b/tsDMARD-treated cohorts defined through SRQ

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)).

Table 4. Definitions of baseline characteristics that are considered potential confounders

Variable	Role	Data source(s)	Operational definition (ICD-10)
Age at start of follow-up	Baseline characteristic and potential confounder	SRQ	
Sex	Baseline characteristic and potential confounder	SRQ	

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Table 4. Definitions of baseline characteristics that are considered potential confounders

Variable	Role	Data source(s)	Operational definition (ICD-10)
Calendar year	Potential confounder	SRQ	
Number of previous biologics	Baseline characteristic and potential confounder	SRQ	
Prior number of days in inpatient care	Baseline characteristic and potential confounder	Inpatient component of the National Patient Register	Any ICD10 code, total days in hospital in previous year
History of infection (ever/never)	Baseline characteristic and potential confounder	Main diagnosis in inpatient component of Patient Register.	A00-B99, D73.3, E06.0, 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, J38.3, 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, N10, N11, N12, 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
History of Myocardial infarction (MI) (last 5 years) (Y/N)	Baseline characteristic and potential confounder	Main or secondary diagnoses from the Inpatient and Outpatient components of the Patient Register.	I21, I22

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Table 4. Definitions of baseline characteristics that are considered potential confounders

Variable	Role	Data source(s)	Operational definition (ICD-10)
History of Diabetes mellitus (last 5 years) (Y/N)	Baseline characteristic and potential confounder	Main or secondary diagnoses from the Inpatient and Outpatient components of the Patient Register.	E10-E14, O24
History of Chronic obstructive pulmonary disease (COPD) (last 5 years) (Y/N)	Baseline characteristic and potential confounder	Main or secondary diagnoses from the Inpatient and Outpatient components of the Patient Register.	J41-J44
History of joint Knee or hip replacement (ever/never)	Baseline characteristic and potential confounder	Operation codes from the Patient register	NGB, NFB
Rheumatoid factor positive (RF+/RF-)	Baseline characteristic and potential confounder	SRQ	
HAQ at start of follow-up (continuous)	Baseline characteristic and potential confounder	SRQ	Most recent value recorded in a rheumatology visit recorded in the SRQ within 30 days of treatment start
RA disease duration at start of of follow-up (<5, 5+ years)	Baseline characteristic and potential confounder	SRQ	Value at treatment start as recorded in the SRQ
DAS28 at start of follow-up (continuous)	Baseline characteristic and potential confounder	SRQ	Most recent value recorded in a rheumatology visit recorded in the SRQ within 30 days of treatment start
Concomittant csDMARDs at start of	Baseline characteristic and potential	SRQ	Value at treatment start as recorded in the

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Table 4. Definitions of baseline characteristics that are considered potential confounders

Variable	Role	Data source(s)	Operational definition (ICD-10)
follow-up (Y/N)	confounder		SRQ
Oral steroids at start of follow-up (Y/N)	Baseline characteristic and potential confounder	SRQ	Value at treatment start as recorded in the SRQ

Note: Some of variables listed above will be included in the Cox regression models.

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).

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:

Table 5. Definitions of VTE risk factors

Variable	Data source(s)	Operational definition (ICD10)
Age at start of of follow-up	SRQ	
Previous VTE (Y/N)	Main diagnosis in the Patient Register (in- or out-patient component.	I26, I80-I82
Undergoing major surgery from date of hospital admission to one month after date of discharge (Y/N)	Any intervention code recorded in the National Patient Register in the three months prior to cohort entry	Intervention codes starting with: J, F, L, N
Myocardial infraction (MI) (within previous 3 months prior to index date)	Main diagnosis in the Patient Register (in- or	I21, I22

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Table 5. Definitions of VTE risk factors

Variable	Data source(s)	Operational definition (ICD10)
(Y/N)	out-patient component.	
History of heart failure (Y/N)	Main diagnosis in the Patient Register (in- or out-patient component.	I50
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (Y/N)	Dispensation recorded in the prescribed drug register	ATC=G03A, G03CA
History of Malignancy (ever/never)	The Cancer register	All except benign malignancies
History of Diabetes mellitus (last 5 years) (Y/N)	The Patient Register	E10-E14, O24
History of hypetension (Y/N)	The Patient Register	I10-I15
Inpatient care because of RA (i.e., RA as main diagnostic listing; from date of admission to date after discharge)	Main diagnoses from the Inpatient component of Patient Register.	M05, M060, M062, M063, M068, M069, M123

6. HANDLING OF MISSING VALUES

No imputation of missing values is performed. For baseline tables, a missing category will be added for patients with missing a characteristic (categorical) of interest. For the multivariable Cox proportional hazard regressions, two models will be provided: 1) a complete case analysis and 2) a missing category analysis.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Statistical analysis will be the responsibility of the Clinical Epidemiology Division of the Department of Medicine, Karolinska Institutet, Stockholm, Sweden. All work will be performed 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.

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7.1. Statistical methods

Descriptive statistics for each of the cohorts will be presented for all baseline characteristics. Descriptive statistics for the ts/bDMARD exposed cohorts will be additionally displayed separately by the number of previous b/tsDMARDs (0, 1-2, 3+).

Crude incidence rates and the number of events will be tabulated for each cohort and outcome. They will also be presented by the number of previous b/tsDMARDs for the relevant cohorts (0, 1-2, 3+ previous b/tsDMARDs). Age/sex-standardized rates will calculated for each outcome, using the tofacitinib cohort as standard; a direct standardization approach will be implemented, using the age-sex-distribution of person-time in the tofacitinib cohort. The approach for estimation of the 95% confidence intervals follows the methods described in the Rothman et al. textbook entitled Modern Epidemiology (p.242); Wald confidence limits are estimated for the log rate.

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.

Pending feasibility, adjusted hazard ratios will be estimated with Cox proportional hazards regression using attained age as the time scale. The comparisons to be made will be: tofacitinib vs. bDMARD, tofacitinib vs. B/tsDMARD-naïve, tofacitinib vs. general popuation. There will not be conditioning on the matching set in the Cox models. To assess the potential confounding effect of baseline covariates and potential impact of missingness, four models will be fit:

Model #1 will adjust for sex, number of previous b/tsDMARDs (0, 1-2, 3+) and calendar year of entry.

Model #2 will adjust for sex, number of previous b/tsDMARDs, calendar year of entry and additionally for pre-baseline comorbidities and healthcare utilization: prior number of days in inpatient care, history of infection, cancer, myocardial infarction (MI), diabetes, chronic obstructive pulmonary disease (COPD), and joint replacement surgery, see Table 3, Table 4, and Table 5 for definitions.

Model #3 will adjust for all these covariates, but also include RA-specific covariates (pertaining to status at treatment start): rheumatoid-factor (RF) status, health assessment questionnaire (HAQ), RA disease duration, disease activity score on 28 joints (DAS28), use of DMARDs and steroids.

There are expected to be non-negligible amounts of missing data on DAS28 and HAQ, so to ensure that any difference between Model #2 and #3 is not due to loss of observations, we will also fit an additional model, **Model #4**, where these covariates will be modeled as categorical (split in quartiles), and with missing information coded as a separate category.

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Due to data availability, Model #3 and #4 will only be fitted for the tofacitinib and bDMARD cohorts ascertained through SRQ.

Adjusted hazard ratios will additionally be estimated within each number of previous b/tsDMARD groups (0,1-2, 3+) by fitting separate Cox proportional hazards models in each group with covariates as described previously (minus the number of previous b/tsDMARDs variable). Stratified Cox models will also be fitted for each outcome with the previous number of b/tsDMARD variable as the stratum variable, and adjustments as listed above.

Covariates will be parameterized as described in Table 3, Table 4, and Table 5 above. Cohort-outcome combinations with less than 5 events will not included in Cox proportional hazards regressions; in such a case, only numbers, crude and age/sex-adjusted incidence rates will be estimated.

SAS version 9.4 will be used for all analyses.

7.2. Statistical Analyses

Crude incidence rates and number of events will be presented by age subgroups (age <65 vs. ≥65 years at cohort entry) for all outcomes and all cohorts. Crude rates will also be estimated (using the primary approach for follow-up) for:

(1) the outcome of VTE stratified by number of VTE risk factors (≥1 VTE risk factors versus no VTE risk factors)

(2) the outcomes of MACE and MI stratified by number of CV risk factors (≥1 CV risk factors versus no CV risk factors)

(3) the outcome of VTE will be 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)

(4) 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)

(5) For lymphoma, incidence rates will be stratified by lymphoma subtypes; not limited but including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphatic leukemia

7.2.1. Sample Size Calculations

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

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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 6 and Table 7 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.

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 6), 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 6). 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 6) 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 7).

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

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Table 6. 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

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Table 7. 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
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.

7.2.2. Safety Analyses

Not applicable

7.2.3. Summary of Analyses

Primary Analyses:

- **Descriptive statistics** for each of the cohorts will be presented for all baseline characteristics. **[Table 1] Descriptive statistics** for the ts/bDMARD exposed cohorts will be additionally displayed separately by the number of previous b/tsDMARDs (0, 1-2, 3+). **[Table 2]**

- **Crude incidence rates** and the number of events will be tabulated for each cohort and outcome. They will also be presented by the number of previous b/tsDMARDs for the relevant cohorts (0, 1-2, 3+ previous b/tsDMARDs). Age/sex-standardized rates will calculated for each outcome, using the tofacitinib cohort as standard; a direct standardization approach will be implemented, using the age-sex-distribution of person-time in the tofacitinib cohort. The approach for estimation of the 95% confidence intervals follows the methods described in the Rothman et al. textbook entitled Modern Epidemiology (p.242); Wald confidence limits are estimated for the log rate. **[Table 3]**

- The **primary analysis** for **non-malignancy** and **non-all-cause mortality** outcomes will include followed up until the first of the following time points: event of interest, first date of emigration from Sweden, date of death, end of data collection, or end of treatment +90 days. Where end of treatment was defined as the end of treatment date recorded by the treating rheumatologist in the SRQ. When a patient initiated a new therapy within the 90 day extention, the follow-up time and events during the overlapping period was assigned to both treatments. **[Table 3]**

- The **primary analysis** for **malignancy** and **All-Cause Mortality** will be an 'ever exposed' analysis. For the ever exposed approach end of follow-up was defined as the first of the following: event of interest, first date of emigration from Sweden, date of death, or end of data collection. **[Table 3]**

- Pending feasibility, **adjusted hazard ratios** will be estimated with Cox proportional hazards regression using attained age as the time scale. The comparisons to be made will be: tofacitinib vs. bDMARD, tofacitinib vs. B/tsDMARD-naïve, tofacitinib vs. general popuation. There will not be conditioning on the matching set in the Cox models. **[Table 4]**

- Results from adjusted Cox regressions comparing the tofacitinib cohort to the bDMARD cohort will also be stratified by the number of previous biologic drugs [**Table 5**]

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Secondary Analyses:

- The **secondary analysis** for malignancy and all-cause mortality will be a censor at switch approach end of follow-up was defined as the first of the following dates: event of interest, first date of emigration from Sweden, date of death, end of data collection, or date of switch to a tsDMARD (in the non-tofacitinib cohorts), or date of switch to a non-tsDMARD (in the tofacitinib cohort). 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). **[Table 3, Table 4, Table 5]**

Crude incidence rates be estimated (using the primary approach for follow-up) and number of events will be presented by:

- Age subgroups (age <65 vs. ≥65 years at cohort entry) for all outcomes and all cohorts. [**Table 6**]. The interim reports will include the following outcomes: hospitalized infections, cancer, and all-cause mortality, while the final report will include all outcomes.

