

NON-INTERVENTIONAL STUDY FINAL REPORT ABSTRACT

Title: An Active Surveillance, Post-Authorisation 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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBRA).

Date: 27 July 2026

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

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. 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, patients with RA are at a higher risk of infections, cardiovascular 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. Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA. Unlike biological therapies, such as tumour necrosis factor 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 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 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 data in the British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA). Long term morbidity and mortality event tracking of these cohorts over seven 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. 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 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 study is one of four registry-based post-authorisation safety studies (PASS), which are being conducted in the United Kingdom (UK), Sweden, Spain and Germany. This non-interventional, active surveillance study, embedded within the BSRBR register, is designated as a Post-Authorisation Safety Study (PASS) and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

Research question and objectives: What are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies?

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 outcomes, including fractures, among patients with RA in an existing UK based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients treated with TNFi therapies 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, and MI, VTE, and other

event rates, including fractures, 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.

Study design: This was an active surveillance study using existing data within the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), an ongoing prospective observational cohort study started in 2001 and up to 14 September 2025 for this final report, which aimed to study the safety of new therapies for RA during routine post-marketed clinical use. This report was a descriptive study, and no hypotheses were tested.

Setting: The BSRBR-RA was established in 2001 to study the safety of biologic therapies in patients with RA living in the UK. For the first 7-8 years, the focus was on the safety profile of the first three approved TNFi agents (ie, ADA, ETA and INF) as a class and as individual therapies. Apart from the risk of developing tuberculosis, data within the BSRBR-RA has not demonstrated any clear differences in safety profile between these agents. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies after these agents receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population. Unique features of BSRBR-RA included recruitment and collection of data from two parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries. Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections, and malignancies. All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

External validity (ie, generalizability to patients with RA who were not enrolled in the register), was maximised by encouraging physicians to enroll each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

Within the BSRBR-RA there were 2 comparator cohorts. These represent cohorts of patients exposed to agents which have been studied:

1. The first was a cohort of patients with prevalent active RA (guide disease activity score (DAS) >4.2) on csDMARD recruited between 2002 and 2009 for whom follow-up data were already available. No new data were being collected for this cohort as the 7-year follow-up period since last subject first visit has been surpassed. This cohort consisted of patients who were either being treated before the advent of approved targeted therapies for RA or for whom biologics were not needed or desired. Some of these patients would have subsequently progressed to a biologic or other new therapy, been lost to follow up or died.

2. The second was a cohort of TNFi-exposed patients with active RA registered within 6 months of starting originator ADA, ETA or INF as their first biologic/tsDMARD. Recruitment to this cohort started in 2010 and is ongoing. Patients enrolled in the TNFi-cohort who later initiated tofacitinib were eligible for subsequent enrolment in the tofacitinib-exposed cohort. Per national prescribing restrictions, patients will not be prescribed TNFi and tofacitinib concurrently.

Subjects and study size, including dropouts: The active surveillance population included RA patients already enrolled in the register who met the criteria for the study cohorts as well as patients with RA, newly treated with tofacitinib following EMA approval and UK launch of the product (fully available January 2018) and registered with the BSRBR-RA. In the BSRBR-RA, there were two comparison cohorts readily available which included the csDMARD comparison cohort containing 3600 biologic-naïve patients and the anti-TNF comparison cohort containing 2100 biologic-exposed patients. Some tofacitinib-exposed patients were newly enrolled in the register, having been recruited to the BSRBR-RA within 6 months of their first dose. Others were already enrolled in the BSRBR-RA as prior biologic disease modifying antirheumatic drug (bDMARD) initiators but switched to tofacitinib during follow up. Key clinical data at time of switch were requested. For patients enrolled during the 6-month period after initiation, the baseline date was reported as the drug start date rather than the date of registration. The first post-baseline visit occurred 6 months after tofacitinib initiation, regardless of date of enrolment.

Variables and data sources: For patients enrolled during the 6-month period after initiation, the baseline date was reported as the drug start date rather than the date of registration. The first post-baseline visit occurred at 6 months after tofacitinib initiation, regardless of date of enrolment. Key clinical data at the time of switching are collected.

The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) was launched in October 2001. The primary aim was to investigate the long-term outcomes of patients with rheumatoid arthritis (RA) treated with biologic (bDMARD) or targeted synthetic (tsDMARD) agents with particular reference to safety. The study has been organised under the auspices of the British Society for Rheumatology (BSR) and is based at the Centre for Epidemiology Versus Arthritis (formerly Arthritis Research UK Centre for Epidemiology) at The University of Manchester, UK.

Between 2001 and 2008, the BSRBR-RA focussed on recruiting and following patients with RA who were starting bDMARD (anti-TNF) therapy (mainly Humira, Enbrel, Remicade) alongside an appropriate comparison cohort, used to put any findings into context. As new agents were licensed in the UK, there were invited to join this national effort.

Results: Following the application of study-specific inclusion and exclusion criteria, as of 14 September 2025, a total of 136 patients with RA have registered into the BSRBR-RA starting Xeljanz (tofacitinib), plus a further 225 have started during BSRBR-RA follow-up, giving a total of 361 patients starting Xeljanz (Tofacitinib) in this analysis. There were 2063 bDMARD (anti-TNF) treated patients and 2831 bDMARD naïve (csDMARD) treated patients that were recruited to the BSRBR-RA. Patients for the Xeljanz (tofacitinib) cohort were recruited from 86 hospitals across the UK prescribing the treatment for RA. In patients

starting Xeljanz (tofacitinib), there were 39 registered starting the drug as their first b/tsDMARD, whilst 322 patients started Xeljanz (tofacitinib) after switching from another b/tsDMARD therapy.

There were more females than males across all three cohorts with similar gender distributions and age was generally comparable across all three treatment cohorts, with most patients being aged 55 or older.

The mean (standard deviation) ages were 61.0 (11.9) years, 60.2 (12.3) years, and 57.1 (12.9) in the tofacitinib, bDMARD naïve (csDMARD), and bDMARD (anti-TNF) treated cohorts, respectively. In all three cohorts, female accounted for at least 75% of patients, reflecting their higher prevalence of RA among women. Categories of race/ethnicity were distributed similarly between the three treatment cohorts, with White race/ethnicity as most common category (96.7% in tofacitinib treated, 97.7% in bDMARD naïve (csDMARD) treated, and 94.5% in bDMARD (anti-TNF) treated patients). Across all three treatments, a higher proportion of patients were diagnosed with RA from 2000 through 2019 with 80% diagnosed in this period from the bDMARD (anti-TNF) group versus 61.8% and 49.8% in the tofacitinib and bDMARD naïve (csDMARD) treated cohorts, respectively. For the remaining baseline and demographic characteristics, distributions and mean estimates were similar across the three treatment cohorts.

Across all three treatment groups, overall, the rates of safety endpoints tended to be higher in males compared to females.

Compared to the bDMARD (anti-TNF) cohort, findings suggest that there was an increased crude risk for NMSC (ever or on drug) and death (ever exposed) for the tofacitinib treated cohort, but that after confounder adjustment in a multivariable model the elevated association was no longer statistically significant. No statistically significant differences were observed for rates of safety endpoints between bDMARD (anti-TNF) treated and tofacitinib treated cohorts; no changes were observed following sensitivity analyses for select safety endpoints.

Compared to the bDMARD naïve (csDMARD) treated patient cohort, adjusted analyses suggest that the tofacitinib treated cohort had a statistically significant reduced risk of several safety endpoints, including total malignant events (ever or on drug), malignancies (except NMSC), solid tumours, and death (ever exposed). The relative hazard was higher among tofacitinib treated as compared with bDMARD naïve (csDMARD) treated patients for total serious infections, other serious infections (i.e. not pre-specified), and NMSC, but these differences were no longer statistically significant after adjustment. Results from the sensitivity analyses demonstrated no change in the effect estimates.

Overall, rates across safety endpoints were higher for patients ≥ 65 years old for all three patient cohorts, compared to patients < 65 . Total serious infections were the most common safety endpoint in both the ≥ 65 -year- and < 65 -year-old age groups, with pneumonia being the most frequent infection in both age groups. The rate of other serious infections was higher in the tofacitinib treated cohort compared to bDMARD naïve (csDMARD) and bDMARD (anti-TNF) treated cohorts; this was consistent in both age groups. In the < 65 -year-old age group, < 5 events of death on drug were observed in the tofacitinib group and the incidence of death in the ever-exposed group was lower in the tofacitinib treated group

compared to the bDMARD naïve (csDMARD) treated group but higher compared to the bDMARD (anti-TNF) treated group.

Discussion: Study findings are generally consistent with the known safety profile of tofacitinib. There were elevated incidence rates for NMSC, death, total serious infections, and other serious infections (NSMC and serious infections are important identified risks in the EU RMP) in the tofacitinib cohort relative to the bDMARD patients. However, after adjustment for multiple confounders, these were no longer statistically significant. The meta-analysis of the four tofacitinib PASS (details provided in Appendix 8 and in Appendix 4 SAP) compared tofacitinib and bDMARD cohorts and demonstrated a pooled estimate of aHR=1.03 (0.75, 1.41) for all-cause death (using the on drug approach); a pooled estimate of aHR=2.08 (1.55, 2.79) for NMSC (using the on drug approach); no pooled estimates were available for total or serious infections. 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 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.

In summary, results are generally consistent with known safety profile of tofacitinib. This final report describes the occurrence of pre-defined safety endpoints in UK patients with RA and included data on 361, 2831, and 2063 respective tofacitinib, bDMARD naïve (csDMARD), and bDMARD (anti-TNF) treated patients from tofacitinib start date (entry for the tofacitinib cohort was defined as date of treatment start from 01 May 2017) until 14 September 2025.

Marketing Authorization Holder: Pfizer Europe, Boulevard de la Plaine 17, 1050 Bruxelles Belgium.

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NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	An Active Surveillance, Post-Authorisation 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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBRA).
Protocol number	A3921312
Version identifier	1.0
Date	27 July 2026
EU Post Authorisation Study (PAS) register number	EUPAS31126
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz [®] (tofacitinib)
Product reference	EMA/H/C/004214
Procedure number	EMA/PAM/0000261850
Marketing Authorisation Holder (MAH)	Pfizer Europe
Joint Post-Authorisation Safety Study (PASS)	No
Research question and objectives	Research Question: What are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies?

	Objectives: • To evaluate the rates of serious infections, malignancy (overall, excluding non-melanoma skin cancer), subtypes of lymphoma, lung cancer, cardiovascular events, MACE, MI, VTE (DVT and PE), and other specified outcomes, including fractures, among patients with RA in United Kingdom (UK)-based register who initiate tofacitinib. Rates will also be estimated among RA patients who initiate tumour necrosis factor inhibitor (TNFi) drugs (ie, patients receiving Humira (adalimumab) (ADA), Enbrel (etanercept) (ETA), or Remicade (infliximab) (INF)) 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 methods to adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities and other potential confounders.
Country of study	United Kingdom (UK)



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Annex 1. List of stand-alone documents

[Appendix 1. SIGNATURES](#)

[Appendix 2.1 Protocol](#)

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

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 8. ADDITIONAL DOCUMENTS](#)

[Meta-Analysis Results for Tofacitinib Post-Approval Safety Study](#)

1. ABSTRACT (STAND-ALONE DOCUMENT)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
bDMARD	biologic disease modifying antirheumatic drug
BID	bis in die (twice a day)
BP	blood pressure
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
BSRBR-RA	British Society for Rheumatology Biologics Register- Rheumatoid Arthritis
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	Cardiovascular
CVD	cardiovascular disease
DAS	Disease activity score
DMARD	disease modifying antirheumatic drug
DMEC	Data Monitoring and Ethics Committee
DVT	Deep venous thrombosis
EBV	Epstein Barr Virus
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and
EPITT	European Pharmacovigilance Issues Tracking Tool
EQ-5D	EuroQol Five Dimensions Questionnaire
ESR	erythrocyte sedimentation rate
ETA	etanercept
EU	European Union
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	health assessment questionnaire
HLT	high level term
ICD	International classification of diseases
IEC	independent ethics committee
IL	Interleukin
INF	infliximab
IRB	institutional review board

Abbreviation	Definition
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
LLT	Low level term
LTE	long term extension
MACE	major adverse cardiovascular events
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial infarction
MTX	Methotrexate
NDA	New Drug Application
NEC	Not elsewhere classifiable
NHL	non-Hodgkin's lymphoma
NHS	National Health Service
NI	non-interventional
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	Post-authorisation study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PV	pharmacovigilance
PY	person-years
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAP	statistical analysis plan
SEER	Surveillance and Epidemiology End Results
SIR	standardised incidence ratio
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
TB	Tuberculosis
TBD	to be determined
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor

Abbreviation	Definition
UK	United Kingdom
VAS	Visual analog scale
VTE	Venous thromboembolism

3. INVESTIGATORS

Principal Investigators of the Protocol

Name, degree(s)	Title	Affiliation
Cherise Wong, PhD	Safety Surveillance Research Scientist	Pfizer, Inc.
Michelle Iannacone, PhD	Methods Lead and Safety Surveillance Research Scientist	Pfizer, Inc.
Kimme Hyrich, MD, PhD, FRCPC	Professor of Epidemiology and Consultant Rheumatologist	The University of Manchester

4. OTHER RESPONSIBLE PARTIES

Not Applicable

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Registration in the HMA-EMA Catalogues of RWD Studies	01 September 2019	26 August 2019	
Start of data collection	15 September 2019	01 September 2019	
End of data collection	14 September 2025	14 September 2025	
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	
Final report of study results	14 August 2026	14 August 2026	

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, patients with RA are at a higher risk of infections, cardiovascular 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 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 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 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 data in the British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA). Long term morbidity and mortality event tracking of these cohorts over seven 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.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 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 study is one of four registry-based post-authorisation safety studies (PASS), which are being conducted in the United Kingdom (UK), Sweden, Spain and Germany. This non-interventional, active surveillance study, embedded within the BSRBR register, is designated as a Post-Authorisation 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 patients with RA 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.^{5,6} The mechanism by which infection risk is increased in patients with RA 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,^{6,7,8,9} however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.¹⁰ 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}

Serious infections, including tuberculosis and herpes zoster are important identified risks for patients with RA 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.^{17,14} 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 patients with RA 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 the general population.¹⁹ The body of published evidence for increased risk of serious CV events among patients with RA 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 BSRBR-RA register collects data on other safety events of interest in the RA population including central nervous system (CNS) events, pregnancy and mortality. These events were also analyzed to identify new safety signals.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question: What are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies?

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 outcomes, including fractures, among patients with RA in an existing UK based register who initiate tofacitinib. Rates will also be estimated among existing

cohorts of patients treated with TNFi therapies to provide context for rates observed on tofacitinib.

No a priori hypotheses will be tested in this descriptive study.

- Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, and MI, VTE, and other event rates, including fractures, 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.

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 endpoint). 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.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	Septemb er 2021	Substantial	Title Page	Updated to replace old Pfizer logo with new one Updated to include EU PAS Register Number Updated objectives to align with changes in protocol. Updated contact information for protocol author. Updated contact information for the MAH Contact Person	Editorial change Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor
	Septemb er 2021		Section 2	Updated to include new abbreviations	Editorial change
	Septemb er 2021		Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principal investigator.
	Septemb er 2021		Section 4	Revised version and date.	Pharmacovigilance Risk Assessment

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				Updated Objective and Variables to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated Data Analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes.	Committee (PRAC) request and clarification.
	September 2021		Section 7	Updated to include information on changes to protocol resulting from June 2021 signal evaluation procedures. Also 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		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		Section 9.2.4	Updated Risk Window to include sensitivity analysis for the 90-extension period.	PRAC request and clarification.
	September 2021		Section 9.3.1	Updated to include CV risk factors	PRAC request and clarifications
	September 2021		Section 9.3.2	Updated to include lymphoproliferative malignancy subtypes, lung cancer and MACE as	PRAC request and clarifications

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Table 1. Amendments to the Protocol

Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				additional safety endpoints. Updated to include fracture as additional safety endpoint. Updated to include all-cause mortality as a safety endpoint.	Based on available data, Pfizer has identified fractures as a potential risk Editorial Change.
	September 2021		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		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		Section 11	Minor clarifications to safety reporting language	Editorial change
	September 2021		Annex 2	Author name changed. Signature and signature date updated	Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author.
	September 2021		Appendix 1	Updated to include definitions for additional endpoints.	PRAC request and clarifications
2.0	February 2022	Substantial	Title Page	Updated Research Questions and Objectives to include change in terminology from 'lymphoproliferative malignancy' to 'lymphoma'	PRAC request and clarification

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				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).	
	February 2022		Section 2	Updated to include new abbreviations	Editorial change
	February 2022		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. Updated the Milestones to remove reference to the reports provide to MAH every 6 months.	Editorial change PRAC request and clarification PRAC request and clarification
	February 2022		Section 7	Updated the Cardiovascular Disease section to remove MACE as an "important identified risk".	PRAC request and clarification
	February 2022		Section 8	Updated Objective to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added	PRAC request and clarification

Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				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).	
	February 2022		Section 9.3.1	Updated Baseline Data to include additional CV risk factors	PRAC request and clarification
	February 2022		Section 9.3.2	Updated the Endpoints to replace the term 'lymphoproliferative malignancy' with 'lymphoma'. Update the abbreviations for DVT and PE.	PRAC request and clarification Editorial change
	February 2022		Section 9.7	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
	February 2022		Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
	February 2022		All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
	February 2022		Annex 2	Signature date updated	Editorial change.
3.0	March 2025	Substantial	Title Page	Updated Author information and MAH Contact	Editorial change.
	March 2025		Section 2	Added abbreviation for Heads of Medicines Agencies-European Medicines Agency	Editorial change.

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
	March 2025		Section 6	Updated name of EMA register.	Editorial change
	March 2025		Section 9.2.2	Added exclusion two exclusion criterion including to 1) exclude anyone that doesn't meet the inclusion criteria and 2) 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.
	March 2025		Section 9.7	Added sensitivity analysis for the final report to assess potential confounding by prior non- tofacitinib JAKi	To assess potential confounding via stratification (since excluding patients with prior use would reduce sample size substantially)
4.0	July 2025	Substantial	Title Page	Product Reference and Procedure Number was updated	Editorial change to align with IRIS requirements
	July 2025		Title Page	MAH Contact Person Information was Updated	Editorial change
	July 2025		Section 9.2.2	Removed exclusion criteria to exclude patients with prior history of the specific safety event of interest being analyzed. Included statement "There are no exclusion criteria for this study."	Per PRAC request. prior history will be accounted for using model adjustment for baseline comorbidities. Editorial change to match MAH protocol template instructions.
	July 2025		Section 9.2.4	To align with amendment to section 9.2.2, removed word "/exclusion" from the last sentence that now reads as follows "Patients	Editorial change.