- Number of VTE risk factors for the outcome of VTE [**Table 8**]. These analyses will be in the final report.

- Number of CV risk factors for the outcomes of MACE and MI [**Table 9**]. These analyses will be in the final report.

- 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). [**Table 10**]. These analyses will be in the final report.

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). [**Table 11**]. These analyses will be in the final report.

Sensitivity Analyses:

- Additional 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 in the SRQ. These sensitivity analysis results will be presented as summary statistics of those with and without previous tofacitinib use. [**Table 7**]

- In the final report, an additional sensitivity analysis will be conducted for the malignancy outcomes restricted to patients with no prior history of malignancy [**Tables 12, 13**].

In addition, the final report will include the number of births or pregnancies surviving up to 25 weeks of gestation

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To summarize:

- The interim reports will include Tables 1-7, where Table 6 will only include the outcomes of hospitalized infections, malignancies, and all-cause mortality.

- The final report will include Tables 1-13, where Table 6 will include all outcomes. The final report will also include the number of births or pregnancies surviving up to 25 weeks of gestation.

Reports summarizing the rate of safety events of interest will be provided by ARTIS to Pfizer on a semi-annual basis. 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.

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 4 (in the protocol) 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).[3] 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.

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 in the protocol. 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 methotrexate (MTX) specifically will be described if sample sizes are sufficient, in the interim and final reports. 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 multivariable regression. The final report

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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. If feasible, for the final study report, the ICD-algorithm will be 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).

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

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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 used. To summarize the data from the Cox-proportional hazard regression models from the ARTIS, BIOBADASER, BSRBR, and RABBIT registries, and to allow for an overall risk assessment, a fixed effects meta-analysis will be conducted as it was not expected that the associations between the exposures and outcomes would vary substantially between the four registries. The inverse variance method in the fixed effects meta-analyses, which weighted the registry-specific estimates of association by the inverse of the within-registry variance, will be applied. This approach as several limitations, including differences in the type of variables available in each registry to be included in the adjusted analyses. Additionally, comparator cohorts may be defined differently in the registries.

The meta-analytic analyses are beyond the scope of this SAP and will be handled separately.

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8. LIST OF TABLES AND TABLE SHELLS

Table 1. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts

	Main cohort	**Comparator cohorts**		
Status at entry	Tofacitinib	bDMARD	b/tsDMARD-naïve	General population
N patients				
Demographics				
Age (median, IQR)				
Sex (% females)				
Disease-related characteristics				
Rheumatoid factor positive (%)				
Rheumatoid factor positive missing (%)				
Disease duration (median, IQR)				
Disease duration missing (%)				
Calendar year of dx (median)				
DAS28 (median, IQR)				
DAS28 missing (%)				
HAQ (median, IQR)				
HAQ missing (%)				
Concomitant DMARDs (%)				
Concomitant DMARDs missing (%)				
Oral steroids (%)				
Oral steroids missing (%)				
Combination therapy with MTX (%) ***				
NSAIDs (%)				
NSAIDs missing (%)				
Smoking				
Ever				
Never				
Missing				
csDMARDs (%)				
Number of previous b/tsDMARDs				
0				
1-2				
3+				
Disease history				
Serious infection (%)				
Opportunistic infection (%)				
Herpes zoster (%)				

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Table 1. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts

	Main cohort	Comparator cohorts		
Fracture (%)				
Malignancies, excl. NMSC (%)				
NMSC (%)				
Lymphoma (%)				
Lung cancer (%)				
Joint replacement surgery (%)				
COPD (%)				
Diabetes mellitus (%)				
MI (%)				
Hypertension (%)				
Statin use (%)				
CHD (%)				
CKD (%)				
Stable angina pectoris (%)				
Procedures to treat CVD (%)				
VTE (%)				
Undergoing major surgery from date of hospital admission to one month after date of discharge (%)				
Heart failure (%)				
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)				
Inpatient care because of RA (%)				
Total days in hosp (median, IQR)				
Reason for discontinuing previous b/tsDMARD				
Safety, of those with info. (%)				
Inefficacy, of those with info. (%)				
Non-medical switch, of those with info. (%)				
Other, of those with info. (%)				
Missing, of total (%)				

Notes: Restricted comparator cohorts to diagnoses of RA that occurred after 1st January 2012 to ensure a contemporaneous cohort. Procedures to treat CVD include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI)).

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; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; MTX, methotrexate

chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI,

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Table 1. Baseline Characteristics of Swedish RA Patients Initiating Tofacitinib and Comparator Cohorts

	Main cohort	Comparator cohorts

myocardial infarction; MTX, methotrexate
*** Pending feasibility

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Table 2. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Line of Therapy

	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 positive missing (%)						
Disease duration (median, IQR)						
Disease duration missing (%)						
Calendar year of dx (median)						
DAS28 (median, IQR)						
DAS28 missing (%)						
HAQ (median, IQR)						
HAQ missing (%)						
Concomitant DMARDs (%)						
Concomitant DMARDs missing (%)						
Oral steroids (%)						
Oral steroids missing (%)						
Combination therapy with MTX (%)***						
NSAIDs (%)						
NSAIDS missing (%)						
Smoking						
Ever						
Never						
Disease history						

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Table 2. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Line of Therapy

	0 previous b/tsDMARDs		1-2 previous b/tsDMARDs		3+ previous b/tsDMARDs	
Serious infection (%)						
Opportunistic infection (%)						
Herpes zoster (%)						
Fracture (%)						
Malignancies, excl. NMSC (%)						
NMSC (%)						
Lymphoma (%)						
Lung cancer (%)						
Joint replacement surgery (%)						
COPD (%)						
Diabetes mellitus (%)						
MI (%)						
Hypertension (%)						
Statin use (%)						
CHD (%)						
CKD (%)						
Stable angina pectoris (%)						
Procedures to treat CVD (%)						
VTE (%)						
Undergoing major surgery from date of hospital admission to one month after date of discharge (%)						
Heart failure (%)						
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)						
Inpatient care because of RA (%)						
Total days in hosp (median, IQR)						

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Table 2. Baseline Characteristics of Swedish Patients Initiating Tofacitinib or bDMARD, Stratified by Line of Therapy

	0 previous b/tsDMARDs		1-2 previous b/tsDMARDs		3+ previous b/tsDMARDs	
Reason for discontinuing previous b/tsDMARD						
Safety, of those with info. (%)						
Inefficacy, of those with info. (%)						
Non-medical switch, of those with info. (%)						
Other, of those with info. (%)						
Missing, of total (%)						

Notes: Restricted comparator cohorts to diagnoses of RA that occurred after 1st January 2012 to ensure a contemporaneous cohort. Procedures to treat CVD include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI)).
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; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; MTX, methotrexate
*** Pending feasibility

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Hospitalized infections							
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							
Opportunistic infections							
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							
Herpes Zoster (hospitalized)							
Tofacitinib							
0 previous b/tsDMARDs							
1-2 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	3+ previous b/tsDMARDs							
	bDMARD							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	B/tsDMARD-naïve Patients							
	General Population							
Hepatitis								
	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							
Fractures								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	bDMARD							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
3+ previous b/tsDMARDs							
B/tsDMARD-naïve Patients							
General Population							
Cancer, ever exposed*							
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							
Cancer, treatment switch**							
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 v							
B/tsDMARD-naïve Patients							
General Population							
NMSC, ever exposed*							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	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							
NMSC, treatment switch**								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous v							
	3+ previous b/tsDMARDs							
	bDMARD							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	B/tsDMARD-naïve Patients							
	General Population							
Lung Cancer, ever exposed*								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	bDMARD							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	B/tsDMARD-naïve Patients							
	General Population							
Lung Cancer, treatment switch**								
	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							
Lymphoma (overall), ever exposed*								
	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							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
B/tsDMARD-naïve Patients							
General Population							
Lymphoma (overall), treatment switch **							
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							
Non-Hodgkin Lymphoma, ever exposed*							
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							
Non-Hodgkin Lymphoma,							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
treatment switch **								
	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							
Hodgkin lymphoma, ever exposed*								
	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							
Hodgkin lymphoma, treatment switch**								
	Tofacitinib							
	0 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	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							
Chronic Lymphatic Leukemia, ever exposed*								
	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							
Chronic Lymphatic Leukemia, treatment switch **								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	bDMARD							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	B/tsDMARD-naïve Patients							
	General Population							
CV events (MACE)								
	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							
Myocardial infarction (MI)								
	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							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	General Population							
VTE (DVT and PE)								
	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							
DVT								
	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							
PE								
	Tofacitinib							
	0 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	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							
Congestive Heart Failure								
	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							
GI perforations								
	Tofacitinib							
	0 previous b/tsDMARDs							
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	bDMARD							
	0 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	1-2 previous b/tsDMARDs							
	3+ previous b/tsDMARDs							
	B/tsDMARD-naïve Patients							
	General Population							
PML, ever exposed*								
	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							
PML, treatment switch**								
	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							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Interstitial lung disease***								
	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							
All-cause mortality (overall) , ever exposed*								
	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							
All-cause mortality, treatment switch **								
	Tofacitinib							
	0 previous b/tsDMARDs							

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Table 3. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years)

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
	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							
All-cause mortality (among patients with a combination therapy with MTX) ***								
	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							

Notes:
IR Incidence Rate; 95% CI 95% confidence interval; Std IR standardised to the age/sex distribution in the tofacitinib cohort.
*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. A 90-day risk window will be applied to the censoring at switch approach.
***pending feasibility