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				switching therapies are eligible to move between cohorts if inclusion criteria are met."	
	July 2025		Annex 2	Signature date updated.	Editorial change.
5.0	Decemb er 2025	Substantial	Section 4	Revised Abstract by: - Updating description of second comparator cohort. - Updating text regarding the availability of characteristics captured at baseline. - Updating the biologic naïve (non-biologic control cohort) sample size available for analysis.	- To align with Section 9.2.1 Inclusion Criteria. - To align with amendments made to Section 9.3.1. - The Registry provided an update on the sample size available for the biologic naïve control cohort.
	Decemb er 2025		Section 9.2	In Study Population section, updated the biologic naïve (non-biologic control cohort) sample size.	The Registry provided an update on the sample size available for the biologic naïve control cohort.
	Decemb er 2025		Section 9.3.1	Removing baseline characteristics that are not collected by Registry: Diagnosis (including the presence or absence of those features listed in 1987 American College of Rheumatology (ACR) criteria for RA)	Reason for removal of baseline characteristics: BSRBR-RA only includes patients with "consultant rheumatologist diagnosis of rheumatoid arthritis (RA)" as eligible for

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				- Year of recalled symptom onset or year of diagnosis - Duration of previous therapy recorded as start/month/year - Ever use at baseline of combined hormonal contraceptives or hormone replacement therapy (Y/N) - Inpatient care because of RA (i.e., RA as main diagnostic listing; from date of admission to date after discharge - History of chronic kidney disease, statin use, as proxy for history of hypercholesterolemia, coronary heart disease - Current working status Updated description of baseline characteristics: - Updated "oral steroid use" to "steroid use" - Updated "MI within previous 3 months prior to index date" to MI - Updated malignancy events by removing "(i.e., history of malignancies	inclusion in the study cohorts - BSRBR-RA standardised form at baseline does not collect information on years of symptom onset or year of diagnosis - BSRBR-RA standardised form used at baseline does not include dates of previous therapy exposure to information duration of use prior to index date - BSRBR-RA standardised form used at baseline does not include information on ever use at baseline of combined hormonal contraceptives or hormone replacement therapy - BSRBR-RA standardised form used at baseline does not include information on inpatient care because of RA - BSRBR-RA standardised form used at baseline does not include information on

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
				excluding NMSC, and specifically history of NMSC) - Added History of Renal Disease - Updated vaccination to "Herpes Zoster Vaccination"	history of chronic kidney disease, hypercholesterolemia, or coronary heart disease - BSRBR-RA standardised form used at baseline does not include information on current working status Reason for updating the description of the baseline characteristics: - BSRBR-RA standardised form used at baseline does not include information on type of administration of steroid use - BSRBR-RA standardised form used at baseline does not include information on date of comorbidity therefore it is not possible to identify MI within 3 months of the index date - BSRBR-RA standardised form used at baseline does not include information on type/site of malignancy

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Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
					- BSRBR-RA standardised form used at baseline collects information on history of renal disease, which was added since chronic kidney disease information is not collected - Vaccination status refers only to vaccination to herpes zoster
	Decemb er 2025		Section 9.4	Updated information under <i>Baseline</i> description of data source regarding information collected at baseline.	To align with amendments made to Section 9.3.1.
	Decemb er 2025		Section 9.9	Updated Limitations to Research Methods to include limitations in data capture of baseline characteristics that may limit data interpretation.	To provide clarity of potential limitations in interpretation of study findings due to missing baseline data leading to inability to adjust for potential differences in distribution across study cohorts.
	Decemb er 2025		Section 9.9	Updated Limitations to Research Methods to include limitations in data capture by enrollment date of registry patient.	Baseline data for history of VTE, history of heart failure, and history of angina will be missing for all registry patients that were registered prior to February 2021. Data for ethnicity will be missing for registry patients registered between 2019 and 2024.

Table 1. Amendments to the Protocol

Amendme nt number	Date	Amendment Type (Substantial or administrati ve)	Protocol section(s) changed	Summary of amendment(s)	Reason
	Decemb er 2025		Annex 2	Signature date updated.	Editorial change.
6.0	March 2026	Substantial	Section 9.3.1	Added variable "year of RA diagnosis" to Baseline Data.	PRAC Request
	March 2026		Section 9.9	Updated Limitations Section by removing "and history of angina" from paragraph 4, line 11. This change was made following confirmation from BSRBR that information on history of angina is avai lable prior to February 2021 and will be included in the Final Report.	PRAC Request
	March 2026		Annex 2	Signature date updated.	Editorial change.
7.0	April 2026	Administrativ e	Table of Contents and Correspondi ng Sections of Document Body	The Table of Contents was updated to correct the section numbers to match the most recent version of the internal Pfizer CT-24 protocol template for secondary data collection.	Editorial change.
	April 2026		Annex 2	Signature date updated.	Editorial change.

9. RESEARCH METHODS

This section includes the research methods used in this study as described in the [study protocol, version 7.1 dated 15 April 2026](#) the [statistical analysis plan \(SAP\), version 3.0 dated 23 April 2026](#).

9.1. Study Design

This was an active surveillance study using existing data within the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), an ongoing prospective observational cohort study started in 2001 and up to 14 September 2025 for this final report, which aimed to study the safety of new therapies for RA during routine post-marketed clinical use. This was a descriptive study, and no hypotheses were tested. This study estimated the incidence rates (IRs) of safety events of interest among patients starting

tofacitinib (fully approved and available in the UK starting from January 2018). Rates were estimated among (1) an existing cohort of patients starting originator TNFi (ADA, ETA and INF) since 2010 and (2) an existing historic cohort of patients with active RA who had not started a targeted therapy (recruited between 2002 and 2009) but were on csDMARD.

9.2. Settings

For the purpose of analyses in this report, all exposure time was calculated from the registration date or the date of drug start (i.e. index date), whichever came later. Registration date is defined as the date on which patient data, including biologic start date, are received by the BSRBR-RA team in Manchester following rheumatologist-led enrolment and informed consent. See [Section 9.9.2.1](#) for details on index date definition by cohort. The BSRBR-RA was established in 2001 to study the safety of biologic therapies in patients with RA living in the UK. For the first 7-8 years, the focus was on the safety profile of the first three approved TNFi agents (ie, ADA, ETA and INF) as a class and as individual therapies. Apart from the risk of developing tuberculosis, data within the BSRBR-RA has not demonstrated any clear differences in safety profile between these agents. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies after these agents receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA included recruitment and collection of data from two parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.²⁰ Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections,⁶ and malignancies.^{18,21} All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

External validity, ie, generalizability to patients with RA who were not enrolled in the register, was maximised by encouraging physicians to enroll each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

Within the BSRBR-RA there were 2 comparator cohorts. These represent cohorts of patients exposed to agents which have been studied:

1. The first was a cohort of patients with prevalent active RA (guide disease activity score (DAS) >4.2) on csDMARD recruited between 2002 and 2009 for whom follow-up data were already available. No new data were collected for this cohort as the 7-year follow-up period since last subject first visit has been surpassed. This cohort consisted of patients who were either being treated before the advent of approved targeted therapies for RA or for whom biologics were not needed or desired. Some of these patients would have subsequently progressed to a biologic or other new therapy, been lost to follow up or died. For the purpose of analysis (see below), their follow-up was censored at the time of the first occurrence of the censoring events specified in [section 9.4.1](#), thus they

only contributed patient months of follow-up to this cohort up to the first censoring event. Patients initially enrolled in the first cohort who later initiated a targeted therapy were eligible for subsequent enrolment in the corresponding cohort, eg, biologic or tofacitinib.

2. The second was a cohort of TNFi-exposed patients with active RA registered within 6 months of starting originator ADA, ETA or INF as their first biologic/tsDMARD. Recruitment to this cohort started in 2010 and is ongoing. Patients enrolled in the TNFi-cohort who later initiated tofacitinib were eligible for subsequent enrolment in the tofacitinib-exposed cohort. Per national prescribing restrictions, patients will not be prescribed TNFi and tofacitinib concurrently.

9.3. Subjects

The active surveillance population included RA patients already enrolled in the register who met the criteria for the cohorts as defined in [Section 9.2.1 \(in the protocol, Version 7.1\)](#) as well as patients with RA, newly treated with tofacitinib following EMA approval and UK launch of the product (fully available January 2018) and registered with the BSRBR-RA. In the BSRBR-RA, there were two comparison cohorts readily available which included the csDMARD comparison cohort containing 3600 biologic-naïve patients and the anti-TNF comparison cohort containing 2100 biologic-exposed patients. Some tofacitinib-exposed patients were newly enrolled in the register, having been recruited to the BSRBR-RA within 6 months of their first dose. Others were already enrolled in the BSRBR-RA as prior biologic disease modifying antirheumatic drug (bDMARD) initiators but switched to tofacitinib during follow up. Key clinical data at time of switch were requested. For patients enrolled during the 6-month period after initiation, the baseline date was reported as the drug start date rather than the date of registration. The first post-baseline visit occurred 6 months after tofacitinib initiation, regardless of date of enrolment.

9.3.1. Inclusion Criteria

The inclusion criteria for eligibility for inclusion in the BSRBR-RA included 1) willingness to give informed consent to participate in the study with access to medical records, 2) aged over 16 years, and 3) consultant RA diagnosis. In addition to the BSRBR-RA eligibility criteria, patients met all the following criteria at baseline to be eligible for inclusion in the study.

9.3.1.1. Inclusion Criteria: Tofacitinib Exposed Cohort

- Eligible for BSRBR-RA.
- Initiation of tofacitinib, regardless of prior therapy (within 6 months of register enrolment).

9.3.1.2. Inclusion Criteria: bDMARD Naïve Cohort (csDMARD Comparator Cohort 1)

- Eligible for BSRBR-RA.
- Active RA (guide DAS >4.2 (to ensure comparable disease activity to tofacitinib and bDMARD initiators).
- Prevalent use of csDMARD without bDMARD or tofacitinib.
- Enrolled in register between 2002-2009.

9.3.1.3. Inclusion Criteria: bDMARD Exposed Cohort (Anti-TNF Comparator Cohort 2)

- Eligible for BSRBR-RA.
- Initiation of originator ADA, ETA or INF as their first bDMARD within 6 months of register enrolment.

9.3.2. Exclusion Criteria

There were no exclusion criteria for this study.

9.4. Variables

For patients enrolled during the 6-month period after initiation, the baseline date was reported as the drug start date rather than the date of registration. The first post-baseline visit occurred at 6 months after tofacitinib initiation, regardless of date of enrolment. Key clinical data at the time of switching are collected.

9.4.1. Exposure to RA Treatments

Table 2 includes the medications used to treat RA for each of the study cohorts described above. At baseline, hospitals were asked for details of previous RA therapies. For biologics, drug and start/stop dates were requested. For csDMARDs and steroids, it was only asked if they have ever received it.

Table 2. Classification of Medications for the Treatment of RA by cohort

Tofacitinib	bDMARD (anti-TNF)	bDMARD naïve (csDMARD)
Xeljanz	Adalimumab	Methotrexate
	Etanercept	Azathioprine
	Infliximab	Cyclophosphamide
		Leflunomide
		Cyclosporine

9.4.2. Safety Endpoints

The BSRBR-RA is an existing data collection system for evaluating a range of safety outcomes associated with therapies used to treat RA including cancers,^{18,21} CV events²² and serious infections.⁶

The following pre-specified safety endpoints of interest were captured:

1. Hematologic disorders:
 - Aplastic Anaemia
 - Pancytopenia
 - Agranulocytosis
 - Other dyscrasia (includes other serious dyscrasia for serious haematologic events that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis)

- Serious Neutropenia
- Serious Haemorrhage
- 2. Disorders of the nervous system:
 - Cerebrovascular Accident
 - Demyelination
 - Peripheral neuropathy
 - Other CNS (other serious CNS events that are not classed as central demyelination, peripheral neuropathy or stroke)
 - Optic Neuritis
- 3. Death (all-cause mortality)
- 4. Fractures
- 5. Hepatitis B Reactivation
- 6. Malignancies (overall, excluding NMSC)
- 7. Malignancies (overall)
 - Lymphoproliferative
 - Lymphoma (overall)
 - Non-Hodgkin lymphoma
 - Hodgkin lymphoma
 - Myeloma
 - Leukaemia
 - Chronic lymphatic leukemia
 - Non-melanoma Skin Cancer (NMSC)
 - Other malignant solid tumours
 - Brain neoplasms
 - Glioblastoma
 - Lung cancer
 - Melanoma
- 8. Cardiac disorders (total) and by subtype:
 - Serious Congestive Heart failure (new or worsening of condition associated with treatment)
 - Myocardial infarction
 - Acute Coronary Syndrome
 - MACE (including MI, stroke, and death due to cardiovascular events)
 - Other serious cardiac events not classified as MI or heart failure
- 9. Pregnancy Occurrence
- 10. Progressive multifocal leukoencephalopathy (PML)
- 11. Thromboembolic events (VTE) and its components separately:
 - Deep vein thrombosis (DVT)
 - Pulmonary embolism (PE)
- 12. Serious Infusion/Immunologic Reaction
- 13. Serious Hypersensitivity Reaction

14. Serious infection (overall) and by subtype:

- Pneumonia (non-opportunistic and opportunistic)
- Septicaemia (non-opportunistic and opportunistic)
- Bone/joint infection (non-opportunistic and opportunistic)
- Herpes zoster (including hospitalized and non-hospitalized events). (non-opportunistic and opportunistic)
- Other serious infection (non-opportunistic and opportunistic); not classified as pneumonia, septicaemia, bone/joint infection, or herpes zoster

15. Tuberculosis (TB)

16. Serious Hepatic Dysfunction/Failure

17. Gastrointestinal (GI) perforation

- Serious Lower Gastrointestinal Ulcer/Bleed/Perforation

18. Serious Lupus/Lupus-Like Illness

19. Serious Skin Reaction (e.g., Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis)

20. Interstitial lung disease

9.4.3. Baseline Data

The following baseline data were derived from BSRBR information reported by the recruiting clinician, using a standardised form. Data from all patient cohorts was collected in and identical fashion.

1. Diagnosis of RA by rheumatologist; year of RA diagnosis;
2. Age at treatment start, gender;
3. Ethnicity (patient form);
4. Previous drug history of immunosuppressive csDMARDs and biologics, biosimilar or other advanced therapy;
5. Co-morbidity (e.g., history of diabetes mellitus, history of MI, history of hypertension, and ever for malignancy events) (<https://bsrbr.org/hospitals/data-collection/>);
6. All current therapy;
7. Findings necessary to calculate the DAS28 (indicator of disease severity);
8. Health Assessment Questionnaire (HAQ) and EuroQol Five Dimensions Questionnaire (EQ-5D);
9. Height, weight, single blood pressure (BP) measurement at baseline;
10. Steroid use (baseline and ever exposure);
11. Smoking history (current, past, never – patient form);

12. Herpes zoster vaccination;

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 below:

1. Age (patients ≥ 65 years versus < 65 years)
2. Previous VTE (*if feasible*)
3. History of major surgery
4. MI
5. Heart failure
6. Malignancy
7. Diabetes
8. Hypertension

To facilitate the evaluation of the safety endpoints of MI and MACE, the following CV risk factors will also be evaluated at baseline:

1. Age (patients ≥ 65 years versus < 65 years)
2. History of diabetes
3. History of renal disease
4. History of hypertension
5. History of previous MI
6. History of stable angina pectoris

9.5. Data Sources and Measurement

The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) was launched in October 2001. The primary aim was to investigate the long-term outcomes of patients with rheumatoid arthritis (RA) treated with biologic (bDMARD) or targeted synthetic (tsDMARD) agents with particular reference to safety. The study has been organised under the auspices of the British Society for Rheumatology (BSR) and is based at the Centre for Epidemiology Versus Arthritis (formerly Arthritis Research UK Centre for Epidemiology) at The University of Manchester, UK.

Between 2001 and 2008, the BSRBR-RA focussed on recruiting and following patients with RA who were starting anti-TNF therapy (mainly Humira, Enbrel, Remicade) alongside an appropriate comparison cohort, used to put any findings into context. As new agents were licensed in the UK, there were invited to join this national effort.

Baseline

BSRBR was the source of the core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardised form. In addition, some BSRBR personal and medical information reflect data obtained directly from each patient recruited (e.g, on smoking history).

Follow-up

BSRBR data were the source of information on anti-rheumatic treatment, updated every 6 months/year. This included continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of DAS28 was also collected.

BSRBR data included reports from patients contacted every 6 months for the first three years of their follow-up period and asked to complete a patient diary which included data about hospital admissions and new hospital referrals. Data collection instruments were distributed by post to patients and their physicians according to schedule. One attempt was made to follow-up non-responders. Non-responders at one follow-up point are (unless further follow up is refused) contacted again at the next follow-up point and all follow-up data since the last completed study follow-up was requested. Patients lost to follow up continue to be followed for death and cancer endpoints through the respective registers.

Endpoints

BSRBR data included reports of serious morbidity, either by subject or enrolling physician during regularly scheduled assessments, and the referring physician was immediately contacted by the BSRBR-RA and asked to provide further details, where available. For specific morbidities of interest certain specific details were requested. All serious morbidities reported to BSRBR were coded by a trained nurse using the Medical Dictionary for Regulatory Activities (MedDRA).

BSRBR used the UK national death and cancer registers allowing the “flagging” of individuals such that if they died or were entered in a cancer register, the BSRBR-RA learned of the event and obtained death certificate details or cancer register details. By law, deaths due to natural causes were to be registered within 5 days. However, the lag-time between cancer incidence and registration in the national cancer database took longer depending on confirmatory diagnoses, tests, national cancer register requirements and local resources. BSRBR-RA downloaded which patients have been flagged for incident cancer or death once per year based on personal identifiers.