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	bDMARD								
	B/tsDMARD-naïve								
	General population								
Opportunistic infections	bDMARD								
	B/tsDMARD-naïve								
	General population								
Herpes Zoster (hospitalized)	bDMARD								
	B/tsDMARD-naïve								
	General population								
Heptatitis	bDMARD								
	B/tsDMARD-naïve								
	General population								
Fractures	bDMARD								
	B/tsDMARD-naïve								
	General population								
Cancer, ever exposed*	bDMARD								
	B/tsDMARD-naïve								
	General population								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Cancer, treatment switch**	bDMARD								
	B/tsDMARD-naïve								
	General population								
NMSC, ever exposed*	bDMARD								
	B/tsDMARD-naïve								
	General population								
NMSC, treatment switch**	bDMARD								
	B/tsDMARD-naïve								
	General population								
Lung Cancer	bDMARD								
	B/tsDMARD-naïve								
	General population								
Lung Cancer, treatment switch **	bDMARD								
	B/tsDMARD-naïve								
	General population								
Lymphoma (overall), ever exposed *	bDMARD								
	B/tsDMARD-naïve								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population								
Lymphoma (overall), treatment switch **	bDMARD								
	B/tsDMARD-naïve								
	General population								
Non-Hodgkin Lymphoma, ever exposed *	bDMARD								
	B/tsDMARD-naïve								
	General population								
Non-Hodgkin Lymphoma, treatment switch **	bDMARD								
	B/tsDMARD-naïve								
	General population								
Hodgkin lymphoma, ever exposed *	bDMARD								
	B/tsDMARD-naïve								
	General population								
Hodgkin lymphoma, treatment switch **	bDMARD								
	B/tsDMARD-naïve								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	General population								
Chronic Lymphatic Leukemia, ever exposed *	bDMARD								
	B/tsDMARD-naïve								
	General population								
Chronic Lymphatic Leukemia, treatment switch **	bDMARD								
	B/tsDMARD-naïve								
	General population								
CV events (MACE)	bDMARD								
	B/tsDMARD-naïve								
	General population								
Myocardial infarction (MI)	bDMARD								
	B/tsDMARD-naïve								
	General population								
VTE	bDMARD								
	B/tsDMARD-naïve								
	General population								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
DVT	bDMARD								
	B/tsDMARD-naïve								
	General population								
PE	bDMARD								
	B/tsDMARD-naïve								
	General population								
CHF	bDMARD								
	B/tsDMARD-naïve								
	General population								
GI perforations	bDMARD								
	B/tsDMARD-naïve								
	General population								
PML, ever exposed*	bDMARD								
	B/tsDMARD-naïve								
	General population								
PML, treatment switch**	bDMARD								
	B/tsDMARD-naïve								
	General population								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Interstitial lung disease***	bDMARD								
	B/tsDMARD-naïve								
	General population								
All-cause mortality (overall), ever exposed *	bDMARD								
	B/tsDMARD-naïve								
	General population								
All-cause mortality (overall), treatment switch **	bDMARD								
	B/tsDMARD-naïve								
	General population								
All-cause mortality (among patients with a combination therapy with MTX) ***	bDMARD								
	B/tsDMARD-naïve								
	General population								

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Table 4. Results from Adjusted Cox Regressions Comparing Main Cohort to Comparator Cohorts for Each Outcome

Outcome	Tofacitinib versus	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI

Notes:
HR: Hazard Ratio. CI: Confidence Interval. VTE: venous thromboembolism.
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, 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.
*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. A 90-day risk window will be applied to the censoring at switch approach.
***pending feasibility

Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Hospitalized infections	0								
	1-2								
	3+								
	Aggregate estimate								
Opportunistic infections	0								
	1-2								
	3+								
	Aggregate estimate								
Herpes Zoster (hospitalized)	0								
	1-2								
	3+								
	Aggregate estimate								
Heptatitis	0								
	1-2								

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Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	3+								
	Aggregate estimate								
Fractures	0								
	1-2								
	3+								
	Aggregate estimate								
Cancer, ever exposed*	0								
	1-2								
	3+								
	Aggregate estimate								
Cancer, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
NMSC, ever exposed*	0								
	1-2								
	3+								
	Aggregate estimate								
NMSC, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
Lung Cancer, ever exposed *	0								
	1-2								
	3+								
	Aggregate estimate								

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Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Lung Cancer, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
Lymphoma (overall), ever exposed *	0								
	1-2								
	3+								
	Aggregate estimate								
Lymphoma (overall), treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
Non-Hodgkin Lymphoma, ever exposed *	0								
	1-2								
	3+								
	Aggregate estimate								
Non-Hodgkin Lymphoma, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
Hodgkin lymphoma, ever exposed *	0								
	1-2								

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Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	3+								
	Aggregate estimate								
Hodgkin lymphoma, treatment switch **	0								
	1-2								
	3+								
	Aggregate estimate								
Chronic Lymphatic Leukemia, ever exposed *	0								
	1-2								
	3+								
	Aggregate estimate								
Chronic Lymphatic Leukemia, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
CV events (MACE)	0								
	1-2								
	3+								
	Aggregate estimate								
Myocardial infarction (MI)	0								
	1-2								
	3+								
	Aggregate estimate								
VTE	0								
	1-2								

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Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
	3+								
	Aggregate estimate								
DVT	0								
	1-2								
	3+								
	Aggregate estimate								
PE	0								
	1-2								
	3+								
	Aggregate estimate								
CHF	0								
	1-2								
	3+								
	Aggregate estimate								
GI perforations	0								
	1-2								
	3+								
	Aggregate estimate								
PML, ever exposed*	0								
	1-2								
	3+								
	Aggregate estimate								
PML, treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								

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Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Interstitial lung disease***	0								
	1-2								
	3+								
	Aggregate estimate								
All-cause mortality (overall), ever exposed *	0								
	1-2								
	3+								
	Aggregate estimate								
All-cause mortality (overall), treatment switch**	0								
	1-2								
	3+								
	Aggregate estimate								
All-cause mortality (among patients with a combination therapy with MTX) ***	0								
	1-2								
	3+								
	Aggregate estimate								

Notes:
HR: Hazard Ratio. CI: Confidence Interval. VTE: venous thromboembolism.
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, 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.
*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

Table 5. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI

of follow-up; whichever occurs first. A 90-day risk window will be applied to the censoring at switch approach.
***pending feasibility

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Table 6. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person Years) – Patients Aged Less Than 65 Years vs. 65 Years and Older at Cohort Entry

Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Repeat rows of Table 3 for all outcomes with one row per age group for comparison							

Notes:
Restricted comparator cohorts to diagnoses of RA that occurred after 1st January 2012 to ensure a contemporaneous cohort. Analysis was only made for comparisons where both cohorts had at least 5 observed events (therefore, additional outcomes from **5.2 Safety endpoints** may be reported than currently presented in this table shell). Some rows were intentionally deleted.
IR Incidence Rate; 95% CI 95% confidence interval; Std IR standardized to the age/sex distribution in the tofacitinib cohort.
*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. A 90-day risk window will be applied to the censoring at switch approach.

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Table 7. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
N patients		
Demographics		
Age (median, IQR)		
Sex (% females)		
Disease-related characteristics		
Rheumatoid factor positive (%)		
Rheumatoid factor positive missig (%)		
Disease duration (median, IQR)		
Disease duration missing (%)		
Calendar year (median)		
DAS28 (median, IQR)		
DAS28 missing (%)		
HAQ (median, IQR)		
HAQ missing (%)		
Concomitant DMARDs (%)		
Concomitant DMARDs missing (%)		
Oral steroids (%)		
Oral steroids missing (%)		
Combination therapy with MTX (%) ***		
NSAIDs (%)		
NSAIDs missing (%)		
Smoking		
Ever		
Never		

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Table 7. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
Number of previous b/tsDMARDs		
0		
1-2		
3+		
Disease history		
Serious infection (%)		
Opportunistic infection (%)		
Herpes zoster (%)		
Fracture (%)		
Malignancies, excl. NMSC (%)		
NMSC (%)		
Lymphoma (%)		
Lung cancer (%)		
Joint replacement surgery (%)		
COPD (%)		
Diabetes mellitus (%)		
MI (%)		
Hypertension (%)		
Statin use (%)		
CHD (%)		
CKD (%)		
Stable angina pectoris (%)		
Procedures to treat CVD (%)		
VTE (%)		
Undergoing major surgery from date of hospital admission to one month after date of		

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Table 7. Baseline Characteristics of Swedish RA Patients Initiating bDMARDs, by Previous Tofacitinib Use

Status at entry	No previous tofacitinib use	Previous tofacitinib use
discharge (%)		
Heart failure (%)		
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (%)		
Inpatient care because of RA (%)		
Total days in hosp (median, IQR)		
Reason for discontinuing previous biologic		
Safety, of those with info. (%)		
Inefficacy, of those with info. (%)		
Non-medical switch, of those with info. (%)		
Other, of those with info. (%)		
Missing, of total (%)		

Notes: Procedures to treat CVD include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI)).
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; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; MTX, methotrexate
*** Pending feasibility

Table 8. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by VTE Risk factors

	Among Patients with no VTE risk factors						
Cohort	**Patients**	**Events**	**Person-Years**	**IR**	**95% CI**	**Std IR**	**Mean follow-up, years**
VTE							
Tofacitinib							
0 previous b/tsDMARDs							

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Table 8. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by VTE Risk factors

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							
	Among Patients with ≥1 VTE risk factors						
VTE							
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							

Table 9. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by CV Risk factors

	Among Patients with no CV risk factors						
Cohort	**Patients**	**Events**	**Person-Years**	**IR**	**95% CI**	**Std IR**	**Mean follow-up, years**
MACE							

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Table 9. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by CV Risk factors

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							
	Among Patients with ≥1 CV risk factors						
MACE							
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							
	Among Patients with no CV risk factors						
MI							
Tofacitinib							
0 previous b/tsDMARDs							

Table 9. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by CV Risk factors

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							
	Among Patients with ≥1 CV risk factors						
MI							
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							

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Table 10. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors

	Time period prior to 31 January 2020						
Cohort	**Patients**	**Events**	**Person-Years**	**IR**	**95% CI**	**Std IR**	**Mean follow-up, years**
VTE							
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							
	Time period after 31 January 2020						
VTE							
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							

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Table 11. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

	Time period prior to June 2021						
Cohort	**Patients**	**Events**	**Person-Years**	**IR**	**95% CI**	**Std IR**	**Mean follow-up, years**
NMSC, ever exposed							
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							
	Time period after June 2021						
NMSC, ever exposed							
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							

Table 11. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

	Time period before June 2021						
Lung Cancer, ever exposed							
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							
	Time period after June 2021						
Lung Cancer, ever exposed							
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							
	Time period before June 2021						
Lymphoma, ever exposed							
Tofacitinib							
0 previous b/tsDMARDs							
1-2 previous b/tsDMARDs							
3+ previous b/tsDMARDs							
bDMARD							
0 previous b/tsDMARDs							
1-2 previous b/tsDMARDs							

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Table 11. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

3+ previous b/tsDMARDs							
B/tsDMARD-naïve Patients							
General Population							
	Time period after June 2021						
Lung Cancer, ever exposed							
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							
	Time period before June 2021						
MACE							
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							
	Time period after June 2021						
MACE							
Tofacitinib							
0 previous b/tsDMARDs							
1-2 previous b/tsDMARDs							
3+ previous b/tsDMARDs							

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Table 11. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person-Years) – Stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with malignancy and CV risk factors

bDMARD							
0 previous b/tsDMARDs							
1-2 previous b/tsDMARDs							
3+ previous b/tsDMARDs							
B/tsDMARD-naïve Patients							
General Population							
	Time period before June 2021						
MI							
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							
	Time period before June 2021						
MI							
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							

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Table 12. Total Number of Events, Crude and Standardized Incidence Rates (per 100 Person Years) – Restricted to Patients without prior history of malignancy

	Cohort	Patients	Events	Person-Years	IR	95% CI	Std IR	Mean follow-up, years
Repeat rows of Table 3 for all malignancy outcomes								

Notes:
Restricted comparator cohorts to diagnoses of RA that occurred after 1st January 2012 to ensure a contemporaneous cohort. Analysis was only made for comparisons where both cohorts had at least 5 observed events (therefore, additional outcomes from **5.2 Safety endpoints** may be reported than currently presented in this table shell). Some rows were intentionally deleted.
IR Incidence Rate; 95% CI 95% confidence interval; Std IR standardized to the age/sex distribution in the tofacitinib cohort.
*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. A 90-day risk window will be applied to the censoring at switch approach.

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Table 13. Results from Adjusted Cox Regressions Comparing the Tofacitinib Cohort to the bDMARD Cohort, Stratified by the Number of Previous Biologic Drugs

Outcome	Number of previous b/tsDMARDs	HRa	95% CI	HRb	95% CI	HRc	95% CI	HRd	95% CI
Repeat rows of Table 5 for all malignancy outcomes									

Notes:
HR: Hazard Ratio. CI: Confidence Interval. VTE: venous thromboembolism.
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, 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.
*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. A 90-day risk window will be applied to the censoring at switch approach.
***pending feasibility

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APPENDICES

Not applicable

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NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Title	Meta-Analysis for Tofacitinib RA PASS
Protocol number	A3921312, A3921314, A3921316, A3921317
Version identifier of the study report	1.0
Date	26-Jul-2026
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Country(-ies) of study	United Kingdom (A3921312) Sweden (A3921314) Spain (A3921316) Germany (A3921317)

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Appendix 1. META ANALYSIS STATISTICAL ANALYSIS PLAN

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	adalimumab
ARTIS	Anti-Rheumatic Treatment in Sweden
bDMARD	biologic disease-modifying antirheumatic drug
BIOBADASER	Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases
BSRBR-RA	British Society for Rheumatology Biologics Register for Rheumatoid Arthritis
CI	confidence interval
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CV	cardiovascular
DMARD	disease-modifying antirheumatic drug
DVT	deep vein thrombosis
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
ETA	etanercept
EU	European Union
HR	hazard ratio
IL	interleukin
INF	infliximab
JAK	Janus kinase
IR	incidence rate
MACE	major adverse cardiovascular events
MI	myocardial infarction
NI	non-interventional

Abbreviation	Definition
NSAID	nonsteroidal anti-inflammatory drug
NMSC	non-melanoma skin cancer
PASS	post-authorization safety study
PE	pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PY	person-years
RA	rheumatoid arthritis
Q1	first quartile
Q3	third quartile
RABBIT	German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	risk management plan
SAP	statistical analysis plan
TB	tuberculosis
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
VTE	venous thromboembolism

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2. 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 comorbidities.

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 nonsteroidal 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.[3,6] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[4] 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 comorbidities 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 endpoints overall and within strata of disease severity, treatment history, and other concomitant therapy. 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.[5] 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

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treated with tofacitinib for rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma 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.

To enable assessment of safety endpoints of special interest, including rare events and endpoints with long latency periods, Pfizer implemented post-approval, active surveillance studies of tofacitinib-exposed patients using actively collected prospective data in the BSRBRRA register (A3921312 study), the ARTIS register (A3921314 study), the BIOBADASER register (A3921316 study), and the RABBIT register (A3921317 study). These four studies were designated as PASS and were conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

The four PASS studies aimed to compare the rates of safety events of interest in RA patients treated with tofacitinib to those in the comparator cohorts. The analysis of observations within each individual study was based on data accumulated in the registries within the corresponding country.

Additionally, a meta-analysis integrated country-specific results, providing a more precise and robust evaluation of the risks associated with tofacitinib in the post-approval real-world setting to support safe prescribing practices and regulatory oversight. A quantitative meta-analysis permitted 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 revealed between-study heterogeneity such that a subset of more comparable studies could be included in a single estimate. Heterogeneity was expected, for example, due to differences in local prescribing practices, patient populations, competing risks, and prevalence of comorbidities and risk factors. Such heterogeneity existed 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 was unknown.

3. RESEARCH QUESTION AND OBJECTIVES

- To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV, MACE, MI, VTE (DVT and PE) and other specified endpoints, including fractures, among patients with RA who initiate tofacitinib.

- To estimate the rates of the same events of interest among the comparator groups.

4. RESEARCH METHODS

4.1. Study Design

A3921312 was an active surveillance study using existing data within the existing British Society for Rheumatology Biologics Register for RA (BSRBR-RA), an ongoing prospective observational cohort study started in 2001, which had the primary aim to study the safety of new therapies for RA during routine post-marketed clinical use.

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A3921314 was 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 were deterministic based on unique patient identifiers.

A3921316 was an active surveillance study using existing data within BIOBADASER, an ongoing prospective observational cohort study started in 2000 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use.

A3921317 was an active surveillance study using existing data within the existing German register Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT), an ongoing prospective observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use. RABBIT is being conducted by Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center) (DFRZ), with industry funding.

Refer to the individual study protocols and SAPs for details on study designs.

4.2. Subjects

Refer to the individual study protocols and SAPs for details on source population and eligibility criteria for the study population.

4.3. Variables

The following are pre-specified safety endpoints of interest that were included in the meta-analysis. Some studies have additional endpoints of interest that are unique to them and therefore cannot be pooled across studies.

The following endpoints were pooled across all four PASS.

1. All-cause mortality
2. Malignancies (overall, excluding NMSC)
3. NMSC
4. Lung Cancer
5. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia)
6. Herpes zoster (hospitalized)
7. Fractures
8. Major Adverse Cardiovascular Events (MACE)
9. Deep vein thrombosis (DVT)
10. Pulmonary embolism (PE)
11. Venous Thromboembolism (VTE (DVT/PE))
12. Gastrointestinal (GI) perforations
13. Progressive multifocal leukoencephalopathy (PML)

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The following endpoints were pooled across A3921312, A3921316 and A3921317. These endpoints were not reported in A3921314 study.

14. Pneumonia
15. Bone/join infection
16. Tuberculosis (TB)
17. Hematologic disorders
18. Agranulocytosis (Decreased White Blood Cells)
19. Disorders of the nervous system (excluding infections)
20. Peripheral neuropathy

4.4. Data Sources And Measurement

The names of the registries are provided in Table 1. Refer to individual study reports for details on the sources of data and details of methods of collection and measurement.

Table 1. Registries Contributing Observations

PASS	Country	Registry
A3921312	United Kingdom	British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBRRA)
A3921314	Sweden	Anti Rheumatic Treatment in Sweden (ARTIS)
A3921316	Spain	Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER)
A3921317	Germany	German Registry Rheumatoide Arthritis: Beobachtung der Biologika Therapie (RABBIT)

4.5. Study Size

A3921312, A3921314, A3921316, and A3921317 were active surveillance studies and were not intended to test a pre-specified statistical hypothesis. No minimum sample size was required.

For A3921312, the study enrolment goal was 500 patients in the tofacitinib arm, but success depended largely on use of tofacitinib in UK. Enrolment would not be capped at 500 but continue throughout the study period. Based on the first 12 months of enrolment of tofacitinib exposed patients in BSRBR, 110 patients were 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 remained constant over the period.

For A3921314, all eligible patients in the Swedish registers were to be included, with no upper limit on the sample size. Based on the first 9 months of enrolment of tofacitinib exposed patients in ARTIS, 344 patients were projected to be enrolled in the first 24 months,

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allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remained constant over the period.

For A3921316, based on the first 10 months of enrolment of tofacitinib exposed patients in BIOBADASER, 187 patients were 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 remained constant over the period.

For A3921317, the targeted sample size for tofacitinib treated patients was 500. Enrolment would not be capped at 500 but continue throughout the study period. Based on the first 16 months of enrolment of tofacitinib exposed patients in RABBIT, 558 patients were 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 remained constant over the period.

Contingent on sufficient sample size, the protocols included conducting quantitative, confounding controlled comparisons. The power to detect a 2-fold difference in event rates between tofacitinib initiators and bDMARD-initiators for various incidence rates based on the projected sample sizes were presented in the respective study protocols.

4.6. Statistical methods

4.6.1. Treatment/Cohort Labels

Table 2 provides a comparison of the cohorts across the studies. Refer to the respective study reports for more details on cohort definitions.

Considering the heterogeneity in the comparator cohorts across the 4 studies, the meta-analysis planned to include the following two cohorts:

- Main Cohort: Tofacitinib Cohort in each study. This cohort would be referred to as “Tofacitinib Cohort” in the meta-analysis.
- Comparator Cohort: This cohort would be referred to as “bDMARD Cohort” in the meta-analysis. The following cohorts were regarded as comparable because, in each study, they all included eligible patients who initiated bDMARD therapy after enrolling in the registry. In contrast, the Historical bDMARD Cohort in A3921316 did not meet this criterion and was therefore not considered comparable.
    - “bDMARD Exposed” Cohort in A3921312
    - “Treated with bDMARD” Cohort in A3921314 and A3921317
    - Contemporaneous “Treated with bDMARD” Cohort in A3921316

While cohorts of RA patients not treated with bDMARD were present in studies A3921312, A3921314, and A3921316, they are not comparable and therefore would not be pooled in the meta-analysis. In A3921312, the “bDMARD naïve” cohort excluded patients with any prior bDMARD or tofacitinib use. In contrast, the “ts/bDMARD naïve” cohort in A3921314 and the “nbDMARD cohort” in A3921317 excluded patients with previous exposure to either tsDMARDs or bDMARDs. Additionally, the “nbDMARD cohort” in A3921317 required failure of at least one DMARD and the initiation of a new DMARD, a criterion not required for inclusion in the “ts/bDMARD naïve” cohort in A3921314.

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Table 2. Comparison of Cohorts in Each Study

Cohorts		A3921312	A3921314	A3921316	A3921317
Main Cohort	RA patients initiating **tofacitinib**	X	X	X	X
Comparator Cohorts	RA patients initiating **bDMARDs**				
	• "**bDMARD exposed**": (Initiation of ADA, ETA or INF as their first bDMARD within 6 months of register enrolment)	X			
	• Contemporaneous "**Treated with bDMARD**": Initiate bDMARD		X	X	X
	• **Historical bDMARD cohort** (on/before 31-Dec-15)			X	
	RA patients not treated with bDMARDs				
	• "**bDMARD naïve" cohort**: Prevalent use of **csDMARD** without prior bDMARD or tofacitinib (historical – data from 2001-2008)	X			
	• RA patients who are **"ts/bDMARD naïve"**		X		
	• "**nbDMARD cohort**": Failure of at least 1 DMARD and initiation of a new csDMARD, no previous exposure to ts/bDMARD				X
	General population (Randomly selected from general population and region-, age- and sex-matched to RA patient cohorts, up to 5 population controls per tofacitinib exposed patient)		X		

- Only cohorts for the final report are included in this table. All cohorts require patients to be at least 18 years old.
- Abbreviations: ADA = adalimumab (Humira), bDMARD = biologic disease modifying antirheumatic drug, csDMARD = conventional synthetic disease modifying antirheumatic drug, ETA = etanercept (Enbrel), INF = Infliximab (Remicase), nbDMARD = non-biologic disease modifying antirheumatic drug, RA = rheumatoid arthritis, tsDMARD = targeted synthetic disease modifying antirheumatic drug

4.6.2. Main Statistical Methods

A meta-analysis was planned to be conducted using an inverse-variance method[2] to provide pooled estimates of crude IR across the studies for applicable safety endpoints (Section 4.3) in the two cohorts defined in Section 4.6.1. In addition, pooled estimates of HR were provided for applicable safety endpoints.