9.6. Bias

This study was designed to assess the safety of tofacitinib within the clinical practice setting utilising the BSRBR-RA, a well-established UK-based rheumatology register. Despite the strengths of the register, data must be evaluated considering their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, residual confounding and generalizability were of concern when comparing event rates.

Despite its availability in the EU RA treatment armamentarium, it is possible that patients treated with tofacitinib 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 increased risk for safety events of interest. Biases resulting from channeling may present as increased rates of safety events of interest. Comparison to internal comparators were included to help illuminate such channeling.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing these events. The rates of events of interest and their distribution among patient-types may have changed over time. The comparators in this study were not contemporaneous to tofacitinib treated patients. Analyses were 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 the BSRBR-RA 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.

This study included patients followed for a period of 7-years after the first tofacitinib patient was enrolled in the register. Conclusions may not be generalizable outside of the 7-year period since initiation of therapy.

9.7. Study Size

This active surveillance descriptive study was not intended to test a pre-specified statistical hypothesis; therefore, no minimum sample size was required. While the primary objective of the study was active surveillance, conducting quantitative, confounding controlled comparisons depended on having a sufficient sample by the end of the study. The details on the impact of sample size on the power to detect a 2- fold difference in event rates between tofacitinib-initiators and bDMARD-initiators are discussed in the [study protocol section 9.5](#) (Refer to [Appendix 1](#)).

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the [statistical analysis plan \(SAP\) version 3.0, dated 23 April 2026](#), filed and maintained by the sponsor ([Appendix 4](#)).

In BSRBR-RA data are collected via the hospital (at 6 monthly intervals for three years and annually thereafter) and patient questionnaires (at 6 monthly intervals for three years). Patient and physician assessments are sent via post to the study team at the University of Manchester who then enter the data into the study database.

9.9. Statistical Methods

The study population will comprise all patients with RA enrolled within BSRBR who receive tofacitinib following European Medicines Agency (EMA) approval and UK launch. For

contextualization purposes, the study population will also include BSRBR patients treated with bDMARDs and naïve to bDMARDs (treated with csDMARDs).

Detailed methodology for summary and statistical analyses of data collected in this study is documented in the [statistical analysis plan \(SAP\); version 3.0 dated 23 April 2026 in Appendix 4](#). All data management and analyses were conducted using Stata version 14.0.

9.9.1. Main Summary Measures

Means and standard deviations were used to describe baseline continuous variables. Number of events and crude and age-sex-standardised IRs of safety events were presented as rates per 1000 PY (95% confidence intervals (CI)), for each cohort and each safety endpoint of interest. Crude and adjusted hazard ratios were presented with corresponding 95% CI.

9.9.2. Main Statistical Methods

Crude incidence rates and number of events were tabulated for each treatment cohort and safety endpoint. Age- and sex-standardised rates were calculated for each safety endpoint, using the tofacitinib treated cohort as standard; a direct standardization approach was implemented, use the age-sex distribution of person-time in the tofacitinib treated cohort.

Analyses of endpoints included rates of events overall and in subgroups defined by baseline characteristics. including age ≥ 65 and < 65 (given the age-dependent rate events of interest) and sex (male/female).

Adjusted hazard ratios were estimated with Cox proportional hazards regression using time from index as the time scale. Comparisons were made for tofacitinib vs. bDMARD (anti-TNF)-exposed, and tofacitinib vs. bDMARD naïve (csDMARD)-exposed. Models were adjusted using deciles of a propensity score which was calculated using the following variables: 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. All variables were recorded at start of treatment for people who registered in bDMARD Naïve (csDMARD), bDMARD (anti-TNF) or tofacitinib cohorts (the detail of registered patients versus switcher patients at [Section 9.9.2.3](#)). For patients who registered in the non-tofacitinib cohorts and switched to tofacitinib treatment without re-registration, or switchers, smoking status, rheumatoid factor status, number of co-morbidities and steroid status which were recorded at registration were carried forward to the treatment start date. Comparison of time to first event was included in Cox proportional hazards regressions only when a minimum of 10 events across tofacitinib and comparator cohorts was observed with at least five events in each cohort. When cohort outcome combinations had less than 5 events, only numbers, crude and age/sex-adjusted incidence rates were estimated.

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](#)). Detailed methodology

for the meta-analyses to combine the results of this study with the results from other participating European registers (studies A3921314, A3921316, and A3921317) is also documented in the [statistical analysis plan \(SAP\); version 3.0 dated 23 April 2026 in Appendix 4](#). All data management and analyses were conducted using Stata version 14.0.

9.9.2.1. Index Date

9.9.2.1.1. Main Cohort: Patients with RA who Initiate Tofacitinib

The index date for the tofacitinib cohort was defined as the date of registry entry or the first tofacitinib dose taken, whichever came later. Entry will be defined as the date of the start of treatment from 01 May 2017 through 14 September 2025. Patients with prior use of bDMARDs or other therapies (e.g., other JAK inhibitors) during the baseline period were not excluded.

9.9.2.1.2. Comparator Cohort: bDMARD Naïve (csDMARD) Cohort

The index date for bDMARD naïve comparator cohort was date of entry into the BSRBR register.

9.9.2.1.3. Comparator Cohort: bDMARD Exposed (anti-TNF) Cohort

The index date for bDMARD (anti-TNF) exposed comparator cohort was the date of registry entry or the first dose of ETA, ADA, or INF, whichever came later.

Patients who switched to a subsequent therapy were eligible for enrollment as an initiator of the subsequent therapy, and the initiation date was defined as the date of initiating the subsequent therapy.

9.9.2.2. Follow-up and Risk Window

Within each cohort each patient was evaluated for safety events of interest and accrued person time from the cohort index date until the first occurrence of the event of interest, initiation of biologic (comparator cohort 1), discontinuation of biologic (comparator cohort 2), discontinuation of tofacitinib (tofacitinib exposed cohort), death, loss to follow up, exit from the register or after 7-years of follow up. Differences in duration of therapy were examined (similar to censoring patterns).

Follow-up was uniquely determined for each safety endpoint of interest, falling under one of two broad categories (see [Appendix 4 SAP Section 4.7.1](#) for details):

9.9.2.2.1. (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,
- Date of last received follow-up form,
- Date of death,

- Loss to follow up,
- Exit from the register,
- End of data collection (cut-off date for the report),
- End of treatment* +90 days (even in cases of subsequent switching to another biologic agent during the 90-days following end of therapy), or
- After 7 years of follow up. (Interim reports did not censor the existing comparison cohorts to match the tofacitinib cohort on index date or duration of follow up. The final report censored all patients at 7 years.)

*End of treatment was defined as the end of treatment date recorded by the treating rheumatologist. The healthcare team at the hospital will be contacted every 6 months for the first 3 years and then annually thereafter and asked to complete a standard data form covering any change in treatment over the preceding 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. 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. 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 captured.

For bDMARD Naïve (csDMARD) control patients, follow-up time starts at entry to study and continues until death, the date of last received follow-up form, the cut-off date for this report, or until patient starts a biologic drug. The report can only include patients for whom at least one follow-up form has been returned.

9.9.2.2.2. (2) Analysis for Malignancy, Progressive multifocal leukoencephalopathy (PML), and All-Cause Mortality outcomes

These outcomes were evaluated using two approaches: 1) an 'ever exposed' approach, and 2) a censor at switch approach as the secondary analysis.

9.9.2.2.2.1. Ever Exposed Follow-up

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

- Event of interest,
- Date of last received follow-up form (PML only),
- Date of death,
- End of data collection
- After 7 years of follow-up

For analyses of risk of malignancy, the analysis assumes an ever exposed model of risk assessment and therefore, the **risk window** for the Tofacitinib or anti-TNF cohorts includes all person-time in the register from start of therapy and extends until death or the cut-off date for the report, whichever comes first, even in case of subsequent switching to another biologic agent. For bDMARD Naïve (csDMARD) control patients, follow-up time starts at entry to study and continues until death, the cut-off date or patient starts biologic drug.

With the **ever exposed** (also known as **always at risk**) approach, follow up for each exposure cohort continued after switching to a new drug or discontinuation of treatment. This approach maximized 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 were double counted if a patient indexed to bDMARD switched to tofacitinib and a malignancy occurred subsequent to tofacitinib exposure. That is, the event was assigned to both the bDMARD and the tofacitinib exposure cohorts as were the corresponding PY from the index date to the respective cohorts. For bDMARD naïve (csDMARD) control patients, follow-up time starts at entry to study and continues until death, the cut-off date or patient starts biologic drug. 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 PY 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. [3](#), [11](#) [18](#), [23](#)

9.9.2.2.2. Censoring Follow-up at Switch

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

- Event of interest,
 - Date of last received follow-up form,
 - Date of death,
 - End of data collection,
 - Date of switch.
1. Tofacitinib cohort: switch to another JAK inhibitor, or switch to a non-JAK-inhibitor based advanced systemic therapy. Follow-up time starts from the tofacitinib start date until tofacitinib stop plus 90-day extension.

2. bDMARD cohort: switch to tofacitinib or other non-biological advanced systemic therapy (JAK inhibitors, non-TNF bDMARDs, certolizumab and golimumab). Follow-up time starts from bDMARD start date until bDMARD stop date plus 90-day extension.
3. bDMARD naïve cohort: switch to a non-csDMARD therapy (all b/tsDMARDs for RA). Follow-up time will end when patient starts a biologic drug, so they would not have a 90-day extension.

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).

9.9.2.3. Registered Patients Versus Switcher Patients

The term “registered” patient refers to all patients who registered with the BSRBR-RA and upon starting their biologic/biosimilar/other targeted therapy, completed a clinical and patient baseline form. If a patient switched from their registered drug to a new biologic/biosimilar/other targeted therapy, they were usually encouraged to re-register prompting the completion of a new baseline form to identify patient and disease characteristics at the start of their new therapy. These patients also counted as “registered” patients.

However, in some cases patients switched biologic/biosimilar/other targeted therapy and did not re-register in the study. These patients are referred to as “switchers”. This is because, whilst BSRBR continued to follow them up for safety events, BSRBR did not receive new baseline forms with the patient’s updated disease characteristics at the point of starting their new therapy.

So, for example, if a patient registered in Anti-TNF and switched to Tofacitinib treatment without re-registration, “age” and “disease duration” can be re-calculated for Tofacitinib treatment, “gender” was carried forward. Other variables were coded as missing and will be handled as mentioned in Section 9.9.3 Missing Values.

Baseline characteristics were only reported for the “registered” patients. For re-registering/switching patients on a biologic, biosimilar other new targeted therapy who were already participating in the registry, there was a simplified baseline information form which captures a subset of the baseline data most likely to change over time.

9.9.3. Missing Values

For baseline tables, no imputation of missing values was performed, and a missing category was added for patients missing a characteristic (categorical) of interest. For calculations of event rates, missing baseline covariate data were replaced using multiple imputation. For the multivariable Cox proportional hazard regressions, two models were provided: 1) a complete case analysis and 2) a missing category analysis.

The database forced entry for dates of treatment start and for dates of occurrence of an event, therefore, no special handling or imputation was needed for missing drug exposure data.

9.9.4. Sensitivity Analyses

9.9.4.1. bDMARD Comparator Cohort Never Exposed To Tofacitinib Or Other Non-Biologic Advanced Therapies

A sensitivity analyses was conducted that restricted the bDMARD comparator cohort to patients who were never exposed to tofacitinib or other non-biologic advanced therapies (e.g. baricitinib (Olmiant) and upadacitinib (Rinvoq)) and compared the characteristics of those bDMARD patients who were never not those who were ever exposed to tofacitinib or other non-biologic advanced therapies. These sensitivity analysis results were presented as summary statistics of those without and with previous tofacitinib use or other non-biologic advanced therapies (in [Table 11](#)).

9.9.4.2. Potential Confounding by Non-Tofacitinib JAK Inhibitors

To evaluate and account for potential confounding by prior non-tofacitinib JAK inhibitors, a sensitivity analyses with stratified results by the absence ([Table 12](#)) versus presence ([Table 13](#)) of prior non-tofacitinib JAK inhibitors was conducted.

9.9.4.3. MACE, MI, Serious Infection, VTE, herpes zoster, PML, and Gastrointestinal Perforation Events

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.

9.9.5. Subgroup Analyses

9.9.5.1. Subgroup Analysis For Age-Dependent Events

Given the age-dependent rate events of interest, analysis will be stratified by older adult patients aged ≥ 65 years versus patients under the age of 65 ([Table 14](#) and [15](#)).

9.9.5.2. Subgroup Analysis By Risk Factors And Time Periods

For the safety endpoints of VTE (overall and by subtype), incidence rates were stratified by patients with ≥ 1 VTE risk factors versus no VTE risk factors ([Table 16](#)). Likewise, for the safety endpoints of cardiac disorders (overall and stratified by subtype), incidence rates were stratified by patients with ≥ 1 CV risk factors versus no CV risk factors ([Table 18](#)).

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 were also conducted (i.e., period prior to 31 January 2020 vs. period after 31 January 2020) ([Table 17](#)). Likewise, stratification of the incidence rates by time period (i.e. before and after

June 2021) was conducted to account for changes in the SmPC for CV events (i.e. MACE and MI) (Table 19) and malignant events (i.e. malignancy excluding NMSC, lung cancer, lymphoma) (Table 20).

9.9.6. Amendments to the Statistical Analysis Plan

As data for "History of VTE" and "History of Heart failure" at baseline was collected since February 2021, it was not used in this report and in the assessment of VTE risk factors.

Regarding the treatment of missing data, SAP (v.3; Section 3.6) described that the multivariable Cox proportional hazard regression would employ two models, one of which would use a missing category analysis. However, since missing baseline covariate data were replaced using multiple imputation, the missing category analysis was not conducted.

9.10. Quality Control

Data used in this study are secondary data collected as part of the existing BSRBR, which has established quality control practices.

9.11. Protection of Human Subjects

Subject Information and Consent

Not Applicable.

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

The final protocol, any amendments, and informed consent documentation were reviewed and approved by a local data protection agency for each site participating in the study.

The BSRBR-RA protocols were approved by the North West 5 Research Ethics Committee (REC 00/8/053 with most recent approval amendment (#27) approval date of 06-Dec-2018).

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 (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), EMA guidelines, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. RESULTS

The results from this final analysis are presented in Table 3– 20.

10.1. Participants

The baseline details of the three cohorts are presented in Table 3. Following the application of study-specific inclusion and exclusion criteria, as of 14 September 2025, a total of 136 patients with RA have registered into the BSRBR-RA starting Xeljanz (tofacitinib), plus a

further 225 have started during BSRBR-RA follow-up, giving a total of 361 patients starting Xeljanz (Tofacitinib) in this analysis. There were 2831 csDMARD treated patients and 2063 bDMARD (anti-TNF) treated patients that were recruited to the BSRBR-RA. Patients for the Xeljanz (tofacitinib) cohort were recruited from 86 hospitals across the UK prescribing the treatment for RA. In patients starting Xeljanz (tofacitinib), there were 39 registered starting the drug as their first b/tsDMARD, whilst 322 patients started Xeljanz (tofacitinib) after switching from another b/tsDMARD therapy. There were more females (75 to 78%) than males (22-25%) across all three cohorts and age was generally comparable across all three treatment cohorts, with most patients being aged 55 or older (>50%).

Table 3. Baseline details of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts,

		Tofacitinib Cohort Patients	bDMARD Naïve (csDMARD) Cohort Patients	bDMARD (Anti-TNF) Cohort Patients
Cumulative number of registrations		361	2831	2063
Cumulative number by gender	Male	81 (22%)	708 (25%)	506 (25%)
	Female	280 (78%)	2123 (75%)	1557 (75%)
Cumulative number by age at treatment start	16-18	0 (0%)	<5 (<1%)	<5 (<1%)
	19-34	11 (3%)	88 (3%)	136 (7%)
	35-44	29 (8%)	246 (9%)	198 (10%)
	45-54	66 (18%)	510 (18%)	488 (24%)
	55-64	108 (30%)	929 (33%)	610 (30%)
	65-74	105 (29%)	737 (26%)	503 (24%)
	75 +	42 (12%)	319 (11%)	126 (6%)

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Refer to [Section 9.3.1](#) for cohort definitions.

[Table 4](#) presents the total exposure time in person-years for patients in all three patient cohorts used to estimate the incidence rates of the safety endpoints of interest. Median follow-up (i.e. person time at risk) by cohort differed by which outcomes were being assessed. For instance, for malignancy, a median follow up of six to seven years was observed across all three cohorts.

Table 4. Total exposure included in the analysis for patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]		bDMARD Naïve (csDMARD) Patients [N = 2831]		bDMARD (Anti-TNF) Patients [N = 2063]	
Outcome		N	Person-years	N	Person-years	N	Person-years
All SAEs except malignancy or death but including pregnancy (on-treatment)	Male	81	200.3	708	3370.3	506	1421.6
	Female	279	639.9	2122	10445.3	1556	4336.7
	Total	360	840.2	2830	13815.6	2062	5758.2
	Min	-	<0.1	-	<0.1	-	<0.1
	Mean	-	2.3	-	4.9	-	2.8
	Median	-	1.6	-	6.7	-	2.3
	Max [#]	-	7.0	-	7.0	-	7.0
Death (on-treatment)	Male	81	206.5	708	3632.9	506	1443.8
	Female	279	659.4	2123	11100.0	1556	4411.9
	Total	360	865.9	2831	14732.8	2062	5855.7
	Min	-	0.2	-	<0.1	-	<0.1
	Mean	-	2.4	-	5.2	-	2.8
	Median	-	1.6	-	7.0	-	2.4
	Max [#]	-	7.0	-	7.0	-	7.0
Malignancy (ever-exposed)	Male	81	445.2	708	3632.9	506	3305.9
	Female	280	1544.9	2123	11100.0	1557	10367.3
	Total	361	1990.1	2831	14732.8	2063	13673.2
	Min	-	0.2	-	<0.1	-	0.1
	Mean	-	5.5	-	5.2	-	6.6
	Median	-	6.0	-	7.0	-	7.0
	Max [#]	-	7.0	-	7.0	-	7.0

Data cut at 7 years after start of therapy.

Note: refer to [Section 9.3.1.](#) for cohort definitions Refer to [Section 9.9.2.2.](#) For the definitions of the above exposure windows.

For each individual outcome exposure is calculated separately and can be found in the relevant subsequent tables.

The 1 difference between on-treatment analysis (e.g., infection) and ever-exposed analysis (e.g., cancer) is because of the change in the index date definition (the later of the tofacitinib start date and the registration date).