For Endpoints 1-13 in Section 4.3, as a main analysis, results from all four PASS were planned to be combined to provide pooled estimates for the “Tofacitinib Cohort” and the “bDMARD Cohort” defined above. For supportive analyses, only results from applicable studies were combined depending on the endpoint and the analysis method.

For Endpoints 14-20 in Section 4.3, as a main analysis, results from A3921312, A3921316 and A3921317 were planned to be combined to provide pooled estimates for the “Tofacitinib Cohort” and the “bDMARD Cohort” defined in Section 4.6.1. These endpoints were not reported in A3921314 study.

Table 3 summarizes whether censor-at-switch approach, double-count approach, and ever-exposed approach are applicable to each type of endpoints in the four PASS. Only analyses in Tofacitinib Cohort and bDMARD Cohort are considered in this summary. Definitions of the three approaches are provided below.

1. Censor-at-Switch Approach:

    - For all-cause mortality and malignancy endpoints: 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 other endpoints: if a new medication is started during the 90-day window after discontinuation of a previous medication, initiation of the new medication stopped the 90-day risk window, and any event prior to the new medication start was assigned to the discontinued medication.

2. Double-Count Approach: when a patient initiated a new therapy within the 90-day extension, the follow-up time and events during the overlapping period were assigned to both treatments. This approach is only applicable to non-mortality and non-malignancy endpoints.

3. Ever-Exposed Approach: follow up for each exposure cohort continued after switching to a new drug or discontinuation of treatment. This approach is only applicable to all-cause mortality and malignancy endpoints.

    - With the “Ever-Exposed Approach Plus Latency Period” Approach, the time at risk was calculated from the day 6 months after drug initiation until the end of follow-up.

Refer to the Meta-Analysis SAP for more details. To align terminology with the individual study reports, the methods are renamed in this meta-analysis report as follows: the double-count approach corresponds to “double-count” method under the on-drug approach, the censor-at-switch approach corresponds to “assign-to-prior” method under the on-drug approach, and the ever-exposed approach remains unchanged.

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Table 3. Application of Censor-at-Switch Approach, Double-Count Approach, and Ever-Exposed Approach by Type of Endpoints in Each Study (Tofacitinib Cohort and bDMARD Cohort)

	Double-Count	Censor-at-Switch	Ever-Exposed
All-Cause Mortality (Endpoint 1)		All 4 PASS	All 4 PASS
Malignancy Endpoints (Endpoints 2-5)		All 4 PASS	A3921312 A3921314 A3921316 A3921317 (with 6-month latency period)
Non-malignancy and Non-mortality (Endpoints 6-13)	A3921312 A3921314 A3921316	All 4 PASS[a]	
Non-malignancy and Non-mortality (Endpoints 14-20)	A3921312 A3921316	A3921317	

a. In A3921312, A3921314 and A3921316, this method was planned for MACE, VTE, herpes zoster, PML, and GI perforation as a sensitivity analysis.

4.6.3. Changes In Planned Meta-Analyses

As summarized in Table 3, for Endpoints 14–20, double-count results were available only from A3921312 and A3921316, and censor-at-switch results were available only from A3921317. Therefore, the meta-analysis for Endpoints 14–20 could not be conducted because it was planned for at least three studies.

5. RESULTS

5.1. Participants

In A3921312, as of 14-Sep-2025, a total of 361 patients starting Xeljanz (Tofacitinib) and 2063 anti-TNF treated patients were included in this analysis.

In A3921314, a total of 542 RA patients initiating tofacitinib treatment between 01-Jan-2017 and 31-Dec-2024 and 13521 bDMARD treated patients were included in this analysis.

In A3921316, a total of 479 patients initiating tofacitinib and 5084 initiating contemporaneous bDMARDs were included in the analysis.

In A3921317, from 01-May-2017 until 31-Dec-2024, there were 398 new users in the tofacitinib cohort and 4427 new users in the bDMARD cohort.

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5.2. Demographics And Baseline Characteristics

Table 4 describes the demographics of RA patients initiating tofacitinib and in the comparator cohort in the 4 PASS. Only the cohorts included in the meta-analysis are summarized in this section. Refer to the individual study reports for complete summaries of demographic and baseline characteristics.

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Table 4. Demographics and Baseline Characteristics of RA Patients in Main Cohort and Comparator Cohort in Each Study

	A3921312		A3921314		A3921316		A3921317	
	Main Cohort	**Comparator Cohort**	**Main Cohort**	**Comparator Cohort**	**Main Cohort**	**Comparator Cohort**	**Main Cohort**	**Comparator Cohort**
Status at entry	**Tofacitinib**	**bDMARD**	**Tofacitinib**	**bDMARD**	**Tofacitinib**	**bDMARD**	**Tofacitinib**	**bDMARD**
Number of patients	361	2063	542	13521	479	5084	398	4427
Demographics								
Age Median (Q1, Q3)[a]	61.0 (11.9)	57.1 (12.9)	59 (49, 68)	61 (50, 71)	56.12 (46.82, 64.44)	57.81 (49.28, 66.00)	60.3 (52.8, 68.1)	59.8 (51.5, 67.9)
Female, n (%)[b]	280 (77.6)	1557 (75.5)	80%	77%	392 (81.8)	3985 (78.4)	288 (72.4)	3184 (71.9)
Disease duration, Median (Q1, Q3)[a]	16.8 (11.0)	8.8 (9.2)	13.1 (6.8, 23.1)	9.8 (3.5, 19.1)	10.06 (5.19, 16.40)	7.01 (2.54, 14.02)	8.2 (3.8, 15.6)	5.7 (2.1, 12.3)
Rheumatoid factor positive, n (%)[b]	197 (63.1)	1115 (62.5)	70%	74%	221 (46.1)	3278 (64.5)	255 (65.1)	2895 (66.9)
DAS28-ESR, Median (Q1, Q3)[a]	5.4 (1.3)	5.9 (1.0)	4.7 (3.6, 5.8)	4.5 (3.6, 5.4)	4.71 (3.74, 5.55)	4.62 (3.65, 5.47)	4.8 (3.8, 5.8)	4.5 (3.6, 5.4)
Tender Joint Count (28), Median (Q1, Q3)[a]	11.1 (7.2)	14.4 (7.2)	/	/	4.00 (1.00, 6.00)	3.00 (1.00, 6.00)	7.0 (3.0, 12.0)	6.0 (2.0, 10.0)
Swollen Joint Count (28), Median (Q1, Q3)[a]	6.8 (4.1)	8.5 (5.0)	/	/	6.00 (2.00, 10.00)	5.00 (2.00, 9.00)	4.0 (2.0, 8.0)	3.0 (1.0, 6.0)
On oral steroids, n (%)[b]	27 (19.9)	465 (22.5)	52%	38%	293 (61.2)	2978 (58.6)	215 (54.0)	2322 (53.5)

Percentages are based on patients with non-missing data within each cohort.
a. For A3921312, mean (SD) is reported.
b. For A3921314, only percentage is reported.
Data source: A3921312 Study Report Table 5, A3921314 Study Report Table 5, A3921316 Study Report Table 2, 1317 Study Report Table 10-1.

5.3. Outcome Data

Table 5 displays pooled crude IRs and adjusted HRs for all-cause mortality (Endpoint 1)

- Analysis 1: Ever-exposed approach. All 4 PASS were planned to be included in this analysis.
- Analysis 2: Censor-at-switch approach. All 4 PASS were planned to be included in this analysis.

Table 6 and Table 7 display pooled crude IRs and adjusted HRs for malignancy endpoints (Endpoints 2-5)

- Analysis 1 (Table 6): Ever-exposed approach. Only A3921312, A3921314 and A3921316 results were planned to be included in this analysis. In A3921317, this analysis includes a 6-month latency period, therefore excluded from pooled estimate.
- Analysis 2 (Table 7): Censor-at-switch approach. All 4 PASS were planned to be included in this analysis.

Table 8 and Table 9 display pooled crude IRs and adjusted HRs for non-malignancy endpoints (Endpoints 6-13)

- Analysis 1 (Table 8): Double-count approach. This analysis result was only available in A3921312, A3921314 and A3921316. Results from these 3 studies were planned to be included in this analysis.
- Analysis 2 (Table 9): Censor-at-switch approach. Results from all 4 PASS were planned to be included in this analysis.

For A3921312, comparisons were performed only when at least 10 events were observed across the Xeljanz (tofacitinib) and anti-TNF groups, with a minimum of 5 events in each cohort. For endpoints with fewer than 5 events in either cohort, event counts were derived using incidence rates and person-years to support the pooled estimation.

The following adjusted HR were included in the pooled estimates:

- A3921312: hazard ratios adjusted using deciles of a propensity score which was calculated using variables including age, disease duration, HAQ, DAS28, tender joint count (TJC), swollen joint count (SJC), ESR, CRP, Global Heath VAS, gender, smoking status, rheumatoid factor status, number of co-morbidities (zero, one, or two or more of the following: high blood pressure, ischemic heart disease [angina/MI], stroke, epilepsy, asthma, COPD, renal disease, liver disease, demyelination, diabetes, previous cancer), on steroid status and interactions..
- A3921314: hazard ratios adjusted for sex, calendar year and number of previous b/tsDMARDs, history of infection, cancer, MI, diabetes, COPD, joint replacement surgery, and number of hospitalization days RF, HAQ, RA disease duration, DAS28, DMARDs and steroids. A missing indicator and quartiles for HAQ and DAS28 were used.

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- A3921316: hazard ratios adjusted for age at treatment initiation (greater than 65 vs below), sex, DAS28, Charlson index, disease duration, corticosteroid use, year of treatment initiation (included as a continuous variable), rheumatoid factor, ACPA, cardiovascular comorbidities (hypertension, myocardial infarction, stroke, diabetes), and malignancy-related comorbidities.

- A3921317: hazard ratios adjusted for age, sex, RA disease duration, RF/ACPA, year of treatment start, DAS28-ESR, FFbH, previous b/tsDMARDs, glucocorticoid dosage, smoking and outcome-specific variables specified in A3921317 SAP.

In general, a study was excluded from the pooled estimate for a given endpoint and cohort if the number of events, person-years, or adjusted HR was unavailable in the individual study report. Because the SAP did not prespecify formal pooling of only two studies, pooled results based on contributions from just two PASS should be considered descriptive.

5.4. Main Results

This meta-analysis is supportive in nature, and no formal statistical comparisons were planned. Accordingly, statistical significance is not claimed.

5.4.1. All-Cause Mortality

Table 5 summarizes study-specific and pooled estimates of crude incidence rates and adjusted hazard ratios for all-cause mortality in the tofacitinib and bDMARD cohorts under the ever-exposed approach and the censor-at-switch approach. In the ever-exposed analysis, the pooled crude incidence rate was 14.09 per 1000 person-years (95% CI: 12.03, 16.51) in the tofacitinib cohort and 11.95 per 1000 person-years (95% CI: 11.36, 12.58) in the bDMARD cohort, with a pooled adjusted hazard ratio of 1.07 (95% CI: 0.87, 1.31). Study-specific adjusted hazard ratios under the ever-exposed approach ranged from 0.93 to 1.66. In the censor-at-switch analysis, the pooled crude incidence rate was 10.19 per 1000 person-years (95% CI: 7.76, 13.37) in the tofacitinib cohort and 11.15 per 1000 person-years (95% CI: 10.50, 11.84) in the bDMARD cohort, with a pooled adjusted hazard ratio of 1.03 (95% CI: 0.75, 1.41). Across the individual PASS, adjusted hazard ratios for the censor-at-switch approach ranged from 0.55 to 1.61.

Overall, pooled crude incidence rates for all-cause mortality were generally comparable between the tofacitinib and bDMARD cohorts in both analyses, with pooled adjusted hazard ratios close to 1, indicating no meaningful difference between groups.

5.4.2. Malignancy Endpoints

Table 6 summarizes study-specific and pooled estimates of crude incidence rates and adjusted hazard ratios for malignancy endpoints in the tofacitinib and bDMARD cohorts under the ever-exposed approach. Results under the censor-at-switch approach are summarized in Table 7.

For malignancies overall excluding NMSC, the pooled crude incidence rate in the ever-exposed analysis was 11.25 per 1000 person-years (95% CI: 8.72, 14.52) in the tofacitinib cohort and 10.45 per 1000 person-years (95% CI: 9.78, 11.17) in the bDMARD cohort, with a pooled adjusted hazard ratio of 1.26 (95% CI: 0.95, 1.68). In the censor-at-switch analysis, the pooled crude incidence rate was 10.67 per 1000 person-years (95% CI: 8.21, 13.87) in

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the tofacitinib cohort and 10.36 per 1000 person-years (95% CI: 9.70, 11.07) in the bDMARD cohort, with a pooled adjusted hazard ratio of 1.27 (95% CI: 0.95, 1.70).

For NMSC, the pooled crude incidence rate in the ever-exposed analysis was 16.97 per 1000 person-years (95% CI: 13.59, 21.19) in the tofacitinib cohort and 12.56 per 1000 person-years (95% CI: 11.74, 13.44) in the bDMARD cohort, with a pooled adjusted hazard ratio of 1.94 (95% CI: 1.50, 2.51). In the censor-at-switch analysis, the pooled crude incidence rate was 14.61 per 1000 person-years (95% CI: 11.30, 18.90) in the tofacitinib cohort and 11.82 per 1000 person-years (95% CI: 11.01, 12.69) in the bDMARD cohort, with a pooled adjusted hazard ratio of 2.08 (95% CI: 1.55, 2.79).

For lung cancer, the pooled crude incidence rate in the ever-exposed analysis was 2.34 per 1000 person-years (95% CI: 1.33, 4.13) in the tofacitinib cohort and 1.31 per 1000 person-years (95% CI: 1.09, 1.58) in the bDMARD cohort. In the censor-at-switch analysis, the pooled crude incidence rate was 2.65 per 1000 person-years (95% CI: 1.55, 4.51) in the tofacitinib cohort and 1.40 per 1000 person-years (95% CI: 1.17, 1.67) in the bDMARD cohort, with a pooled adjusted hazard ratio of 2.32 (95% CI: 1.25, 4.29).

For lymphoma overall and its subtypes, adjusted hazard ratios were not available; however, pooled crude incidence rates and 95% confidence intervals were estimated. In the ever-exposed analysis, pooled crude incidence rates for lymphoma overall and non-Hodgkin lymphoma were slightly higher in the tofacitinib cohort, while Hodgkin lymphoma and chronic lymphatic leukemia remained uncommon in both cohorts. Similar results were observed in the censor-at-switch analysis.

Overall, pooled incidence rates were higher for NMSC and lung cancer in the tofacitinib cohort, and the corresponding adjusted hazard ratios and 95% CIs were above 1. Lymphoma and its subtypes were rare in both cohorts.

5.4.3. Non-Malignancy Endpoints

Table 8 summarizes study-specific and pooled estimates of crude incidence rates and adjusted hazard ratios for Endpoints 6-13 in the tofacitinib and bDMARD cohorts using the double-count approach.

For herpes zoster, the pooled crude incidence rate was 10.56 per 1000 person-years (95% CI: 6.88, 16.19) in the tofacitinib cohort and 4.94 per 1000 person-years (95% CI: 4.23, 5.77) in the bDMARD cohort. For fractures, the pooled crude incidence rate was 27.93 (95% CI: 22.31, 34.97) and 35.71 (95% CI: 34.20, 37.29) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively, with a pooled adjusted hazard ratio of 0.93 (95% CI: 0.73, 1.18). For MACE, the pooled crude incidence rate was 10.75 (95% CI: 7.72, 14.97) and 12.26 (95% CI: 11.43, 13.16) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively, with a pooled adjusted hazard ratio of 1.05 (95% CI: 0.72, 1.52). For DVT, the pooled crude incidence rate was 1.96 (95% CI: 0.91, 4.22) and 3.03 (95% CI: 2.62, 3.51) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively. For pulmonary embolism, the pooled crude incidence rate was 4.32 (95% CI: 2.36, 7.91) and 3.33 (95% CI: 2.89, 3.84) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively. For VTE, the pooled crude incidence rate was 5.99 (95% CI: 3.77, 9.51) and 6.19 (95% CI: 5.59, 6.86) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively. For GI perforations, the pooled crude incidence rate was 2.94 (95% CI: 1.58,

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5.46) and 1.90 (95% CI: 1.61, 2.25) per 1000 person-years in the tofacitinib and bDMARD cohorts, respectively.

Results using the censor-at-switch approach are summarized in Table 9 and are generally consistent with the results using the double-count approach. Pooled estimates using the censor-at-switch approach for DVT and PE are only based on two studies and should be considered descriptive only. Progressive multifocal leukoencephalopathy was uncommon in both cohorts, and adjusted hazard ratios were unavailable from all four PASS.

Overall, pooled incidence rates for non-malignancy endpoints were broadly similar between cohorts. Higher rates were observed for herpes zoster in the tofacitinib cohort, while fracture, cardiovascular risks and GI perforations were comparable. Progressive multifocal leukoencephalopathy was rare in both cohorts. Adjusted hazard ratios, where available, were generally close to 1 with wide confidence intervals.

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Table 5. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of All-Cause Mortality Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach and Ever-Exposed Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
All-cause mortality (censor-at-switch approach)	14	871	16.1	(9.5, 27.1)	54	5891	9.2	(7.0, 12.0)	1.61 (0.72, 3.58)
All-cause mortality (ever-exposed approach)	36	1997	18.0	(13.0, 25.0)	159	13784	11.5	(9.9, 13.5)	1.24 (0.76, 2.00)
A3921314									
All-cause mortality (censor-at-switch approach)	20	1532	13.05	(8.42, 20.23)	815	60811	13.40	(12.51, 14.35)	1.03 (0.65, 1.61)
All-cause mortality (ever-exposed approach)	36	2743	13.13	(9.47, 18.20)	887	67431	13.15	(12.32, 14.05)	0.96 (0.68, 1.36)
A3921316									
All-cause mortality (censor-at-switch approach)	3	1273.64	2.4	(0.8, 7.3)	82	17966.11	4.6	(3.7, 5.7)	0.55 (0.17,1.75)
All-cause mortality (ever-exposed approach)	15	1456.27	10.3	(6.2, 17.1)	136	21131.62	6.4	(5.4, 7.6)	1.66 (0.96, 2.86)
A3921317									
All-cause mortality (censor-at-switch approach)	15	2341.33	6.41	(3.59, 10.57)	102	17507.14	5.83	(4.75, 7.07)	0.94 (0.52, 1.71)
All-cause mortality (ever-exposed approach)	66	4797.94	13.76	(10.64, 17.50)	302	24846.52	12.15	(10.82, 13.61)	0.93 (0.66, 1.31)
Pooled Estimates[6]									
All-cause mortality (censor-at-switch approach)	52	6017.97	10.19	(7.76, 13.37)	1053	102175.25	11.15	(10.50, 11.84)	1.03 (0.75, 1.41)
All-cause mortality (ever-exposed approach)	153	10994.21	14.09	(12.03, 16.51)	1484	127193.14	11.95	(11.36, 12.58)	1.07 (0.87, 1.31)

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Table 5. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of All-Cause Mortality Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach and Ever-Exposed Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]

With Censor-at-Switch approach, if 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.
With Ever-Exposed Approach, follow up for each cohort continued after switching to a new drug or discontinuation of treatment.
Footnotes:

1. Number of occurrences of events of interest that occur during the study period.
2. Total person-years at risk is the sum of the number of years during which each patient is at risk for the event.
3. Incidence Rates per 1000 person-years calculated as number of events/total person-years at risk.
4. Confidence Intervals for crude incidence rates using exact Poisson method.
5. Adjusted hazard ratios estimated with Cox proportional hazards regression.
6. Calculated using inverse-variance method.

Data source: A3921312 Study Report Table 10 (adjusted HR), A3921314 Study Report Table 7 and Table 8 (HRd), A3921316 Study Report Table 4 and Table 6, A3921317 Study Report Table 10-9, Table 10-11, Table 10-13 (Model C), Table 10-15 (Model C).

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Table 6. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Ever-Exposed Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
All malignancies overall (excluding NMSC)	11	1977	5.6	(3.1, 10.0)	112	13494	8.3	(6.9, 10.0)	0.52 (0.24, 1.13)
NMSC	16	1952	8.2	(5.0, 13.4)	38	13631	2.8	(2.0, 3.8)	1.39 (0.63, 3.07)
Lung cancer	<5	1995	1.0	(0.3, 4.0)	9	13781	0.7	(0.3, 1.3)	-
Lymphoma	0	1997	-	-	9	13761	0.7	(0.3, 1.3)	-
Non-Hodgkin lymphoma	0	1997	-	-	<5	13780	0.1	(0.01, 0.5)	-
Hodgkin lymphoma	0	1997	-	-	0	13784	-	-	-
Chronic lymphatic leukemia	0	1997	-	-	0	13784	-	-	-
A3921314									
All malignancies overall (excluding NMSC)	29	2195	13.21	(9.18, 19.01)	584	50107	11.65	(10.75, 12.64)	1.29 (0.87, 1.91)
NMSC	53	2113	25.08	(19.16, 32.82)	751	49496	15.17	(14.13, 16.30)	1.89 (1.41, 2.53)
Lung cancer	5	2229	2.24	(0.93, 5.39)	77	51044	1.51	(1.21, 1.89)	2.04 (0.78, 5.34)
Lymphoma	3	2227	1.35	(0.43, 4.18)	33	51060	0.65	(0.46, 0.91)	-
Non-Hodgkin lymphoma	3	2227	1.35	(0.43, 4.18)	27	51072	0.53	(0.36, 0.77)	-
Hodgkin lymphoma	0	2234	0	-	1	51121	0.02	(0.0, 0.14)	-
Chronic lymphatic leukemia	0	2234	0	-	5	51112	0.10	(0.04, 0.24)	-
A3921316									
All malignancies overall (excluding NMSC)	19	1434.8	13.2	(8.4, 20.8)	176	20883.24	8.4	(7.3, 9.8)	1.74 (1.07, 2.85)
NMSC	9	1453	6.2	(3.2, 11.9)	51	21337.73	2.4	(1.8, 3.1)	2.99 (1.45, 6.17)
Lung cancer	5	1453.8	3.4	(1.4, 8.3)	23	21491.62	1.1	(0.7, 1.6)	3.56 (1.32, 9.61)
Lymphoma	0	1465.51	-	-	1	21565.82	0	(0.0, 0.3)	-
Non-Hodgkin lymphoma	0	1465.51	-	-	1	21570.3	0	(0.0, 0.3)	-
Hodgkin lymphoma	0	1465.51	-	-	0	21582.51	-	-	-