10.2. Descriptive Data

[Table 5](#) describes the baseline and demographic characteristics of the tofacitinib-treated and the two comparator cohorts. The mean (standard deviation) ages were 61.0 (11.9) years, 60.2 (12.3) years, and 57.1 (12.9) in the tofacitinib, bDMARD Naïve (csDMARD), and bDMARD (anti-TNF) treated cohorts, respectively. In all three cohorts, female accounted for

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at least 75% of RA patients. Categories of race/ethnicity were distributed similarly between the three treatment cohorts, with White race/ethnicity as most common category (96.7% in tofacitinib treated, 97.7% in bDMARD Naïve (csDMARD)treated, and 94.5% in bDMARD (anti-TNF) treated patients). Across all three treatments, a higher proportion of patients were diagnosed with RA from 2000 through 2019, with 80% diagnosed in this period from the bDMARD (anti-TNF) group versus 61.8% and 49.8% in the tofacitinib and bDMARD naïve (csDMARD) treated cohorts, respectively. For the remaining baseline and demographic characteristics in [Table 5](#), distributions and mean estimates were similar across the three treatment cohorts, including for DAS28.

Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
Gender	Male	81	22.4%		708	25.0%		506	24.5%	
	Female	280	77.6%		2123	75.0%		1557	75.5%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
Age in Years	Male	81	62.0	10.6	708	61.8	11.7	506	58.8	11.2
	Female	280	60.7	12.2	2123	59.7	12.5	1557	56.6	13.3
	Total	361	61.0	11.9	2831	60.2	12.3	2063	57.1	12.9
	Missing	0	0.0%		0	0.0%		0	0.0%	
Ethnicity	White	178	96.7%		2282	97.7%		1438	94.5%	
	Black African/Caribbean/Black British/Black Other	<5	-		19	0.8%		23	1.5%	
	Asian/Asian British	<5	-		28	1.2%		51	3.4%	
	Mixed/multiple ethnic groups	<5	-		<5	-		<10	<0.7%	
	Other ethnic groups	0	0.0%		<5	-		<5	-	
	Missing	177	49.0%		495	17.5%		542	26.3%	

Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
Height (cm)	Male	61	175.2	10.5	676	174.7	7.4	376	175.2	7.7
	Female	180	163.2	6.9	2048	160.9	7.1	1179	162.3	7.8
	Total	241	166.2	9.5	2724	164.3	9.3	1555	165.4	9.5
	Missing	120	33.2%		107	3.8%		508	24.6%	
Weight (kg)	Male	72	86.6	15.2	696	82.9	17.1	468	88.7	20.2
	Female	237	77.0	20.3	2094	71.2	17.2	1419	75.3	19.0
	Total	309	79.3	19.6	2790	74.1	17.9	1887	78.6	20.1
	Missing	52	14.4%		41	1.4%		176	8.5%	
BMI ≥30 kg/m ²	Yes	83	34.9%		721	26.7%		548	35.7%	
	No	155	65.1%		1984	73.3%		987	64.3%	
	Missing	123	34.1%		126	4.5%		528	25.6%	
Systolic blood pressure	Male	28	138.6	13.0	689	138.7	18.8	455	137.9	18.1
	Female	77	137.0	22.1	2040	137.4	20.8	1346	135.4	20.6
	Total	105	137.4	20.0	2729	137.7	20.3	1801	136.0	20.0



Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
	Missing	256	70.9%		102	3.6%		262	12.7%	
Diastolic blood pressure	Male	28	81.2	7.3	691	80.0	11.1	454	81.9	11.0
	Female	77	80.5	10.9	2050	79.2	11.1	1345	79.1	11.1
	Total	105	80.7	10.0	2741	79.4	11.1	1799	79.9	11.2
	Missing	256	70.9%		90	3.2%		264	12.8%	
Smoking status	Current	54	17.0%		677	24.0%		355	18.8%	
	Previous	106	33.3%		1135	40.3%		767	40.7%	
	Never	158	49.7%		1004	35.7%		764	40.5%	
	Missing	43	11.9%		15	0.5%		177	8.6%	
Herpes Zoster vaccination	Yes	7	25.0%		-	-		11	61.1%	
	No	21	75.0%		-	-		7	38.9%	
	Missing	333	92.2%		2831	100.0%		2045	99.1%	
Year of diagnosis	1945-1959	0	0.0%		18	0.6%		<5	-	
	1960-1979	<10	<2.8%		218	7.7%		45	2.2%	
	1980-1999	123	34.8%		1178	41.8%		350	17.4%	
	2000-2019	218	61.8%		1402	49.8%		1607	80.0%	

Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
Years since diagnosis	2020-2025	<5	-		0	0.0%		<10	<0.5%	
	Missing	8	2.2%		15	0.5%		53	2.6%	
	Male	79	15.8	9.8	702	8.5	9.6	488	7.9	8.2
	Female	274	17.1	11.3	2114	9.9	10.6	1522	9.1	9.5
	Total	353	16.8	11.0	2816	9.5	10.4	2010	8.8	9.2
Rheumatoid factor status	Missing	8	2.2%		15	0.5%		53	2.6%	
	Positive	197	63.1%		1640	58.0%		1115	62.5%	
	Negative	115	36.9%		1189	42.0%		670	37.5%	
ACPA (anti-CCP) positive RA	Missing	49	13.6%		2	0.1%		278	13.5%	
	Yes	123	71.9%		>4	>66.7%		577	69.1%	
	No	48	28.1%		<5	-		258	30.9%	
	Missing	190	52.6%		2825	99.8%		1228	59.5%	
HAQ	Male	31	1.5	0.8	551	1.5	8.8	468	1.3	0.8
	Female	90	1.7	0.8	1727	1.6	0.7	1448	1.6	0.8
	Total	121	1.7	0.8	2278	1.6	0.7	1916	1.5	0.8
	Missing	240	66.5%		553	19.5%		147	7.1%	



Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
DAS28	Male	34	5.5	1.3	708	5.6	1.0	505	5.9	1.1
	Female	101	5.4	1.3	2123	5.6	0.9	1553	6.0	1.0
	Total	135	5.4	1.3	2831	5.6	0.9	2058	5.9	1.0
	Missing	226	62.6%		0	0.0%		5	0.2%	
Tender Joint Count	Male	30	10.9	7.1	706	10.1	6.9	474	14.3	7.5
	Female	89	11.2	7.2	2100	10.2	6.4	1475	14.5	7.1
	Total	119	11.1	7.2	2806	10.1	6.5	1949	14.4	7.2
	Missing	242	67.0%		25	0.9%		114	5.5%	
Swollen Joint Count	Male	30	7.2	4.3	706	7.1	5.5	474	8.9	5.2
	Female	88	6.7	4.0	2100	6.6	4.8	1473	8.4	5.0
	Total	118	6.8	4.1	2806	6.7	5.0	1947	8.5	5.0
	Missing	243	67.3%		25	0.9%		116	5.6%	
ESR	Male	16	40.2	37.5	651	39.7	24.9	369	30.9	26.9
	Female	62	28.8	23.7	1917	39.0	24.6	1160	30.3	24.2
	Total	78	31.1	27.2	2568	39.2	24.7	1529	30.5	24.9



Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
	Missing	283	78.4%		263	9.3%		534	25.9%	
CRP	Male	21	34.3	39.9	238	41.6	41.9	281	26.6	32.3
	Female	53	15.4	15.2	656	34.5	38.0	868	20.9	27.0
	Total	74	20.8	26.0	894	36.4	39.1	1149	22.3	28.4
	Missing	287	79.5%		1937	68.4%		914	44.3%	
Global Health VAS	Male	29	74.2	24.8	705	59.7	21.5	463	71.7	20.3
	Female	85	71.1	21.7	2098	61.6	21.4	1432	73.8	19.9
	Total	114	71.9	22.5	2803	61.1	21.5	1895	73.3	20.0
	Missing	247	68.4%		28	1.0%		168	8.1%	
EuroQol Five Dimensions Questionnaire (EQ-5D)	Male	33	0.4	0.4	225	0.5	0.3	468	0.5	0.3
	Female	95	0.4	0.3	702	0.5	0.3	1424	0.4	0.3
	Total	128	0.4	0.3	927	0.5	0.3	1892	0.4	0.3
	Missing	233	64.5%		1904	67.3%		171	8.3%	



Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
Use of csDMARDs prior to or at baseline	Yes	356	98.6%		2831	100.0%		2055	99.6%	
	No	5	1.4%		0	0.0%		8	0.4%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
Biologically naïve at registration	Yes	39	10.8%		2831	100.0%		2063	100%	
	No	322	89.2%		0	0.0%		0	0.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
Previous use of ADA, ETA, or INF	Yes	196	54.3%		0	0.0%		0	0.0%	
	No	165	45.7%		2831	100.0%		2063	100.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
Previous use of other biologics or biosimilars	Yes	195	54.0%		0	0.0%		0	0.0%	
	No	166	46.0%		2831	100.0%		2063	100.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
Previous use of other targeted synthetic (tsDMARDs)	Yes	48	13.3%		0	0.0%		0	0.0%	
	No	313	86.7%		2831	100.0%		2063	100.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	

Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
On steroids at registration	Yes	27	19.9%		638	22.5%		465	22.5%	
	No	109	80.1%		2193	77.5%		1598	77.5%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of TB	Yes	10	2.8%		60	2.1%		79	3.8%	
	No	351	97.2%		2771	97.9%		1984	96.2%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of diabetes mellitus	Yes	30	8.3%		204	7.2%		166	8.0%	
	No	331	91.7%		2627	92.8%		1897	92.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of hypertension	Yes	101	28.0%		923	32.6%		585	28.4%	
	No	260	72.0%		1908	67.4%		1478	71.6%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of angina	Yes	13	3.6%		217	7.7%		94	4.6%	
	No	348	96.4%		2614	92.3%		1969	95.4%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of MI	Yes	11	3.0%		130	4.6%		62	3.0%	
	No	350	97.0%		2701	95.4%		2001	97.0%	
	Missing	0	0.0%		0	0.0%		0	0.0%	



Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
History of stroke	Yes	6	1.7%		100	3.5%		44	2.1%	
	No	355	98.3%		2731	96.5%		2019	97.9%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of malignancy	Yes	24	6.6%		202	7.1%		91	4.4%	
	No	337	93.4%		2629	92.9%		1972	95.6%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of liver disease	Yes	6	1.7%		56	2.0%		54	2.6%	
	No	355	98.3%		2775	98.0%		2009	97.4%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of renal disease	Yes	9	2.5%		83	2.9%		38	1.8%	
	No	352	97.5%		2748	97.1%		2025	98.2%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of asthma	Yes	34	9.4%		424	15.0%		304	14.7%	
	No	327	90.6%		2407	85.0%		1759	85.3%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of chronic bronchitis/emphysema (COPD)	Yes	25	6.9%		252	8.9%		135	6.5%	
	No	336	93.1%		2579	91.1%		1928	93.5%	

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Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of epilepsy	Yes	13	3.6%		28	1.0%		22	1.1%	
	No	348	96.4%		2803	99.0%		2041	98.9%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of demyelination	Yes	<5	-		9	0.3%		7	0.3%	
	No	>355	>98.3 %		2822	99.7%		2056	99.7%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of depression	Yes	84	23.3%		496	17.5%		437	21.2%	
	No	277	76.7%		2335	82.5%		1626	78.8%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of peptic ulcer	Yes	12	3.3%		185	6.5%		71	3.4%	
	No	349	96.7%		2646	93.5%		1992	96.6%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of hyperthyroidism	Yes	17	4.7%		138	4.9%		73	3.5%	
	No	344	95.3%		2693	95.1%		1990	96.5%	
	Missing	0	0.0%		0	0.0%		0	0.0%	
History of Knee or hip replacement	Yes	51	15.7%		373	13.2%		240	12.0%	
	No	274	84.3%		2457	86.8%		1768	88.0%	

Table 5. Baseline characteristics of patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

		Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]			bDMARD (Anti-TNF) Patients [N = 2063]		
		N	Mean or %	SD	N	Mean or %	SD	N	Mean or %	SD
	Missing	36	10.0%		1	0.0%		55	2.7%	
History of Shoulder/Elbow/Wrist/Hand/Ankle/Foot/Neck joint surgery	Yes	67	20.7%		508	18.0%		244	12.1%	
	No	256	79.3%		232	82.0%		176	87.9%	
	Missing	38	10.5%		1	0.0%		52	2.5%	
Number of comorbidities	0	189	52.4%		125	44.2%		101	49.3%	
	1	99	27.4%		908	32.1%		656	31.8%	
	2+	73	20.2%		671	23.7%		389	18.9%	
	Missing	0	0.0%		0	0.0%		0	0.0%	

Abbreviations: N, number; SD, Standard Deviation; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score 28; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive Protein; VAS, Visual Analog Scale. Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. To prevent back-calculation of non-zero frequencies < 5, the second lowest frequency is also suppressed. For categorical variables percentage is included in the "Mean" column.

"Total" represents the statistics for continuous variables without stratification by gender.

Percentage of missing values refers to the percentage of missing values from the number of total possible observations in each cohort.

Data for "Ethnicity" has not been collected between 2019 and 2024.

Data for "Knee or hip replacement" and "Joint surgery" is available until August 2024.

Number of comorbidities represents the total for the history of high blood pressure, ischemic heart disease [angina/MI], stroke, epilepsy, asthma, COPD, renal disease, liver disease, demyelination, diabetes and cancer.

For tofacitinib switch cases, data recorded at registration has been used for "Smoking status", "Rheumatoid factor status", "ACPA (anti-CCP) positive RA", "Height", "Weight", "Use of csDMARDs prior to or at baseline", comorbidities, "Knee or hip replacement" and "Joint surgery".

Refer to [Section 9.3.1](#) for cohort definitions.

10.3. Outcome Data

Table 6 and 7 describe the number of events and IRs per 1000 PY with 95% CIs for each treatment cohort stratified by gender. Across all three treatment groups, overall, the rates of safety endpoints tended to be higher in males compared to females.

Within the tofacitinib treatment group incidence rates tended to be higher in males compared to females, most notably for bone and joint infections, serious infections, total malignant events (including NMSC), cardiac disorders, death, serious hypersensitivity, and interstitial lung disease (Tables 6 and 7). No incidence rates were higher in females compared to males.

Within the bDMARD naïve (csDMARD) treatment group, incidence rates were higher in males compared to females most notably for infections, including pneumonia and bone and joint infections, malignant events including NMSC and solid tumors, cardiac disorders, and death. Incidence rates were higher in females compared to males notably for fractures, DVT, GI perforation, and serious hypersensitivity reaction (Table 6).



Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Total serious infection	11	191	57.5 (31.9, 103.9)	25	615	40.6 (27.5, 60.1)	132	3098	42.6 (35.9, 50.5)	42.3 (35.7, 50.3)	314	9708	32.3 (29.0, 36.1)	33.3 (29.7, 37.2)
Pneumonia	5	201	24.9 (10.4, 59.9)	13	625	20.8 (12.1, 35.8)	91	3220	28.3 (23.0, 34.7)	28.2 (22.9, 34.6)	176	10050	17.5 (15.1, 20.3)	17.8 (15.3, 20.7)
Non-opportunistic	<5	201	19.9 (7.5, 53.2)	13	625	20.8 (12.1, 35.8)	89	3229	27.6 (22.4, 33.9)	27.5 (22.3, 33.9)	173	10055	17.2 (14.8, 20.0)	17.5 (15.1, 20.4)
Opportunistic	<5	203	4.9 (0.7, 35.0)	0	642	-	6	3355	1.8 (0.8, 4.0)	1.7 (0.8, 3.9)	<5	10440	0.4 (0.1, 1.0)	0.3 (0.1, 0.9)
Septicaemia	0	203	-	<5	642	3.1 (0.8, 12.5)	9	3355	2.7 (1.4, 5.2)	2.6 (1.3, 5.0)	26	10421	2.5 (1.7, 3.7)	2.6 (1.7, 3.8)
Non-opportunistic	0	203	-	<5	642	3.1 (0.8, 12.5)	9	3355	2.7 (1.4, 5.2)	2.6 (1.3, 5.0)	26	10421	2.5 (1.7, 3.7)	2.6 (1.7, 3.8)
Opportunistic	0	203	-	0	642	-	0	3370	-	-	<5	10445	0.1 (0.01, 0.7)	0.1 (0.0, 0.7)
Bone/Joint infection	<5	201	10.0 (2.5, 39.8)	<5	642	1.6 (0.2, 11.1)	18	3331	5.4 (3.4, 8.6)	5.5 (3.4, 8.7)	19	10388	1.8 (1.2, 2.9)	1.9 (1.2, 2.9)
Non-opportunistic	<5	201	10.0 (2.5, 39.8)	<5	642	1.6 (0.2, 11.1)	18	3331	5.4 (3.4, 8.6)	5.5 (3.4, 8.7)	19	10388	1.8 (1.2, 2.9)	1.9 (1.2, 2.9)
Opportunistic	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Herpes Zoster	0	203	-	<5	642	1.6 (0.2, 11.1)	<5	3369	0.3 (0.04, 2.1)	0.3 (0.0, 2.0)	<5	10439	0.1 (0.01, 0.7)	0.1 (0.0, 0.7)

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Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹
<i>Non-opportunistic</i>	0	203	-	<5	642	1.6 (0.2, 11.1)	<5	3369	0.3 (0.04, 2.1)	0.3 (0.0, 2.0)	<5	10439	0.1 (0.01, 0.7)	0.1 (0.0, 0.7)
<i>Opportunistic</i>	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Other serious infection	8	194	41.2 (20.6, 82.3)	14	629	22.3 (13.2, 37.6)	41	3270	12.5 (9.2, 17.0)	12.7 (9.3, 17.2)	164	10050	16.3 (14.0, 19.0)	16.9 (14.5, 19.7)
<i>Non-opportunistic</i>	8	194	41.2 (20.6, 82.3)	14	629	22.3 (13.2, 37.6)	39	3271	11.9 (8.7, 16.3)	12.0 (8.8, 16.5)	164	10050	16.3 (14.0, 19.0)	16.9 (14.5, 19.7)
<i>Opportunistic</i>	0	203	-	0	642	-	<5	3369	0.6 (0.1, 2.4)	0.6 (0.2, 2.4)	<5	10441	0.1 (0.01, 0.7)	0.1 (0.0, 0.7)
TB	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Serious Hepatic Dysfunction/ Failure[#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Fractures[#]	<5	202	5.0 (0.7, 35.2)	<5	632	6.3 (2.4, 16.9)	19	3333	5.7 (3.6, 8.9)	5.6 (3.6, 8.8)	115	10126	11.4 (9.5, 13.6)	11.7 (9.7, 14.1)
Malignancies except NMSC	<5	440	6.8 (2.2, 21.1)	8	1537	5.2 (2.6, 10.4)	82	3498	23.4 (18.9, 29.1)	22.7 (18.3, 28.3)	183	10722	17.1 (14.8, 19.7)	17.4 (15.0, 20.1)
Total malignant events	10	424	23.6 (12.7, 43.8)	16	1512	10.6 (6.5, 17.3)	108	3385	31.9 (26.4, 38.5)	30.7 (25.4, 37.2)	250	10495	23.8 (21.0, 27.0)	24.4 (21.5, 27.6)
Lymphoproliferative	0	448	-	<5	1547	1.3 (0.3, 5.2)	14	3596	3.9 (2.3, 6.6)	3.9 (2.3, 6.5)	25	11049	2.3 (1.5, 3.3)	2.3 (1.5, 3.4)
<i>Lymphoma (NHL, Hodgkins)</i>	0	448	-	0	1549	-	9	3604	2.5 (1.3, 4.8)	2.6 (1.3, 4.9)	15	11067	1.4 (0.8, 2.2)	1.4 (0.8, 2.3)

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Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹
<i>NHL</i> [#]	0	448	-	0	1549	-	<5	3621	0.8 (0.3, 2.6)	0.8 (0.3, 2.6)	8	11078	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)
<i>Hodgkin</i> [#]	0	448	-	0	1549	-	<5	3624	0.6 (0.1, 2.2)	0.6 (0.1, 2.3)	<5	11097	0.2 (0.045, 0.7)	0.2 (0.0, 0.7)
<i>Myeloma</i>	0	448	-	0	1549	-	<5	3627	0.8 (0.3, 2.6)	0.8 (0.3, 2.5)	<5	11091	0.3 (0.1, 0.8)	0.3 (0.1, 0.9)
<i>Leukaemia</i>	0	448	-	<5	1547	1.3 (0.3, 5.2)	<5	3631	0.6 (0.1, 2.2)	0.5 (0.1, 1.9)	7	11092	0.6 (0.3, 1.3)	0.6 (0.3, 1.3)
<i>CLL</i> [#]	0	448	-	0	1549	-	<5	3633	0.3 (0.04, 2.0)	0.2 (0.0, 1.7)	<5	11093	0.4 (0.1, 0.96)	0.4 (0.1, 1.0)
Non-melanoma Skin Cancer	8	428	18.7 (9.3, 37.4)	8	1524	5.3 (2.6, 10.5)	37	3507	10.6 (7.6, 14.6)	10.0 (7.2, 13.9)	81	10852	7.5 (6.0, 9.3)	7.7 (6.2, 9.6)
Other malignant solid tumours	<5	440	6.8 (2.2, 21.1)	6	1540	3.9 (1.8, 8.7)	70	3534	19.8 (15.7, 25.0)	19.1 (15.1, 24.2)	160	10768	14.9 (12.7, 17.3)	15.2 (13.0, 17.7)
<i>Brain neoplasms</i>	0	448	-	0	1549	-	<5	3632	0.3 (0.04, 2.0)	0.3 (0.0, 2.3)	<5	11099	0.3 (0.1, 0.8)	0.3 (0.1, 0.9)
<i>Of which, Glioblastoma</i>	0	448	-	0	1549	-	0	3633	-	-	<5	11099	0.1 (0.01, 0.6)	0.1 (0.0, 0.7)
<i>Lung cancer</i> [#]	0	448	-	<5	1547	1.3 (0.3, 5.2)	16	3619	4.4 (2.7, 7.2)	4.4 (2.7, 7.2)	32	11084	2.9 (2.0, 4.1)	3.0 (2.1, 4.3)
<i>Melanoma</i> [#]	0	448	-	0	1549	-	<5	3621	0.8 (0.3, 2.6)	0.8 (0.3, 2.5)	5	11077	0.5 (0.2, 1.1)	0.5 (0.2, 1.2)

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Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Malignancies except NMSC (on drug ²)	<5	204	4.9 (0.7, 34.7)	<5	659	3.0 (0.8, 12.1)	82	3498	23.4 (18.9, 29.1)	23.2 (18.6, 28.8)	183	10722	17.1 (14.8, 19.7)	17.2 (14.9, 20.0)
Total malignant events (on drug ²)	<5	199	20.1 (7.5, 53.6)	6	655	9.2 (4.1, 20.4)	108	3385	31.9 (26.4, 38.5)	31.4 (26.0, 37.9)	250	10495	23.8 (21.0, 27.0)	24.2 (21.4, 27.4)
Lymphoproliferative (on drug ²)	0	209	-	0	661	-	14	3596	3.9 (2.3, 6.6)	3.9 (2.3, 6.6)	25	11049	2.3 (1.5, 3.3)	2.3 (1.5, 3.4)
Non-melanoma Skin Cancer (on drug ²)	<5	200	20.0 (7.5, 53.3)	<5	658	6.1 (2.3, 16.2)	37	3507	10.6 (7.6, 14.6)	10.3 (7.4, 14.2)	81	10852	7.5 (6.0, 9.3)	7.6 (6.1, 9.5)
Other malignant solid tumours (on drug ²)	<5	204	4.9 (0.7, 34.7)	<5	659	3.0 (0.8, 12.1)	70	3534	19.8 (15.7, 25.0)	19.5 (15.4, 24.7)	160	10768	14.9 (12.7, 17.3)	15.0 (12.9, 17.6)
Lung cancer [#] (on drug ²)	0	209	-	0	661	-	16	3619	4.4 (2.7, 7.2)	4.4 (2.7, 7.2)	32	11084	2.9 (2.0, 4.1)	3.0 (2.1, 4.2)
Total cardiac disorders	8	195	41.1 (20.5, 82.2)	<5	637	6.3 (2.4, 16.7)	92	3174	29.0 (23.6, 35.6)	28.9 (23.5, 35.4)	125	10139	12.3 (10.3, 14.7)	12.5 (10.5, 14.9)
CHF (new or worsening)	0	203	-	<5	641	1.6 (0.2, 11.1)	18	3348	5.4 (3.4, 8.5)	5.2 (3.3, 8.2)	27	10414	2.6 (1.8, 3.8)	2.6 (1.8, 3.8)
Myocardial infarction	<5	203	9.9 (2.5, 39.5)	<5	641	3.1 (0.8, 12.5)	33	3297	10.0 (7.1, 14.1)	9.9 (7.0, 13.9)	45	10321	4.4 (3.3, 5.8)	4.4 (3.3, 6.0)
Acute Coronary Syndrome [#]	<5	201	5.0 (0.7, 35.3)	0	642	-	<5	3363	0.9 (0.3, 2.8)	0.6 (0.1, 2.2)	<5	10435	0.3 (0.1, 0.9)	0.3 (0.1, 0.9)
MACE (including MI) [#]	<5	202	19.8 (7.4, 52.8)	<5	641	6.2 (2.3, 16.6)	64	3251	19.7 (15.4, 25.1)	19.4 (15.2, 24.8)	99	10195	9.7 (8.0, 11.8)	10.0 (8.2, 12.2)

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Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹
Other cardiac events	6	195	30.7 (13.8, 68.4)	<5	638	3.1 (0.8, 12.5)	53	3250	16.3 (12.5, 21.3)	16.3 (12.4, 21.3)	70	10272	6.8 (5.4, 8.6)	6.9 (5.5, 8.8)
Venous Thrombotic Event (VTE)	<5	203	4.9 (0.7, 35.0)	<5	639	3.1 (0.8, 12.5)	15	3345	4.5 (2.7, 7.4)	4.4 (2.6, 7.2)	35	10354	3.4 (2.4, 4.7)	3.4 (2.5, 4.8)
DVT [#]	0	203	-	0	642	-	<5	3360	0.6 (0.1, 2.4)	0.6 (0.2, 2.4)	12	10421	1.2 (0.7, 2.0)	1.1 (0.6, 1.9)
PE [#]	<5	203	4.9 (0.7, 35.0)	0	642	-	10	3357	3.0 (1.6, 5.5)	3.2 (1.7, 5.7)	19	10389	1.8 (1.2, 2.9)	2.0 (1.2, 3.1)
Total haematologic events	0	203	-	<5	640	1.6 (0.2, 11.1)	21	3330	6.3 (4.1, 9.7)	6.2 (4.1, 9.6)	48	10337	4.6 (3.5, 6.2)	4.7 (3.5, 6.2)
Aplastic anaemia	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Pancytopenia	0	203	-	0	642	-	<5	3366	0.6 (0.1, 2.4)	0.6 (0.2, 2.4)	7	10433	0.7 (0.3, 1.4)	0.7 (0.3, 1.5)
Agranulocytosis	0	203	-	0	642	-	<5	3366	0.3 (0.04, 2.1)	0.3 (0.0, 2.3)	<5	10444	0.1 (0.01, 0.7)	0.1 (0.0, 0.5)
Other dyscrasia	0	203	-	<5	640	1.6 (0.2, 11.1)	19	3335	5.7 (3.6, 8.9)	5.6 (3.6, 8.8)	42	10344	4.1 (3.0, 5.5)	4.1 (3.0, 5.6)
Serious Neutropenia [#]	0	203	-	0	642	-	5	3356	1.5 (0.6, 3.6)	1.5 (0.6, 3.6)	5	10436	0.5 (0.2, 1.2)	0.5 (0.2, 1.2)
Serious haemorrhage [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-

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Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹	Events	Person year	Rate (95% CI)	Standard Rate (95% CI) ¹
CNS Disorders	<5	202	9.9 (2.5, 39.5)	<5	638	6.3 (2.4, 16.7)	35	3313	10.6 (7.6, 14.7)	10.4 (7.5, 14.5)	80	10221	7.8 (6.3, 9.7)	7.9 (6.3, 9.9)
Central Demyelination	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Peripheral neuropathy	0	203	-	<5	638	1.6 (0.2, 11.1)	7	3359	2.1 (0.99, 4.4)	2.1 (1.0, 4.4)	8	10420	0.8 (0.4, 1.5)	0.8 (0.4, 1.5)
Cerebrovascular accident	<5	202	4.9 (0.7, 35.1)	0	642	-	14	3347	4.2 (2.5, 7.1)	4.1 (2.4, 6.9)	30	10356	2.9 (2.0, 4.1)	3.0 (2.1, 4.3)
Other CNS	<5	203	4.9 (0.7, 35.0)	<5	642	4.7 (1.5, 14.5)	16	3343	4.8 (2.9, 7.8)	4.7 (2.9, 7.6)	46	10325	4.5 (3.3, 5.9)	4.5 (3.3, 6.0)
Optic Neuritis [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Progressive multifocal leukoencephalopathy (PML)[#]	0	312	-	0	1179	-	0	3370	-	-	0	10445	-	-
Progressive multifocal leukoencephalopathy (PML)[#] (on drug²)	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
GI perforation	0	203	-	<5	642	1.6 (0.2, 11.1)	0	3370	-	-	5	10442	0.5 (0.2, 1.2)	0.5 (0.2, 1.2)
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Pregnancy (female only)	NA	-	-	0	642	-	NA	-	-	-	10	10410	0.96 (0.5, 1.8)	1.1 (0.6, 2.1)

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Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Death (on drug ²)	7	209	33.5 (15.9, 70.2)	7	661	10.6 (5.0, 22.2)	162	3633	44.6 (38.2, 52.0)	43.6 (37.4, 50.9)	283	11100	25.5 (22.7, 28.6)	26.2 (23.3, 29.5)
Death (ever exposed)	14	448	31.3 (18.5, 52.8)	22	1549	14.2 (9.3, 21.6)	162	3633	44.6 (38.2, 52.0)	41.7 (35.7, 48.7)	283	11100	25.5 (22.7, 28.6)	26.6 (23.6, 29.8)
Hepatitis B Reactivation [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Serious Infusion/Immunologic Reaction [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Serious Hypersensitivity Reaction [#]	<5	201	5.0 (0.7, 35.3)	0	642	-	<5	3363	0.6 (0.1, 2.4)	0.6 (0.1, 2.3)	15	10407	1.4 (0.9, 2.4)	1.5 (0.9, 2.5)
Serious Lupus/Lupus-Like Illness [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Serious Skin Reaction [#]	0	203	-	0	642	-	0	3370	-	-	0	10445	-	-
Interstitial Lung Disease [#]	<5	203	4.9 (0.7, 35.0)	0	642	-	9	3354	2.7 (1.4, 5.2)	2.8 (1.4, 5.3)	17	10420	1.6 (1.0, 2.6)	1.5 (0.9, 2.5)

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer. - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

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Table 6. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD); stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD Naïve (csDMARD) Patients [N = 2831]							
	Males [N = 81]			Females [N = 280]			Males [N = 708]				Females [N = 2123]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)

² "On drug" corresponds to secondary analysis using the "censor at switch" approach.
Refer to [Section 9.3.1](#). for cohort definitions.

Within the bDMARD (anti-TNF) treatment group, incidence rates were higher in males compared to females most notable for serious infections, including bone and joint infections, total malignant events, including lymphoma and solid tumours, malignancies excluding NMSC, cardiac disorders, CNS disorders, and death. Incidence rates were notably higher in females compared to males for fractures ([Table 7](#)).



Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Total serious infection	11	191	57.5 (31.9, 103.9)	25	615	40.6 (27.5, 60.1)	56	1334	42.0 (32.3, 54.6)	46.6 (35.5, 61.2)	137	4168	32.9 (27.8, 38.9)	37.6 (31.6, 44.7)
Pneumonia	5	201	24.9 (10.4, 59.9)	13	625	20.8 (12.1, 35.8)	27	1390	19.4 (13.3, 28.3)	23.3 (15.8, 34.5)	64	4302	14.9 (11.6, 19.0)	17.8 (13.8, 22.9)
Non-opportunistic	<5	201	19.9 (7.5, 53.2)	13	625	20.8 (12.1, 35.8)	27	1399	19.3 (13.2, 28.1)	23.5 (15.9, 34.8)	63	4303	14.6 (11.4, 18.7)	17.5 (13.5, 22.5)
Opportunistic	<5	203	4.9 (0.7, 35.0)	0	642	-	<5	1416	1.4 (0.4, 5.6)	1.5 (0.4, 5.9)	<5	4363	0.9 (0.3, 2.4)	1.1 (0.4, 2.9)
Septicaemia	0	203	-	<5	642	3.1 (0.8, 12.5)	<5	1424	1.4 (0.4, 5.6)	1.5 (0.3, 6.5)	8	4359	1.8 (0.9, 3.7)	2.1 (1.0, 4.3)
Non-opportunistic	0	203	-	<5	642	3.1 (0.8, 12.5)	<5	1424	1.4 (0.4, 5.6)	1.5 (0.3, 6.5)	8	4359	1.8 (0.9, 3.7)	2.1 (1.0, 4.3)
Opportunistic	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Bone/Joint infection	<5	201	10.0 (2.5, 39.8)	<5	642	1.6 (0.2, 11.1)	7	1423	4.9 (2.3, 10.3)	5.3 (2.5, 11.5)	8	4360	1.8 (0.9, 3.7)	2.2 (1.1, 4.5)
Non-opportunistic	<5	201	10.0 (2.5, 39.8)	<5	642	1.6 (0.2, 11.1)	7	1423	4.9 (2.3, 10.3)	5.3 (2.5, 11.5)	8	4360	1.8 (0.9, 3.7)	2.2 (1.1, 4.5)
Opportunistic	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Herpes Zoster	0	203	-	<5	642	1.6 (0.2, 11.1)	0	1425	-	-	0	4368	-	-
Non-opportunistic	0	203	-	<5	642	1.6 (0.2, 11.1)	0	1425	-	-	0	4368	-	-
Opportunistic	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Other serious infection	8	194	41.2 (20.6, 82.3)	14	629	22.3 (13.2, 37.6)	28	1366	20.5 (14.2, 29.7)	22.7 (15.5, 33.3)	80	4234	18.9 (15.2, 23.5)	21.0 (16.7, 26.3)
Non-opportunistic	8	194	41.2 (20.6, 82.3)	14	629	22.3 (13.2, 37.6)	28	1366	20.5 (14.2, 29.7)	22.7 (15.5, 33.3)	77	4243	18.1 (14.5, 22.7)	20.4 (16.2, 25.6)
Opportunistic	0	203	-	0	642	-	<5	1425	0.7 (0.1, 5.0)	1.0 (0.1, 7.2)	<5	4359	0.7 (0.2, 2.1)	0.6 (0.2, 1.8)
TB	0	203	-	0	642	-	<5	1424	0.7 (0.1, 5.0)	1.0 (0.1, 7.2)	<5	4367	0.2 (0.03, 1.6)	0.2 (0.0, 1.3)
Serious Hepatic Dysfunction/ Failure [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Fractures [#]	<5	202	5.0 (0.7, 35.2)	<5	632	6.3 (2.4, 16.9)	6	1414	4.2 (1.9, 9.4)	5.9 (2.7, 13.3)	33	4319	7.6 (5.4, 10.7)	9.2 (6.5, 13.1)
Malignancies except NMSC	<5	440	6.8 (2.2, 21.1)	8	1537	5.2 (2.6, 10.4)	44	3225	13.6 (10.2, 18.3)	15.6 (11.6, 21.0)	68	10268	6.6 (5.2, 8.4)	7.4 (5.8, 9.5)