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Table 6. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Ever-Exposed Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
Chronic lymphatic leukemia	0	1465.51	-	-	0	21578.03	-	-	-
Pooled Estimates[6]									
All malignancies overall (excluding NMSC)	59	5606.8	11.25	(8.72, 14.52)	872	84484.24	10.45	(9.78, 11.17)	1.26 (0.95, 1.68)
NMSC	78	5518	16.97	(13.59, 21.19)	840	84464.73	12.56	(11.74, 13.44)	1.94 (1.50, 2.51)
Lung cancer	12	5677.8	2.34	(1.33, 4.13)	109	86316.62	1.31	(1.09, 1.58)	2.67 (1.34, 5.33)*
Lymphoma	3	5689.51	0.92	(0.35, 2.45)	43	86386.82	0.61	(0.45, 0.82)	-
Non-Hodgkin lymphoma	3	5689.51	0.92	(0.35, 2.45)	29	86422.3	0.45	(0.32, 0.65)	-
Hodgkin lymphoma	0	5696.51	0.27[#]	(0.05, 1.32)[#]	1	86487.51	0.02	(0.01, 0.10)	-
Chronic lymphatic leukemia	0	5696.51	0.27[#]	(0.05, 1.32)[#]	5	86474.03	0.08	(0.04, 0.18)	-

With Ever-Exposed approach, follow up for each cohort continued after switching to a new drug or discontinuation of treatment.
In A3921317, the ever-exposed approach incorporates a 6-month latency period; therefore, the results from this study are not included in the pooled estimate.
For endpoints with fewer than 5 events in either cohort, event counts in A3921312 were derived using incidence rates and person-years to support the pooled estimation.
* Descriptive result based on two studies; SAP did not pre-specify formal pooling with only two PASS.
[#] A continuity correction was applied to studies with zero events; therefore, pooled incidence rates may be >0 despite no observed events.
Footnotes:

1. Number of occurrences of events of interest that occur during the study period
2. Total person-years at risk is the sum of the number of years during which each patient is at risk for the event.
3. Incidence Rates per 1000 person-years calculated as number of events/total person-years at risk.
4. Confidence Intervals for crude incidence rates using exact Poisson method.
5. Adjusted hazard ratios estimated with Cox proportional hazards regression. Pooled estimate is not presented if adjusted HR is not estimated in any study or only available in one study.
6. Calculated using inverse-variance method.

Data source: A3921312 Study Report Table 10 (adjusted HR), A3921314 Study Report Table 7 and Table 8 (HRd), A3921316 Study Report Table 4 and Table 6.

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Table 7. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
All malignancies overall (excluding NMSC)	<5	864	3.5	(1.1, 10.8)	47	5857	8.0	(6.0, 10.7)	-
NMSC	8	858	9.3	(4.7, 18.7)	19	5861	3.2	(2.1, 5.1)	0.98 (0.32, 3.00)
Lung cancer	0	871	-	-	<5	5890	0.5	(0.2, 1.6)	-
A3921314									
All malignancies overall (excluding NMSC)	20	1253	15.96	(10.30, 24.74)	537	45221	11.87	(10.91, 12.92)	1.57 (0.99, 2.48)
NMSC	34	1211	28.08	(20.06, 39.30)	667	44715	14.92	(13.83, 16.09)	2.23 (1.56, 3.20)
Lung cancer	5	1271	3.93	(1.64, 9.45)	73	46066	1.58	(1.26, 1.99)	3.45 (1.32, 9.04)
Lymphoma	3	1272	2.36	(0.76, 7.31)	31	46085	0.67	(0.47, 0.96)	-
Non-Hodgkin lymphoma	3	1272	2.36	(0.76, 7.31)	25	46094	0.54	(0.37, 0.80)	-
Hodgkin lymphoma	0	1276	0	-	1	46141	0.02	(0.00, 0.15)	-
Chronic lymphatic leukemia	0	1276	0	-	5	46135	0.11	(0.05, 0.26)	-
A3921316									
All malignancies overall (excluding NMSC)	10	1254.02	8.0	(4.3, 14.8)	133	17687.07	7.5	(6.3, 8.9)	1.16 (0.60, 2.21)
NMSC	4	1261.72	3.2	(1.2, 8.4)	37	17807.9	2.1	(1.5, 2.9)	1.59 (0.56, 4.53)
Lung cancer	2	1266.26	1.6	(0.4, 6.3)	20	17980.42	1.1	(0.7, 1.7)	1.54 (0.35, 6.76)
Lymphoma	0	1273.65	0	-	1	18002.71	0.1	(0.0, 0.4)	-
Non-Hodgkin lymphoma	0	1273.65	0	-	1	18002.72	0.1	(0.0, 0.4)	-
Hodgkin lymphoma	0	1273.65	0	-	0	18005.78	0	-	-
Chronic lymphatic leukemia	0	1273.65	0	-	0	18005.77	0	-	-
A3921317									
All malignancies overall (excluding NMSC)	23	2327.22	9.88	(6.26, 14.83)	160	17356	9.22	(7.85, 10.76)	1.06 (0.66, 1.69)
NMSC	12	2324.79	5.16	(2.67, 9.02)	41	17438.22	2.35	(1.69, 3.19)	2.40 (1.21, 4.80)

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Table 7. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
Lung cancer	6	2338.51	2.57	(0.94, 5.58)	23	17503.09	1.31	(0.83, 1.97)	1.86 (0.72, 4.82)
Lymphoma	2	2340.07	0.85	(0.1, 3.09)	6	17497.28	0.34	(0.13, 0.75)	-
Non-Hodgkin lymphoma	1	2341.33	0.43	(0.01, 2.38)	0	17507.29	0.00	(0.00, 0.21)	-
Hodgkin lymphoma	0	2341.33	0.00	(0.00, 1.58)	4	17498.55	0.23	(0.06, 0.59)	-
Chronic lymphatic leukemia	1	2340.07	0.43	(0.01, 2.38)	2	17506.03	0.11	(0.01, 0.41)	-
Pooled Estimates[6]									
All malignancies overall (excluding NMSC)	56	5698.24	10.67	(8.21, 13.87)	877	86121.07	10.36	(9.70, 11.07)	1.27 (0.95, 1.70)
NMSC	58	5655.51	14.61	(11.30, 18.90)	764	85822.12	11.82	(11.01, 12.69)	2.08 (1.55, 2.79)
Lung cancer	13	5746.77	2.65	(1.55, 4.51)	119	87439.51	1.40	(1.17, 1.67)	2.32 (1.25, 4.29)
Lymphoma	5	4885.72	1.39	(0.60, 3.20)	38	81584.99	0.57	(0.41, 0.78)	-
Non-Hodgkin lymphoma	4	4886.98	1.32	(0.52, 3.33)	26	81604.01	0.47	(0.32, 0.69)	-
Hodgkin lymphoma	0	4890.98	0.32[#]	(0.06, 1.59)[#]	5	81645.33	0.12	(0.05, 0.28)	-
Chronic lymphatic leukemia	1	4889.72	0.41	(0.10, 1.64)	7	81646.8	0.10	(0.05, 0.21)	-

With Censor-at-Switch approach, if a malignancy 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 endpoints with fewer than 5 events in either cohort, event counts in A3921312 were derived using incidence rates and person-years to support the pooled estimation.
[#] A continuity correction was applied to studies with zero events; therefore, pooled incidence rates may be >0 despite no observed events.
Footnotes:

1. Number of occurrences of events of interest that occur during the study period
2. Total person-years at risk is the sum of the number of years during which each patient is at risk for the event.
3. Incidence Rates per 1000 person-years calculated as number of events/total person-years at risk.
4. Confidence Intervals for crude incidence rates using exact Poisson method.
5. Adjusted hazard ratios estimated with Cox proportional hazards regression. Pooled estimate is not presented if adjusted HR is not estimated in any study or only available in one study.
6. Calculated using inverse-variance method.

Data source: A3921312 Study Report Table 10 (adjusted HR), A3921314 Study Report Table 7 and Table 8 (HRd), A3921316 Study Report Table 4 and Table 6, A3921317 Study Report Table 10-9 and Table 10-13 (Model C).

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Table 8. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Non-Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Double-Count Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
Herpes zoster	<5	845	1.2	(0.2, 8.4)	0	5793	-	-	-
Fractures	5	834	6.0	(2.5, 14.4)	39	5733	6.8	(5.0, 9.3)	0.78 (0.25, 2.46)
MACE	8	843	9.5	(4.7, 19.0)	37	5726	6.5	(4.7, 8.9)	0.98 (0.35, 2.73)
Deep vein thrombosis (DVT)	0	845	-	-	<5	5791	0.3	(0.1, 1.4)	-
Pulmonary embolism (PE)	<5	845	1.2	(0.2, 8.4)	6	5789	1.0	(0.5, 2.3)	-
Venous Thromboembolism (VTE (DVT/PE))	<5	843	3.6	(1.1, 11.0)	11	5781	1.9	(1.1, 3.4)	-
GI perforation	<5	845	1.2	(0.2, 8.4)	6	5790	1.0	(0.5, 2.3)	-
A3921314									
Herpes zoster	2	1587	1.26	(0.32, 5.04)	26	48509	0.54	(0.36, 0.79)	-
Fractures	57	1436	39.69	(30.61, 51.45)	1852	44582	41.54	(39.69, 43.48)	0.87 (0.66, 1.15)
MACE	22	1561	14.10	(9.28, 21.41)	676	47470	14.24	(13.21, 15.36)	1.08 (0.70, 1.66)
Deep vein thrombosis (DVT)	4	1586	2.52	(0.95, 6.72)	166	48240	3.44	(2.96, 4.01)	-
Pulmonary embolism (PE)	9	1580	5.69	(2.96, 10.94)	179	48278	3.71	(3.20, 4.29)	1.33 (0.67, 2.67)
Venous Thromboembolism (VTE (DVT/PE))	13	1570	8.28	(4.81, 14.26)	338	47988	7.04	(6.33, 7.84)	1.07 (0.60, 1.89)
GI perforation	6	1589	3.78	(1.70, 8.40)	101	48397	2.09	(1.72, 2.54)	1.44 (0.61, 3.39)
A3921316									
Herpes zoster	18	1192.23	15.1	(9.5, 23.9)	132	16980.32	7.8	(6.6, 9.2)	1.99 (1.19, 3.33)
Fractures	14	1210.47	11.6	(6.8, 19.5)	170	16902.51	10.1	(8.7, 11.7)	1.24 (0.71, 2.16)
MACE	5	1254.49	4.0	(1.7, 9.6)	65	17398.71	3.7	(2.9, 4.8)	0.96 (0.34, 2.65)
Deep vein thrombosis (DVT)	2	1262.49	1.6	(0.4, 6.3)	10	17556.44	0.6	(0.3, 1.1)	1.47 (0.18, 11.83)
Pulmonary embolism (PE)	0	1263.44	-	-	5	17582	0.3	(0.1, 0.7)	-
Venous Thromboembolism (VTE (DVT/PE))	2	1257	1.6	(0.4, 6.4)	16	17525.35	0.9	(0.6, 1.5)	1.08 (0.14, 8.40)