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Total malignant events	10	424	23.6 (12.7, 43.8)	16	1512	10.6 (6.5, 17.3)	54	3183	17.0 (13.0, 22.2)	19.4 (14.8, 25.4)	94	10164	9.2 (7.6, 11.3)	10.6 (8.6, 13.0)
Lymphoproliferative	0	448	-	<5	1547	1.3 (0.3, 5.2)	<5	3313	1.2 (0.5, 3.2)	1.2 (0.5, 3.4)	7	10441	0.7 (0.3, 1.4)	0.8 (0.4, 1.6)
Lymphoma (NHL, Hodgkins)	0	448	-	0	1549	-	<5	3313	1.2 (0.5, 3.2)	1.2 (0.5, 3.4)	5	10448	0.5 (0.2, 1.1)	0.6 (0.2, 1.4)
NHL [#]	0	448	-	0	1549	-	0	3322	-	-	<5	10457	0.1 (0.01, 0.7)	0.1 (0.0, 0.9)
Hodgkin [#]	0	448	-	0	1549	-	0	3322	-	-	0	10462	-	-
Myeloma	0	448	-	0	1549	-	0	3322	-	-	0	10462	-	-
Leukaemia	0	448	-	<5	1547	1.3 (0.3, 5.2)	0	3322	-	-	<5	10455	0.2 (0.048, 0.8)	0.2 (0.0, 0.9)
CLL [#]	0	448	-	0	1549	-	0	3322	-	-	0	10462	-	-
Non-melanoma Skin Cancer	8	428	18.7 (9.3, 37.4)	8	1524	5.3 (2.6, 10.5)	10	3280	3.0 (1.6, 5.7)	3.6 (1.9, 6.6)	28	10351	2.7 (1.9, 3.9)	3.3 (2.2, 4.8)
Other malignant solid tumours	<5	440	6.8 (2.2, 21.1)	6	1540	3.9 (1.8, 8.7)	40	3235	12.4 (9.1, 16.9)	14.3 (10.5, 19.5)	61	10289	5.9 (4.6, 7.6)	6.6 (5.1, 8.6)
Brain neoplasms	0	448	-	0	1549	-	0	3322	-	-	0	10462	-	-
Of which, Glioblastoma	0	448	-	0	1549	-	0	3322	-	-	0	10462	-	-

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
<i>Lung cancer[#]</i>	0	448	-	<5	1547	1.3 (0.3, 5.2)	<5	3321	0.6 (0.2, 2.4)	0.7 (0.2, 2.8)	7	10459	0.7 (0.3, 1.4)	0.8 (0.4, 1.6)
<i>Melanoma[#]</i>	0	448	-	0	1549	-	<5	3310	0.6 (0.2, 2.4)	0.7 (0.2, 3.0)	<5	10455	0.2 (0.0, 0.8)	0.2 (0.0, 0.7)
Malignancies except NMSC (on drug²)	<5	204	4.9 (0.7, 34.7)	<5	659	3.0 (0.8, 12.1)	17	1438	11.8 (7.4, 19.0)	14.1 (8.7, 22.9)	30	4420	6.8 (4.7, 9.7)	7.8 (5.4, 11.3)
Total malignant events (on drug²)	<5	199	20.1 (7.5, 53.6)	6	655	9.2 (4.1, 20.4)	23	1426	16.1 (10.7, 24.3)	19.5 (12.9, 29.4)	42	4402	9.5 (7.1, 12.9)	11.4 (8.3, 15.5)
Lymphoproliferative (on drug ²)	0	209	-	0	661	-	<5	1446	2.8 (1.0, 7.4)	2.9 (1.0, 7.9)	5	4441	1.1 (0.5, 2.7)	1.3 (0.5, 3.3)
Non-melanoma Skin Cancer (on drug ²)	<5	200	20.0 (7.5, 53.3)	<5	658	6.1 (2.3, 16.2)	6	1436	4.2 (1.9, 9.3)	5.3 (2.4, 11.8)	13	4426	2.9 (1.7, 5.1)	3.8 (2.2, 6.6)
Other malignant solid tumours (on drug ²)	<5	204	4.9 (0.7, 34.7)	<5	659	3.0 (0.8, 12.1)	13	1439	9.0 (5.2, 15.6)	11.2 (6.5, 19.4)	25	4422	5.7 (3.8, 8.4)	6.5 (4.3, 9.7)
<i>Lung cancer[#] (on drug²)</i>	0	209	-	0	661	-	<5	1446	1.4 (0.3, 5.5)	1.7 (0.4, 7.0)	<5	4443	0.2 (0.03, 1.6)	0.3 (0.0, 2.3)
Total cardiac disorders	8	195	41.1 (20.5, 82.2)	<5	637	6.3 (2.4, 16.7)	22	1384	15.9 (10.5, 24.1)	17.2 (11.2, 26.6)	33	4331	7.6 (5.4, 10.7)	9.3 (6.5, 13.1)
CHF (new or worsening)	0	203	-	<5	641	1.6 (0.2, 11.1)	<5	1424	1.4 (0.4, 5.6)	2.0 (0.5, 8.2)	<5	4364	0.9 (0.3, 2.4)	1.1 (0.4, 2.9)

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Myocardial infarction	<5	203	9.9 (2.5, 39.5)	<5	641	3.1 (0.8, 12.5)	9	1400	6.4 (3.3, 12.4)	7.2 (3.7, 14.3)	9	4353	2.1 (1.1, 4.0)	2.7 (1.4, 5.2)
Acute Coronary Syndrome [#]	<5	201	5.0 (0.7, 35.3)	0	642	-	0	1425	-	-	0	4368	-	-
MACE (including MI) [#]	<5	202	19.8 (7.4, 52.8)	<5	641	6.2 (2.3, 16.6)	17	1393	12.2 (7.6, 19.6)	14.4 (8.8, 23.5)	21	4333	4.8 (3.2, 7.4)	5.5 (3.5, 8.7)
Other cardiac events	6	195	30.7 (13.8, 68.4)	<5	638	3.1 (0.8, 12.5)	13	1407	9.2 (5.4, 15.9)	9.7 (5.5, 17.0)	22	4349	5.1 (3.3, 7.7)	6.1 (4.0, 9.4)
Venous Thrombotic Event (VTE)	<5	203	4.9 (0.7, 35.0)	<5	639	3.1 (0.8, 12.5)	<5	1421	2.8 (1.1, 7.5)	3.2 (1.2, 8.9)	7	4360	1.6 (0.8, 3.4)	2.0 (1.0, 4.3)
DVT [#]	0	203	-	0	642	-	<5	1425	0.7 (0.1, 5.0)	1.0 (0.1, 7.2)	<5	4367	0.2 (0.03, 1.6)	0.3 (0.0, 2.3)
PE [#]	<5	203	4.9 (0.7, 35.0)	0	642	-	<5	1421	2.1 (0.7, 6.5)	2.2 (0.7, 7.2)	<5	4367	0.5 (0.1, 1.8)	0.8 (0.3, 2.7)
Total haematologic events	0	203	-	<5	640	1.6 (0.2, 11.1)	5	1421	3.5 (1.5, 8.5)	4.5 (1.9, 11.0)	15	4356	3.4 (2.1, 5.7)	4.5 (2.7, 7.6)
Aplastic anaemia	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Pancytopenia	0	203	-	0	642	-	0	1425	-	-	<5	4362	0.7 (0.2, 2.1)	0.8 (0.3, 2.7)
Agranulocytosis	0	203	-	0	642	-	<5	1425	0.7 (0.1, 5.0)	1.0 (0.1, 7.2)	<5	4364	0.2 (0.03, 1.6)	0.2 (0.0, 1.3)

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Other dyscrasia	0	203	-	<5	640	1.6 (0.2, 11.1)	<5	1421	2.8 (1.1, 7.5)	3.5 (1.3, 9.5)	13	4361	3.0 (1.7, 5.1)	4.0 (2.3, 6.9)
Serious Neutropenia [#]	0	203	-	0	642	-	0	1425	-	-	6	4366	1.4 (0.6, 3.1)	1.7 (0.7, 3.8)
Serious haemorrhage [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
CNS Disorders	<5	202	9.9 (2.5, 39.5)	<5	638	6.3 (2.4, 16.7)	16	1404	11.4 (7.0, 18.6)	12.9 (7.7, 21.5)	33	4313	7.7 (5.4, 10.8)	8.0 (5.6, 11.4)
Central Demyelination	0	203	-	0	642	-	0	1425	-	-	<5	4367	0.5 (0.1, 1.8)	0.4 (0.1, 1.5)
Peripheral neuropathy	0	203	-	<5	638	1.6 (0.2, 11.1)	0	1425	-	-	<5	4367	0.2 (0.03, 1.6)	0.2 (0.0, 1.3)
Cerebrovascular accident	<5	202	4.9 (0.7, 35.1)	0	642	-	5	1419	3.5 (1.5, 8.5)	3.9 (1.6, 9.7)	5	4358	1.1 (0.5, 2.8)	1.2 (0.5, 3.1)
Other CNS	<5	203	4.9 (0.7, 35.0)	<5	642	4.7 (1.5, 14.5)	12	1410	8.5 (4.8, 15.0)	9.4 (5.2, 17.0)	25	4324	5.8 (3.9, 8.6)	6.2 (4.1, 9.3)
Optic Neuritis [#]	0	203	-	0	642	-	<5	1423	0.7 (0.1, 5.0)	1.0 (0.1, 7.2)	0	4368	-	-
Progressive multifocal leukoencephalopathy (PML)[#]	0	312	-	0	1179	-	0	2675	-	-	0	8297	-	-

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Progressive multifocal leukoencephalopathy (PML) # (on drug ²)	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
GI perforation	0	203	-	<5	642	1.6 (0.2, 11.1)	<5	1425	1.4 (0.4, 5.6)	2.0 (0.5, 8.1)	<5	4366	0.9 (0.3, 2.4)	1.0 (0.4, 2.9)
Serious Lower GI Ulcer/Bleed/Perforation #	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Pregnancy (female only)	NA	-	-	0	642	-	NA	-	-	-	15	4334	3.5 (2.1, 5.7)	2.8 (1.7, 4.7)
Death (on drug ²)	7	209	33.5 (15.9, 70.2)	7	661	10.6 (5.0, 22.2)	19	1447	13.1 (8.4, 20.6)	16.4 (10.4, 25.9)	35	4444	7.9 (5.7, 11.0)	9.8 (7.0, 13.8)
Death (ever exposed)	14	448	31.3 (18.5, 52.8)	22	1549	14.2 (9.3, 21.6)	54	3322	16.3 (12.4, 21.2)	18.6 (14.2, 24.4)	105	10462	10.0 (8.3, 12.2)	12.4 (10.2, 15.1)
Hepatitis B Reactivation [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Serious Infusion/Immunologic Reaction [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Serious Hypersensitivity Reaction [#]	<5	201	5.0 (0.7, 35.3)	0	642	-	0	1425	-	-	5	4367	1.1 (0.5, 2.8)	1.4 (0.6, 3.4)
Serious Lupus/Lupus-Like Illness [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-
Serious Skin Reaction [#]	0	203	-	0	642	-	0	1425	-	-	0	4368	-	-

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Table 7. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD (anti-TNF) cohort; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]						bDMARD (Anti-TNF) Patients [N = 2063]							
	Males [N = 81]			Females [N = 280]			Males [N = 506]				Females [N = 1557]			
	Event s	Perso n year	Rate (95% CI)	Event s	Perso n year	Rate (95% CI)	Event s	Perso n year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Eve nts	Perso n year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Interstitial Lung Disease [#]	<5	203	4.9 (0.7, 35.0)	0	642	-	<5	1424	1.4 (0.4, 5.6)	1.4 (0.4, 5.8)	7	4362	1.6 (0.8, 3.4)	2.0 (0.9, 4.3)

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer. - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1](#). for cohort definitions.

Table 8 describes the event frequency, crude incidence rates, and standardised incidence rates for individual safety endpoints ([Section 9.4.2](#)), observed in each of the exposure and comparator cohorts without stratification by sex. Qualitatively, the incidence rates between the tofacitinib and bDMARD (anti-TNF) cohorts were generally similar (i.e. did not exceed a difference of >10 events per 1000 PYRs) with overlapping confidence intervals, as well as for tofacitinib and bDMARD naïve (csDMARD) cohorts (did not exceed a difference of >15 events per 1000 PYRs).



Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Total serious infection	36	807	44.6 (32.2, 61.9)	446	12806	34.8 (31.7, 38.2)	35.4 (32.2, 38.9)	193	5501	35.1 (30.5, 40.4)	39.7 (34.3, 46.0)
Pneumonia	18	825	21.8 (13.7, 34.6)	267	13270	20.1 (17.8, 22.7)	20.3 (18.0, 22.9)	91	5691	16.0 (13.0, 19.6)	19.1 (15.5, 23.7)
Non-opportunistic	17	825	20.6 (12.8, 33.1)	262	13284	19.7 (17.5, 22.3)	20.0 (17.7, 22.6)	90	5701	15.8 (12.8, 19.4)	18.9 (15.3, 23.4)
Opportunistic	<5	845	1.2 (0.2, 8.4)	10	13796	0.7 (0.4, 1.3)	0.7 (0.4, 1.2)	6	5779	1.0 (0.5, 2.3)	1.2 (0.5, 2.6)
Septicaemia	<5	845	2.4 (0.6, 9.5)	35	13776	2.5 (1.8, 3.5)	2.6 (1.8, 3.6)	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.7)
Non-opportunistic	<5	845	2.4 (0.6, 9.5)	35	13776	2.5 (1.8, 3.5)	2.6 (1.8, 3.6)	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.7)
Opportunistic	0	845	-	<5	13815	0.1 (0.01, 0.5)	0.1 (0.0, 0.6)	0	5793	-	-
Bone/Joint infection	<5	843	3.6 (1.1, 11.0)	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	15	5783	2.6 (1.6, 4.3)	3.0 (1.8, 5.0)
Non-opportunistic	<5	843	3.6 (1.1, 11.0)	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	15	5783	2.6 (1.6, 4.3)	3.0 (1.8, 5.0)
Opportunistic	0	845	-	0	13816	-	-	0	5793	-	-
Herpes Zoster	<5	845	1.2 (0.2, 8.4)	<5	13807	0.1 (0.04, 0.6)	0.1 (0.0, 0.6)	0	5793	-	-
Non-opportunistic	<5	845	1.2 (0.2, 8.4)	<5	13807	0.1 (0.04, 0.6)	0.1 (0.0, 0.6)	0	5793	-	-
Opportunistic	0	845	-	0	13816	-	-	0	5793	-	-



Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Other serious infection	22	823	26.7 (17.6, 40.6)	205	13320	15.4 (13.4, 17.6)	15.9 (13.8, 18.2)	108	5600	19.3 (16.0, 23.3)	21.4 (17.6, 26.0)
<i>Non-opportunistic</i>	22	823	26.7 (17.6, 40.6)	203	13322	15.2 (13.3, 17.5)	15.7 (13.7, 18.1)	105	5609	18.7 (15.5, 22.7)	20.9 (17.2, 25.5)
<i>Opportunistic</i>	0	845	-	<5	13809	0.2 (0.1, 0.7)	0.2 (0.1, 0.7)	<5	5784	0.7 (0.3, 1.8)	0.7 (0.2, 1.9)
TB	0	845	-	0	13816	-	-	<5	5792	0.3 (0.1, 1.4)	0.4 (0.1, 1.6)
Serious Hepatic Dysfunction/ Failure[#]	0	845	-	0	13816	-	-	0	5793	-	-
Fractures[#]	5	834	6.0 (2.5, 14.4)	134	13459	10.0 (8.4, 11.8)	10.2 (8.6, 12.1)	39	5733	6.8 (5.0, 9.3)	8.4 (6.1, 11.6)
Malignancies except NMSC	11	1977	5.6 (3.1, 10.0)	265	14219	18.6 (16.5, 21.0)	18.6 (16.5, 21.0)	112	13494	8.3 (6.9, 10.0)	9.2 (7.6, 11.2)
Total malignant events	26	1936	13.4 (9.1, 19.7)	358	13880	25.8 (23.3, 28.6)	25.7 (23.2, 28.6)	148	13347	11.1 (9.4, 13.0)	12.5 (10.6, 14.7)
Lymphoproliferative	<5	1995	1.0 (0.3, 4.0)	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	11	13754	0.8 (0.4, 1.4)	0.9 (0.5, 1.6)
<i>Lymphoma (NHL, Hodgkins)</i>	0	1997	-	24	14670	1.6 (1.1, 2.4)	1.6 (1.1, 2.4)	9	13761	0.7 (0.3, 1.3)	0.7 (0.4, 1.4)
<i>NHL[#]</i>	0	1997	-	11	14699	0.7 (0.4, 1.4)	0.7 (0.4, 1.3)	<5	13780	0.1 (0.01, 0.5)	0.1 (0.0, 0.7)
<i>Hodgkin[#]</i>	0	1997	-	<5	14721	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)	0	13784	-	-

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Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
<i>Myeloma</i>	0	1997	-	6	14717	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	0	13784	-	-
<i>Leukaemia</i>	<5	1995	1.0 (0.3, 4.0)	9	14723	0.6 (0.3, 1.2)	0.6 (0.3, 1.1)	<5	13778	0.1 (0.04, 0.6)	0.2 (0.0, 0.7)
<i>CLL[#]</i>	0	1997	-	5	14726	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0	13784	-	-
Non-melanoma Skin Cancer	16	1952	8.2 (5.0, 13.4)	118	14358	8.2 (6.9, 9.8)	8.2 (6.8, 9.8)	38	13631	2.8 (2.0, 3.8)	3.3 (2.4, 4.6)
Other malignant solid tumours	9	1980	4.5 (2.4, 8.7)	230	14301	16.1 (14.1, 18.3)	16.1 (14.1, 18.3)	101	13524	7.5 (6.1, 9.1)	8.3 (6.8, 10.1)
<i>Brain neoplasms</i>	0	1997	-	<5	14732	0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0	13784	-	-
<i>Of which, Glioblastoma</i>	0	1997	-	<5	14732	0.1 (0.01, 0.5)	0.1 (0.0, 0.5)	0	13784	-	-
<i>Lung cancer[#]</i>	<5	1995	1.0 (0.3, 4.0)	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	9	13781	0.7 (0.3, 1.3)	0.8 (0.4, 1.5)
<i>Melanoma[#]</i>	0	1997	-	8	14698	0.5 (0.3, 1.1)	0.6 (0.3, 1.1)	<5	13765	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)
Malignancies except NMSC (on drug²)	<5	864	3.5 (1.1, 10.8)	265	14219	18.6 (16.5, 21.0)	18.6 (16.5, 21.0)	47	5857	8.0 (6.0, 10.7)	9.3 (6.9, 12.5)
Total malignant events (on drug²)	10	854	11.7 (6.3, 21.8)	358	13880	25.8 (23.3, 28.6)	25.9 (23.3, 28.7)	65	5828	11.2 (8.7, 14.2)	13.3 (10.3, 17.0)
Lymphoproliferative (on drug ²)	0	871	-	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	9	5887	1.5 (0.8, 2.9)	1.7 (0.9, 3.3)
Non-melanoma Skin Cancer (on drug ²)	8	858	9.3 (4.7, 18.7)	118	14358	8.2 (6.9, 9.8)	8.2 (6.9, 9.9)	19	5861	3.2 (2.1, 5.1)	4.1 (2.6, 6.5)

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Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Other malignant solid tumours (on drug ²)	<5	864	3.5 (1.1, 10.8)	230	14301	16.1 (14.1, 18.3)	16.1 (14.1, 18.3)	38	5862	6.5 (4.7, 8.9)	7.6 (5.5, 10.5)
<i>Lung cancer[#] (on drug²)</i>	0	871	-	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	<5	5890	0.5 (0.2, 1.6)	0.7 (0.2, 2.1)
Total cardiac disorders	12	832	14.4 (8.2, 25.4)	217	13312	16.3 (14.3, 18.6)	16.3 (14.3, 18.7)	55	5714	9.6 (7.4, 12.5)	11.1 (8.5, 14.6)
CHF (new or worsening)	<5	844	1.2 (0.2, 8.4)	45	13762	3.3 (2.4, 4.4)	3.2 (2.4, 4.4)	6	5788	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)
Myocardial infarction	<5	844	4.7 (1.8, 12.6)	78	13618	5.7 (4.6, 7.2)	5.7 (4.6, 7.2)	18	5752	3.1 (2.0, 5.0)	3.8 (2.3, 6.1)
Acute Coronary Syndrome [#]	<5	843	1.2 (0.2, 8.4)	5	13798	0.4 (0.2, 0.9)	0.3 (0.1, 0.8)	0	5793	-	-
MACE (including MI) [#]	8	843	9.5 (4.7, 19.0)	163	13447	12.1 (10.4, 14.1)	12.2 (10.5, 14.3)	37	5726	6.5 (4.7, 8.9)	7.7 (5.5, 10.7)
Other cardiac events	8	833	9.6 (4.8, 19.2)	123	13522	9.1 (7.6, 10.9)	9.1 (7.6, 10.9)	35	5755	6.1 (4.4, 8.5)	7.0 (5.0, 9.8)
Venous Thrombotic Event (VTE)	<5	843	3.6 (1.1, 11.0)	50	13698	3.7 (2.8, 4.8)	3.7 (2.8, 4.8)	11	5781	1.9 (1.1, 3.4)	2.3 (1.3, 4.3)
DVT [#]	0	845	-	14	13780	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)	<5	5791	0.3 (0.1, 1.4)	0.5 (0.1, 2.0)
PE [#]	<5	845	1.2 (0.2, 8.4)	30	13745	2.2 (1.5, 3.1)	2.2 (1.6, 3.2)	6	5789	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)
Total haematologic events	<5	844	1.2 (0.2, 8.4)	69	13666	5.0 (4.0, 6.4)	5.1 (4.0, 6.4)	20	5776	3.5 (2.2, 5.4)	4.5 (2.9, 7.1)
Aplastic anaemia	0	845	-	0	13816	-	-	0	5793	-	-

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Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Pancytopenia	0	845	-	9	13799	0.7 (0.3, 1.3)	0.7 (0.4, 1.3)	<5	5787	0.5 (0.2, 1.6)	0.6 (0.2, 2.0)
Agranulocytosis	0	845	-	<5	13810	0.1 (0.04, 0.6)	0.1 (0.0, 0.5)	<5	5789	0.3 (0.1, 1.4)	0.4 (0.1, 1.6)
Other dyscrasia	<5	844	1.2 (0.2, 8.4)	61	13679	4.5 (3.5, 5.7)	4.5 (3.5, 5.8)	17	5781	2.9 (1.8, 4.7)	3.9 (2.4, 6.3)
Serious Neutropenia [#]	0	845	-	10	13792	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)	6	5791	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)
Serious haemorrhage [#]	0	845	-	0	13816	-	-	0	5793	-	-
CNS Disorders	6	841	7.1 (3.2, 15.9)	115	13534	8.5 (7.1, 10.2)	8.5 (7.1, 10.2)	49	5718	8.6 (6.5, 11.3)	9.2 (6.9, 12.3)
Central Demyelination	0	845	-	0	13816	-	-	<5	5792	0.3 (0.1, 1.4)	0.3 (0.1, 1.1)
Peripheral neuropathy	<5	841	1.2 (0.2, 8.4)	15	13779	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	<5	5792	0.2 (0.02, 1.2)	0.1 (0.0, 1.0)
Cerebrovascular accident	<5	844	1.2 (0.2, 8.4)	44	13703	3.2 (2.4, 4.3)	3.3 (2.4, 4.4)	10	5777	1.7 (0.9, 3.2)	1.9 (1.0, 3.6)
Other CNS	<5	845	4.7 (1.8, 12.6)	62	13669	4.5 (3.5, 5.8)	4.5 (3.5, 5.8)	37	5733	6.5 (4.7, 8.9)	7.0 (5.0, 9.7)
Optic Neuritis [#]	0	845	-	0	13816	-	-	<5	5791	0.2 (0.02, 1.2)	0.2 (0.0, 1.7)
Progressive multifocal leukoencephalopathy (PML)[#]	0	1491	-	0	13816	-	-	0	10972	-	-
Progressive multifocal leukoencephalopathy (PML)[#] (on drug²)	0	845	-	0	13816	-	-	0	5793	-	-



Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
GI perforation	<5	845	1.2 (0.2, 8.4)	5	13812	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	6	5790	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	845	-	0	13816	-	-	0	5793	-	-
Pregnancy (female only)	0	642	-	10	10410	0.96 (0.5, 1.8)	0.8 (0.5, 1.6)	15	4334	3.5 (2.1, 5.7)	2.2 (1.3, 3.6)
Death (on drug ²)	14	871	16.1 (9.5, 27.1)	445	14733	30.2 (27.5, 33.1)	30.4 (27.7, 33.4)	54	5891	9.2 (7.0, 12.0)	11.4 (8.7, 15.0)
Death (ever exposed)	36	1997	18.0 (13.0, 25.0)	445	14733	30.2 (27.5, 33.1)	29.9 (27.3, 32.9)	159	13784	11.5 (9.9, 13.5)	13.8 (11.8, 16.2)
Hepatitis B Reactivation [#]	0	845	-	0	13816	-	-	0	5793	-	-
Serious Infusion/Immunologic Reaction [#]	0	845	-	0	13816	-	-	0	5793	-	-
Serious Hypersensitivity Reaction [#]	<5	843	1.2 (0.2, 8.4)	17	13771	1.2 (0.8, 2.0)	1.3 (0.8, 2.1)	5	5792	0.9 (0.4, 2.1)	1.0 (0.4, 2.6)
Serious Lupus/Lupus-Like Illness [#]	0	845	-	0	13816	-	-	0	5793	-	-
Serious Skin Reaction [#]	0	845	-	0	13816	-	-	0	5793	-	-
Interstitial Lung Disease [#]	<5	845	1.2 (0.2, 8.4)	25	13774	1.8 (1.2, 2.7)	1.8 (1.2, 2.7)	9	5786	1.6 (0.8, 3.0)	1.9 (1.0, 3.7)

Data cut at 7 years after start of therapy.

[#] Coded using MedDRA SMQs and PTs provided by Pfizer. - Rate (95% CI) not generated for zero events.

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Table 8. Number of first events, rates and age-sex standardised rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohort [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Patients [N = 361]			bDMARD Naïve (csDMARD) Patients [N = 2831]				bDMARD (Anti-TNF) Patients [N = 2063]			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

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“Other cardiac events” includes other serious cardiac events that are not classed as CHF or myocardial infarction.

“Other dyscrasia” includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

“Other CNS” includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 “On drug” corresponds to secondary analysis using the “censor at switch” approach.

Refer to [Section 9.3.1](#). for cohort definitions.



10.4. Main Results

Table 9 and 10 describe the number of events and IRs per 1000 PY with 95% CIs for each treatment cohort along with the unadjusted and adjusted hazard ratios with 95% CIs. For safety endpoints listed with event rates <5 counts, IRs and Hazard Ratios could not be estimated.

As shown in Table 9, when comparing the tofacitinib treated cohort to the bDMARD naïve (csDMARD) cohort, there was a numerically higher crude risk of total serious infections (HR=1.18 (0.84, 1.66)), other serious infection (HR=1.66 (1.06, 2.59), NMSC (HR=1.01 (0.60, 1.71) for ever exposed; HR=1.11 (0.54, 2.29) on drug). After multivariable adjustment, adjusted hazards were no longer statistically significant.

A decreased crude risk was observed when comparing the tofacitinib cohort to the bDMARD naïve (csDMARD) cohort for: fractures (HR=0.62 (0.25, 1.51), total malignant events (HR=0.53 (0.35, 0.79) ever; HR=0.43 (0.23, 0.81) on drug), malignancies except NMSC (HR=0.30 (0.17-0.55), other malignant solid tumors (HR=0.29 (0.15, 0.56), total cardiac disorders (HR=0.78 (0.44, 1.41)), CNS disorders (HR=0.79 (0.35, 1.81), and death (HR=0.60 (0.43, 0.85) ever; HR=0.62 (0.36, 1.06) on drug)). After multivariable adjustment, the decreased risk of malignancies except NMSC, total malignant events (ever or on drug), other malignant solid tumours, and death (ever exposed) among tofacitinib patients remained statistically significant.

Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
Total serious infection	446	12806	34.8 (31.7, 38.2)	35.4 (32.2, 38.9)	36	807	44.6 (32.2, 61.9)	1.18 (0.84, 1.66)	1.11 (0.70, 1.76)
Pneumonia	267	13270	20.1 (17.8, 22.7)	20.3 (18.0, 22.9)	18	825	21.8 (13.7, 34.6)	0.98 (0.61, 1.59)	0.87 (0.46, 1.65)
Non-opportunistic	262	13284	19.7 (17.5, 22.3)	20.0 (17.7, 22.6)	17	825	20.6 (12.8, 33.1)	0.95 (0.58, 1.56)	0.84 (0.44, 1.63)



Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
<i>Opportunistic</i>	10	13796	0.7 (0.4, 1.3)	0.7 (0.4, 1.2)	<5	845	1.2 (0.2, 8.4)	-	-
Septicaemia	35	13776	2.5 (1.8, 3.5)	2.6 (1.8, 3.6)	<5	845	2.4 (0.6, 9.5)	-	-
<i>Non-opportunistic</i>	35	13776	2.5 (1.8, 3.5)	2.6 (1.8, 3.6)	<5	845	2.4 (0.6, 9.5)	-	-
<i>Opportunistic</i>	<5	13815	0.1 (0.01, 0.5)	0.1 (0.0, 0.6)	0	845	-	-	-
Bone/Joint infection	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	<5	843	3.6 (1.1, 11.0)	-	-
<i>Non-opportunistic</i>	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	<5	843	3.6 (1.1, 11.0)	-	-
<i>Opportunistic</i>	0	13816	-	-	0	845	-	-	-
Herpes Zoster	<5	13807	0.1 (0.04, 0.6)	0.1 (0.0, 0.6)	<5	845	1.2 (0.2, 8.4)	-	-
<i>Non-opportunistic</i>	<5	13807	0.1 (0.04, 0.6)	0.1 (0.0, 0.6)	<5	845	1.2 (0.2, 8.4)	-	-
<i>Opportunistic</i>	0	13816	-	-	0	845	-	-	-
Other serious infection	205	13320	15.4 (13.4, 17.6)	15.9 (13.8, 18.2)	22	823	26.7 (17.6, 40.6)	1.66 (1.06, 2.59) *	1.50 (0.83, 2.72)
<i>Non-opportunistic</i>	203	13322	15.2 (13.3, 17.5)	15.7 (13.7, 18.1)	22	823	26.7 (17.6, 40.6)	1.67 (1.07, 2.60)*	1.51 (0.83, 2.74)
<i>Opportunistic</i>	<5	13809	0.2 (0.1, 0.7)	0.2 (0.1, 0.7)	0	845	-	-	-
TB	0	13816	-	-	0	845	-	-	-
Serious Hepatic Dysfunction/Failure[#]	0	13816	-	-	0	845	-	-	-

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
Fractures [#]	134	13459	10.0 (8.4, 11.8)	10.2 (8.6, 12.1)	5	834	6.0 (2.5, 14.4)	0.62 (0.25, 1.51)	0.54 (0.17, 1.65)
Malignancies except NMSC	265	14219	18.6 (16.5, 21.0)	18.6 (16.5, 21.0)	11	1977	5.6 (3.1, 10.0)	0.30 (0.17, 0.55) [*]	0.30 (0.14, 0.64) [*]
Total malignant events	358	13880	25.8 (23.3, 28.6)	25.7 (23.2, 28.6)	26	1936	13.4 (9.1, 19.7)	0.53 (0.35, 0.79) [*]	0.49 (0.29, 0.83) [*]
Lymphoproliferative	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	<5	1995	1.0 (0.3, 4.0)	-	-
Lymphoma (NHL, Hodgkins)	24	14670	1.6 (1.1, 2.4)	1.6 (1.1, 2.4)	0	1997	-	-	-
NHL [#]	11	14699	0.7 (0.4, 1.4)	0.7 (0.4, 1.3)	0	1997	-	-	-
Hodgkin [#]	<5	14721	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)	0	1997	-	-	-
Myeloma	6	14717	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	0	1997	-	-	-
Leukaemia	9	14723	0.6 (0.3, 1.2)	0.6 (0.3, 1.1)	<5	1995	1.0 (0.3, 4.0)	-	-
CLL [#]	5	14726	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0	1997	-	-	-
Non-melanoma Skin Cancer	118	14358	8.2 (6.9, 9.8)	8.2 (6.8, 9.8)	16	1952	8.2 (5.0, 13.4)	1.01 (0.60, 1.71)	0.78 (0.39, 1.55)
Other malignant solid tumours	230	14301	16.1 (14.1, 18.3)	16.1 (14.1, 18.3)	9	1980	4.5 (2.4, 8.7)	0.29 (0.15, 0.56) [*]	0.31 (0.13, 0.70) [*]
Brain neoplasms	<5	14732	0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0	1997	-	-	-
Of which, Glioblastoma	<5	14732	0.1 (0.01, 0.5)	0.1 (0.0, 0.5)	0	1997	-	-	-

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
<i>Lung cancer[#]</i>	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	<5	1995	1.0 (0.3, 4.0)	-	-
<i>Melanoma[#]</i>	8	14698	0.5 (0.3, 1.1)	0.6 (0.3, 1.1)	0	1997	-	-	-
Malignancies except NMSC (on drug⁴)	265	14219	18.6 (16.5, 21.0)	18.6 (16.5, 21.0)	<5	864	3.5 (1.1, 10.8)	-	-
Total malignant events (on drug⁴)	358	13880	25.8 (23.3, 28.6)	25.9 (23.3, 28.7)	10	854	11.7 (6.3, 21.8)	0.43 (0.23, 0.81)*	0.38 (0.18, 0.79)*
Lymphoproliferative (on drug ⁴)	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	0	871	-	-	-
Non-melanoma Skin Cancer (on drug ⁴)	118	14358	8.2 (6.9, 9.8)	8.2 (6.9, 9.9)	8	858	9.3 (4.7, 18.7)	1.11 (0.54, 2.29)	0.75 (0.31, 1.83)
Other malignant solid tumours (on drug ⁴)	230	14301	16.1 (14.1, 18.3)	16.1 (14.1, 18.3)	<5	864	3.5 (1.1, 10.8)	-	-
<i>Lung cancer[#] (on drug⁴)</i>	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	0	871	-	-	-
Total cardiac disorders	217	13312	16.3 (14.3, 18.6)	16.3 (14.3, 18.7)	12	832	14.4 (8.2, 25.4)	0.78 (0.44, 1.41)	0.75 (0.37, 1.54)
CHF (new or worsening)	45	13762	3.3 (2.4, 4.4)	3.2 (2.4, 4.4)	<5	844	1.2 (0.2, 8.4)	-	-
Myocardial infarction	78	13618	5.7 (4.6, 7.2)	5.7 (4.6, 7.2)	<5	844	4.7 (1.8, 12.6)	-	-
Acute Coronary Syndrome [#]	5	13798	0.4 (0.2, 0.9)	0.3 (0.1, 0.8)	<5	843	1.2 (0.2, 8.4)	-	-
MACE (including MI) [#]	163	13447	12.1 (10.4, 14.1)	12.2 (10.5, 14.3)	8	843	9.5 (4.7, 19.0)	0.72 (0.35, 1.48)	0.59 (0.25, 1.38)
Other cardiac events	123	13522	9.1 (7.6, 10.9)	9.1 (7.6, 10.9)	8	833	9.6 (4.8, 19.2)	0.93 (0.45, 1.91)	0.97 (0.40, 2.38)

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
Venous Thrombotic Event (VTE)	50	13698	3.7 (2.8, 4.8)	3.7 (2.8, 4.8)	<5	843	3.6 (1.1, 11.0)	-	-
DVT [#]	14	13780	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)	0	845	-	-	-
PE [#]	30	13745	2.2 (1.5, 3.1)	2.2 (1.6, 3.2)	<5	845	1.2 (0.2, 8.4)	-	-
Total haematologic events	69	13666	5.0 (4.0, 6.4)	5.1 (4.0, 6.4)	<5	844	1.2 (0.2, 8.4)	-	-
Aplastic anaemia	0	13816	-	-	0	845	-	-	-
Pancytopenia	9	13799	0.7 (0.3, 1.3)	0.7 (0.4, 1.3)	0	845	-	-	-
Agranulocytosis	<5	13810	0.1 (0.04, 0.6)	0.1 (0.0, 0.5)	0	845	-	-	-
Other dyscrasia	61	13679	4.5 (3.5, 5.7)	4.5 (3.5, 5.8)	<5	844	1.2 (0.2, 8.4)	-	-
Serious Neutropenia [#]	10	13792	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)	0	845	-	-	-
Serious haemorrhage [#]	0	13816	-	-	0	845	-	-	-
CNS Disorders	115	13534	8.5 (7.1, 10.2)	8.5 (7.1, 10.2)	6	841	7.1 (3.2, 15.9)	0.79 (0.35, 1.81)	0.57 (0.21, 1.53)
Central Demyelination	0	13816	-	-	0	845	-	-	-
Peripheral neuropathy	15	13779	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	<5	841	1.2 (0.2, 8.4)	-	-
Cerebrovascular accident	44	13703	3.2 (2.4, 4.3)	3.3 (2.4, 4.4)	<5	844	1.2 (0.2, 8.4)	-	-
Other CNS	62	13669	4.5 (3.5, 5.8)	4.5 (3.5, 5.8)	<5	845	4.7 (1.8, 12.6)	-	-
Optic Neuritis [#]	0	13816	-	-	0	845	-	-	-