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Table 8. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Non-Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Double-Count Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
GI perforation	3	1247.8	2.4	(0.8, 7.5)	27	17526.31	1.5	(1.1, 2.2)	-
Pooled Estimates[6]									
Herpes zoster	21	3624.23	10.56	(6.88, 16.19)	158	71282.32	4.94	(4.23, 5.77)	-
Fractures	76	3480.47	27.93	(22.31, 34.97)	2061	67217.51	35.71	(34.20, 37.29)	0.93 (0.73, 1.18)
MACE	35	3658.49	10.75	(7.72, 14.97)	778	70594.71	12.26	(11.43, 13.16)	1.05 (0.72, 1.52)
Deep vein thrombosis (DVT)	6	3693.49	1.96	(0.91, 4.22)	178	71587.44	3.03	(2.62, 3.51)	-
Pulmonary embolism (PE)	10	3688.44	4.32	(2.36, 7.91)	190	71649	3.33	(2.89, 3.84)	-
Venous Thromboembolism (VTE (DVT/PE))	18	3670	5.99	(3.77, 9.51)	365	71294.35	6.19	(5.59, 6.86)	1.07 (0.62, 1.86)*
GI perforation	10	3681.8	2.94	(1.58, 5.46)	134	71713.31	1.90	(1.61, 2.25)	-

With Double-Count approach, when a patient initiated a new therapy within the 90-day extension, the follow-up time and events during the overlapping period were assigned to both treatments.
A3921317 is not included in this analysis because results using the double-count approach are not available for this study.
For endpoints with fewer than 5 events in either cohort, event counts in A3921312 were derived using incidence rates and person-years to support the pooled estimation.
* Descriptive result based on two studies; SAP did not pre-specify formal pooling with only two PASS.
Footnotes:

1. Number of occurrences of events of interest that occur during the study period
2. Total person-years at risk is the sum of the number of years during which each patient is at risk for the event.
3. Incidence Rates per 1000 person-years calculated as number of events/total person-years at risk.
4. Confidence Intervals for crude incidence rates using exact Poisson method.
5. Adjusted hazard ratios estimated with Cox proportional hazards regression. Pooled estimate is not presented if adjusted HR is not estimated in any study or only available in one study.
6. Calculated using inverse-variance method.

Data source: A3921312 Study Report Table 10 (adjusted HR), A3921314 Study Report Table 7 and Table 8 (HRd), A3921316 Study Report Table 4 and Table 6.

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Table 9. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Non-Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
MACE	-	-	-	-	-	-	-	-	0.99 (0.36, 2.77)
Progressive multifocal leukoencephalopathy (PML)	0	845	-	-	0	5793	-	-	-
A3921314									
Herpes zoster	2	1470	1.36	(0.34, 5.44)	26	48161	0.54	(0.37, 0.79)	-
MACE	20	1445	13.84	(8.93, 21.45)	676	47125	14.34	(13.30, 15.47)	1.05 (0.67, 1.66)
Venous Thromboembolism (VTE (DVT/PE))	11	1455	7.56	(4.19, 13.65)	335	47642	7.03	(6.32, 7.83)	1.00 (0.54, 1.86)
GI perforation	6	1474	4.07	(1.83, 9.06)	101	48050	2.10	(1.73, 2.55)	1.56 (0.66, 3.67)
Progressive multifocal leukoencephalopathy (PML)	0	1532	0	-	3	60811	0.05	(0.02, 0.15)	-
A3921316									
Herpes zoster	18	1199.78	15.0	(9.5, 23.8)	136	17344.49	7.8	(6.6, 9.3)	1.95 (1.17, 3.25)
MACE	6	1264.46	4.7	(2.1, 10.6)	65	17796.74	3.7	(2.9, 4.7)	1.21 (0.48, 3.03)
Deep vein thrombosis (DVT)	2	1272.95	1.6	(0.4, 6.3)	11	17951.67	0.6	(0.3, 1.1)	1.34 (0.17, 10.65)
Pulmonary embolism (PE)	0	1273.65	-	-	5	17988.7	0.3	(0.1, 0.7)	-
Venous Thromboembolism (VTE (DVT/PE))	2	1267.47	1.6	(0.4, 6.3)	17	17922.11	0.9	(0.6, 1.5)	1.01 (0.13, 7.84)
GI perforation	0	1258.11	-	-	30	17916.25	1.7	(1.2, 2.4)	-
Progressive multifocal leukoencephalopathy (PML)	0	1273.65	-	-	0	18005.78	-	-	-
A3921317									
Herpes zoster	49	2258.75	21.69	(16.05, 28.68)	143	17267.16	8.28	(6.98, 9.76)	2.38 (1.65, 3.43)
Fractures	48	2260.7	21.23	(15.66, 28.15)	306	16979.65	18.02	(16.06, 20.16)	1.18 (0.84, 1.66)
MACE	20	2324.69	8.60	(5.26, 13.29)	91	17392.01	5.23	(4.21, 6.42)	1.78 (1.04, 3.06)
Deep vein thrombosis (DVT)	2	2340.85	0.85	(0.10, 3.09)	18	17479.19	1.03	(0.61, 1.63)	-

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Table 9. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Non-Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Censor-at-Switch Approach

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
Pulmonary embolism (PE)	6	2338.9	2.57	(0.94, 5.58)	31	17463.67	1.78	(1.21, 2.52)	1.55 (0.58, 4.11)
Venous Thromboembolism (VTE (DVT/PE))	6	2338.9	2.57	(0.94, 5.58)	41	17450.2	2.35	(1.69, 3.19)	1.14 (0.44, 2.96)
GI perforation	5	2340.53	2.14	(0.69, 4.99)	44	17441.75	2.52	(1.83, 3.39)	-
Progressive multifocal leukoencephalopathy (PML)	0	2341.33	0.00	(0.00, 1.58)	1	17506.88	0.06	(0.00, 0.32)	-
Pooled Estimates[6]									
Herpes zoster	69	4928.53	18.18	(14.36, 23.02)	305	82772.65	6.40	(5.72, 7.16)	2.22 (1.65, 3.00)*
MACE	46	5034.15	9.79	(7.33, 13.07)	832	82313.75	11.54	(10.79, 12.36)	1.26 (0.93, 1.72)
Deep vein thrombosis (DVT)	4*	3613.8*	1.16*	(0.43, 3.09)*	29*	35430.86*	0.85*	(0.59, 1.22)*	-
Pulmonary embolism (PE)	6*	3612.55*	2.22*	(1.03, 4.79)*	36*	35452.37*	1.37*	(0.99, 1.90)*	-
Venous Thromboembolism (VTE (DVT/PE))	19	5061.37	4.56	(2.91, 7.14)	393	83014.31	5.75	(5.21, 6.35)	1.04 (0.63, 1.72)
GI perforation	11	5072.64	2.78	(1.56, 4.95)	175	83408	2.12	(1.83, 2.45)	-
Progressive multifocal leukoencephalopathy (PML)	0	5991.98	0.36#	(0.09, 1.43)#	4	102116.7	0.05	(0.02, 0.12)	-

With Censor-at-Switch approach, 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.
* Descriptive result based on two studies; SAP did not pre-specify formal pooling with only two PASS.
A continuity correction was applied to studies with zero events; therefore, pooled incidence rates may be >0 despite no observed events.
Footnotes:

1. Number of occurrences of events of interest that occur during the study period
2. Total person-years at risk is the sum of the number of years during which each patient is at risk for the event.
3. Incidence Rates per 1000 person-years calculated as number of events/total person-years at risk.
4. Confidence Intervals for crude incidence rates using exact Poisson method.
5. Adjusted hazard ratios estimated with Cox proportional hazards regression. Pooled estimate is not presented if adjusted HR is not estimated in any study or only available in one study.
6. Calculated using inverse-variance method.

Data source: A3921312 Study Report Table 10 (adjusted HR following sensitivity analysis), A3921314 Study Report Table 17 and Table 18 (HRd), A3921316 Study Report Table 13 and Table 6, A3921317 Study Report Table 10-9 and Table 10-13 (Model C).

6. DISCUSSION

6.1. Key Results

Overall, the pooled results showed that crude incidence rates for all-cause mortality were generally similar between the tofacitinib and bDMARD cohorts in both the censor-at-switch and ever-exposed analyses, and the pooled adjusted HRs were close to 1. For malignancy endpoints, pooled estimates of crude incidence rates for NMSC and lung cancer were higher in the tofacitinib cohort and the corresponding adjusted hazard ratios were greater than 1, with 95% CIs excluding 1. Lymphoma and its subtypes were rare in both cohorts. For non-malignancy endpoints, pooled estimates of crude incidence rates for herpes zoster were higher in the tofacitinib cohort than in the bDMARD cohort and the corresponding adjusted hazard ratios were greater than 1, with 95% CIs excluding 1. Other non-malignancy endpoints showed similar pooled estimates between cohorts. These findings provide an integrated summary of the relative occurrence of the prespecified safety endpoints across the included registries under the analytic approaches specified in the meta-analysis.

6.2. Limitations

This meta-analysis has several limitations that should be considered when interpreting the findings. First, the pooled results were derived from observational registry data collected across multiple countries, and differences in healthcare systems, prescribing patterns, patient characteristics, follow-up practices, and endpoint ascertainment may have contributed to between-study heterogeneity. Second, although efforts were made to define comparable cohorts across studies, the comparator cohorts were not identical across the PASS, and some analyses included only a subset of studies because of study-specific methodological differences, such as the 6-month latency period applied in A3921317 for malignancy analyses or the availability of assign-to-prior analyses for selected non-malignancy endpoints. Third, sample sizes differed substantially between the tofacitinib cohort (N=1,780) and the bDMARD cohort (N=25,140). This imbalance may have limited the precision of estimates for rare outcomes in the smaller tofacitinib cohort and contributed to uncertainty in some comparisons. Fourth, several endpoints were rare, resulting in small numbers of events, wide confidence intervals, and in some cases the absence of pooled hazard ratio estimates. Finally, as with all non-interventional studies, the pooled estimates may be affected by residual confounding, incomplete capture of relevant risk factors, and differences in treatment selection that cannot be fully addressed through study-level adjusted analyses.

7. CONCLUSIONS

In this meta-analysis of four PASS in patients with RA, pooled estimates for all-cause mortality were generally similar between the tofacitinib and bDMARD cohorts, while higher pooled estimates of crude incidence rates were observed for NMSC, lung cancer, and herpes zoster in the tofacitinib cohort, with adjusted hazard ratios and the 95% CIs above 1, indicating higher risks for patients treated with tofacitinib. These events (ie, NMSC, lung cancer and herpes zoster) are identified risks in the EU RMP. These findings should be interpreted in the context of the observational design, between-study heterogeneity, and limited precision for rare endpoints.

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