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
Progressive multifocal leukoencephalopathy (PML) [#]	0	13816	-	-	0	1491	-	-	-
Progressive multifocal leukoencephalopathy (PML) [#] (on drug)	0	13816	-	-	0	845	-	-	-
GI perforation	5	13812	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	<5	845	1.2 (0.2, 8.4)	-	-
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	13816	-	-	0	845	-	-	-
Pregnancy (female only)	10	10410	0.96 (0.5, 1.8)	0.8 (0.5, 1.6)	0	642	-	-	-
Death (on drug ⁴)	445	14733	30.2 (27.5, 33.1)	30.4 (27.7, 33.4)	14	871	16.1 (9.5, 27.1)	0.62 (0.36, 1.06)	0.59 (0.32, 1.12)
Death (ever exposed)	445	14733	30.2 (27.5, 33.1)	29.9 (27.3, 32.9)	36	1997	18.0 (13.0, 25.0)	0.60 (0.43, 0.85)*	0.56 (0.36, 0.88)*
Hepatitis B Reactivation [#]	0	13816	-	-	0	845	-	-	-
Serious Infusion/Immunologic Reaction [#]	0	13816	-	-	0	845	-	-	-
Serious Hypersensitivity Reaction [#]	17	13771	1.2 (0.8, 2.0)	1.3 (0.8, 2.1)	<5	843	1.2 (0.2, 8.4)	-	-
Serious Lupus/Lupus-Like Illness [#]	0	13816	-	-	0	845	-	-	-
Serious Skin Reaction [#]	0	13816	-	-	0	845	-	-	-
Interstitial Lung Disease [#]	25	13774	1.8 (1.2, 2.7)	1.8 (1.2, 2.7)	<5	845	1.2 (0.2, 8.4)	-	-

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		
Adjusted Hazard Ratio Following Sensitivity Analysis ³ (95% CI)									
Total serious infection	446	12806	34.8 (31.7, 28.2)	NA	36	787	45.8 (33.0, 63.4)	1.21 (0.86, 1.70)	1.13 (0.71, 1.80)
Herpes Zoster	<5	13807	0.1 (0.04, 0.6)	NA	<5	845	1.2 (0.2, 8.4)	-	-
Myocardial infarction	78	13618	5.7 (4.6, 7.2)	NA	<5	824	4.8 (1.8, 12.9)	-	-
MACE (including MI) [#]	163	13447	12.1 (10.4, 14.1)	NA	8	822	9.7 (4.9, 19.5)	0.74 (0.36, 1.51)	0.60 (0.26, 1.41)
Venous Thrombotic Event (VTE)	50	13698	3.7 (2.8, 4.8)	NA	<5	822	3.6 (1.2, 11.3)	-	-
Progressive multifocal leukoencephalopathy (PML) [#] (on drug)	0	13816	-	NA	0	824	-	-	-
GI perforation	5	13812	0.4 (0.2, 0.9)	NA	<5	824	1.2 (0.2, 8.6)	-	-

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer; Hazard Ratio not generated for events < 5; * p-value < 0.05; NA= Not generated for sensitivity analysis.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements.

Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded as indicated using two systems (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

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Table 9. Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD Naïve (csDMARD) treatment [rates per 1000 person years]

Safety Endpoints	bDMARD Naïve (csDMARD) Patients [N = 2831]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/ 1000 pyrs (95% CI)	Standard ¹ Rate/ 1000 pyrs (95% CI)	Events	Person year	Rate/ 1000 pyrs (95% CI)		

"Other dyscrasia" includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 Adjusted using deciles of a propensity score.

3 Following 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). Note: Number of first events and rates of first events may also change following this sensitivity analysis.

4 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1](#). for cohort definitions.

As shown in [Table 10](#), compared to the bDMARD (anti-TNF) patient cohort, the tofacitinib treated had statistically significant increased crude risks for NMSC (HR=2.87 (1.59, 5.17) ever exposed; HR=2.86 (1.25, 6.56) on drug) and death (HR=1.56 (1.09, 2.25) ever exposed), but after confounder adjustment in the multivariable model these associations were no longer statistically significant.

No other statistically significant crude nor adjusted relative risks were observed for other safety endpoints when comparing the tofacitinib treated patients to bDMARD (anti-TNF) cohorts. These include total serious infection (aHR=0.94 (0.59, 1.51)), fractures (aHR=0.78 (0.25, 2.46)), malignancies except NMSC (aHR=0.52 (0.24, 1.13) ever), total malignant events (aHR=0.81 (0.47, 1.4) ever; aHR=0.55 (0.23, 1.31) on drug), NMSC (aHR=1.39 (0.63, 3.07) ever exposed; aHR=0.98 (0.32, 3.00) on drug), other malignant tumours (aHR=0.46 (0.20, 1.06)), cardiac disorder (aHR=1.13 (0.49, 2.64)), CNS disorders (aHR=0.66 (0.23, 1.88)), and death (aHR=1.61 (0.72, 3.58) on drug).



Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
Total serious infection	193	5501	35.1 (30.5, 40.4)	39.7 (34.3, 46.0)	36	807	44.6 (32.2, 61.9)	1.23 (0.86, 1.75)	0.94 (0.59, 1.51)
Pneumonia	91	5691	16.0 (13.0, 19.6)	19.1 (15.5, 23.7)	18	825	21.8 (13.7, 34.6)	1.30 (0.78, 2.16)	1.09 (0.56, 2.10)
<i>Non-opportunistic</i>	90	5701	15.8 (12.8, 19.4)	18.9 (15.3, 23.4)	17	825	20.6 (12.8, 33.1)	1.25 (0.74, 2.09)	1.06 (0.54, 2.06)
<i>Opportunistic</i>	6	5779	1.0 (0.5, 2.3)	1.2 (0.5, 2.6)	<5	845	1.2 (0.2, 8.4)	-	-
Septicaemia	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.7)	<5	845	2.4 (0.6, 9.5)	-	-
<i>Non-opportunistic</i>	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.7)	<5	845	2.4 (0.6, 9.5)	-	-
<i>Opportunistic</i>	0	5793	-	-	0	845	-	-	-
Bone/Joint infection	15	5783	2.6 (1.6, 4.3)	3.0 (1.8, 5.0)	<5	843	3.6 (1.1, 11.0)	-	-
<i>Non-opportunistic</i>	15	5783	2.6 (1.6, 4.3)	3.0 (1.8, 5.0)	<5	843	3.6 (1.1, 11.0)	-	-
<i>Opportunistic</i>	0	5793	-	-	0	845	-	-	-
Herpes Zoster	0	5793	-	-	<5	845	1.2 (0.2, 8.4)	-	-
<i>Non-opportunistic</i>	0	5793	-	-	<5	845	1.2 (0.2, 8.4)	-	-
<i>Opportunistic</i>	0	5793	-	-	0	845	-	-	-
Other serious infection	108	5600	19.3 (16.0, 23.3)	21.4 (17.6, 26.0)	22	823	26.7 (17.6, 40.6)	1.35 (0.86, 2.14)	0.92 (0.50, 1.70)
<i>Non-opportunistic</i>	105	5609	18.7 (15.5, 22.7)	20.9 (17.2, 25.5)	22	823	26.7 (17.6, 40.6)	1.40 (0.88, 2.21)	0.95 (0.51, 1.76)
<i>Opportunistic</i>	<5	5784	0.7 (0.3, 1.8)	0.7 (0.2, 1.9)	0	845	-	-	-
TB	<5	5792	0.3 (0.1, 1.4)	0.4 (0.1, 1.6)	0	845	-	-	-

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Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
Serious Hepatic Dysfunction/Failure [#]	0	5793	-	-	0	845	-	-	-
Fractures [#]	39	5733	6.8 (5.0, 9.3)	8.4 (6.1, 11.6)	5	834	6.0 (2.5, 14.4)	0.86 (0.34, 2.18)	0.78 (0.25, 2.46)
Malignancies except NMSC	112	13494	8.3 (6.9, 10.0)	9.2 (7.6, 11.2)	11	1977	5.6 (3.1, 10.0)	0.66 (0.35, 1.22)	0.52 (0.24, 1.13)
Total malignant events	148	13347	11.1 (9.4, 13.0)	12.5 (10.6, 14.7)	26	1936	13.4 (9.1, 19.7)	1.19 (0.78, 1.80)	0.81 (0.47, 1.40)
Lymphoproliferative	11	13754	0.8 (0.4, 1.4)	0.9 (0.5, 1.6)	<5	1995	1.0 (0.3, 4.0)	-	-
Lymphoma (NHL, Hodgkins)	9	13761	0.7 (0.3, 1.3)	0.7 (0.4, 1.4)	0	1997	-	-	-
NHL [#]	<5	13780	0.1 (0.01, 0.5)	0.1 (0.0, 0.7)	0	1997	-	-	-
Hodgkin [#]	0	13784	-	-	0	1997	-	-	-
Myeloma	0	13784	-	-	0	1997	-	-	-
Leukaemia	<5	13778	0.1 (0.04, 0.6)	0.2 (0.0, 0.7)	<5	1995	1.0 (0.3, 4.0)	-	-
CLL [#]	0	13784	-	-	0	1997	-	-	-
Non-melanoma Skin Cancer	38	13631	2.8 (2.0, 3.8)	3.3 (2.4, 4.6)	16	1952	8.2 (5.0, 13.4)	2.87 (1.59, 5.17)*	1.39 (0.63, 3.07)
Other malignant solid tumours	101	13524	7.5 (6.1, 9.1)	8.3 (6.8, 10.1)	9	1980	4.5 (2.4, 8.7)	0.59 (0.30, 1.17)	0.46 (0.20, 1.06)
Brain neoplasms	0	13784	-	-	0	1997	-	-	-
Of which, Glioblastoma	0	13784	-	-	0	1997	-	-	-

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Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
<i>Lung cancer[#]</i>	9	13781	0.7 (0.3, 1.3)	0.8 (0.4, 1.5)	<5	1995	1.0 (0.3, 4.0)	-	-
<i>Melanoma[#]</i>	<5	13765	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0	1997	-	-	-
Malignancies except NMSC (on drug⁴)	47	5857	8.0 (6.0, 10.7)	9.3 (6.9, 12.5)	<5	864	3.5 (1.1, 10.8)	-	-
Total malignant events (on drug⁴)	65	5828	11.2 (8.7, 14.2)	13.3 (10.3, 17.0)	10	854	11.7 (6.3, 21.8)	1.07 (0.55, 2.09)	0.55 (0.23, 1.31)
Lymphoproliferative (on drug ⁴)	9	5887	1.5 (0.8, 2.9)	1.7 (0.9, 3.3)	0	871	-	-	-
Non-melanoma Skin Cancer (on drug ⁴)	19	5861	3.2 (2.1, 5.1)	4.1 (2.6, 6.5)	8	858	9.3 (4.7, 18.7)	2.86 (1.25, 6.56)*	0.98 (0.32, 3.00)
Other malignant solid tumours (on drug ⁴)	38	5862	6.5 (4.7, 8.9)	7.6 (5.5, 10.5)	<5	864	3.5 (1.1, 10.8)	-	-
<i>Lung cancer[#] (on drug⁴)</i>	<5	5890	0.5 (0.2, 1.6)	0.7 (0.2, 2.1)	0	871	-	-	-
Total cardiac disorders	55	5714	9.6 (7.4, 12.5)	11.1 (8.5, 14.6)	12	832	14.4 (8.2, 25.4)	1.48 (0.79, 2.77)	1.13 (0.49, 2.64)
CHF (new or worsening)	6	5788	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)	<5	844	1.2 (0.2, 8.4)	-	-
Myocardial infarction	18	5752	3.1 (2.0, 5.0)	3.8 (2.3, 6.1)	<5	844	4.7 (1.8, 12.6)	-	-
Acute Coronary Syndrome [#]	0	5793	-	-	<5	843	1.2 (0.2, 8.4)	-	-
MACE (including MI) [#]	37	5726	6.5 (4.7, 8.9)	7.7 (5.5, 10.7)	8	843	9.5 (4.7, 19.0)	1.44 (0.67, 3.10)	0.98 (0.35, 2.73)
Other cardiac events	35	5755	6.1 (4.4, 8.5)	7.0 (5.0, 9.8)	8	833	9.6 (4.8, 19.2)	1.57 (0.73, 3.39)	1.15 (0.39, 3.35)
Venous Thrombotic Event (VTE)	11	5781	1.9 (1.1, 3.4)	2.3 (1.3, 4.3)	<5	843	3.6 (1.1, 11.0)	-	-

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Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
DVT [#]	<5	5791	0.3 (0.1, 1.4)	0.5 (0.1, 2.0)	0	845	-	-	-
PE [#]	6	5789	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)	<5	845	1.2 (0.2, 8.4)	-	-
Total haematologic events	20	5776	3.5 (2.2, 5.4)	4.5 (2.9, 7.1)	<5	844	1.2 (0.2, 8.4)	-	-
Aplastic anaemia	0	5793	-	-	0	845	-	-	-
Pancytopenia	<5	5787	0.5 (0.2, 1.6)	0.6 (0.2, 2.0)	0	845	-	-	-
Agranulocytosis	<5	5789	0.3 (0.1, 1.4)	0.4 (0.1, 1.6)	0	845	-	-	-
Other dyscrasia	17	5781	2.9 (1.8, 4.7)	3.9 (2.4, 6.3)	<5	844	1.2 (0.2, 8.4)	-	-
Serious Neutropenia [#]	6	5791	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)	0	845	-	-	-
Serious haemorrhage [#]	0	5793	-	-	0	845	-	-	-
CNS Disorders	49	5718	8.6 (6.5, 11.3)	9.2 (6.9, 12.3)	6	841	7.1 (3.2, 15.9)	0.80 (0.34, 1.88)	0.66 (0.23, 1.88)
Central Demyelination	<5	5792	0.3 (0.1, 1.4)	0.3 (0.1, 1.1)	0	845	-	-	-
Peripheral neuropathy	<5	5792	0.2 (0.02, 1.2)	0.1 (0.0, 1.0)	<5	841	1.2 (0.2, 8.4)	-	-
Cerebrovascular accident	10	5777	1.7 (0.9, 3.2)	1.9 (1.0, 3.6)	<5	844	1.2 (0.2, 8.4)	-	-
Other CNS	37	5733	6.5 (4.7, 8.9)	7.0 (5.0, 9.7)	<5	845	4.7 (1.8, 12.6)	-	-
Optic Neuritis [#]	<5	5791	0.2 (0.02, 1.2)	0.2 (0.0, 1.7)	0	845	-	-	-
Progressive multifocal leukoencephalopathy (PML)[#]	0	10972	-	-	0	1491	-	-	-

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Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
Progressive multifocal leukoencephalopathy (PML) # (on drug)	0	5793	-	-	0	845	-	-	-
GI perforation	6	5790	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)	<5	845	1.2 (0.2, 8.4)	-	-
Serious Lower GI Ulcer/Bleed/Perforation#	0	5793	-	-	0	845	-	-	-
Pregnancy (female only)	15	4334	3.5 (2.1, 5.7)	2.2 (1.3, 3.6)	0	642	-	-	-
Death (on drug ⁴)	54	5891	9.2 (7.0, 12.0)	11.4 (8.7, 15.0)	14	871	16.1 (9.5, 27.1)	1.79 (0.99, 3.23)	1.61 (0.72, 3.58)
Death (ever exposed)	159	13784	11.5 (9.9, 13.5)	13.8 (11.8, 16.2)	36	1997	18.0 (13.0, 25.0)	1.56 (1.09, 2.25)*	1.24 (0.76, 2.0)
Hepatitis B Reactivation#	0	5793	-	-	0	845	-	-	-
Serious Infusion/Immunologic Reaction#	0	5793	-	-	0	845	-	-	-
Serious Hypersensitivity Reaction#	5	5792	0.9 (0.4, 2.1)	1.0 (0.4, 2.6)	<5	843	1.2 (0.2, 8.4)	-	-
Serious Lupus/Lupus-Like Illness#	0	5793	-	-	0	845	-	-	-
Serious Skin Reaction#	0	5793	-	-	0	845	-	-	-
Interstitial Lung Disease#	9	5786	1.6 (0.8, 3.0)	1.9 (1.0, 3.7)	<5	845	1.2 (0.2, 8.4)	-	-
Adjusted Hazard Ratio Following Sensitivity Analysis³ (95% CI)									
Total serious infection	193	5501	35.1 (30.5, 40.4)	NA	36	787	45.8 (33.0, 63.4)	1.24 (0.87, 1.77)	0.96 (0.60, 1.53)

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Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		
Herpes Zoster	0	5715	-	NA	<5	845	1.2 (0.2, 8.4)	-	-
Myocardial infarction	18	5675	3.2 (2.0, 5.0)	NA	<5	824	4.8 (1.8, 12.9)	-	-
MACE (including MI) #	37	5649	6.6 (4.7, 9.0)	NA	8	822	9.7 (4.9, 19.5)	1.47 (0.68, 3.2)	0.99 (0.36, 2.77)
Venous Thrombotic Event (VTE)	11	5703	1.9 (1.1, 3.5)	NA	<5	822	3.6 (1.2, 11.3)	-	-
Progressive multifocal leukoencephalopathy (PML) # (on drug)	0	5715	-	NA	0	824	-	-	-
GI perforation	6	5713	1.05 (0.47, 2.34)	NA	<5	824	1.2 (0.2, 8.6)	-	-

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer; Hazard Ratio not generated for events < 5; * p-value < 0.05; NA= Not generated for sensitivity analysis.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements.

Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded as indicated using two systems (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 Adjusted using deciles of a propensity score.



Table 10. Number of first events and rates of first events of in all tofacitinib and bDMARD (anti-TNF) treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs bDMARD (anti-TNF) treatment [rates per 1000 person years]

Serious Adverse Events	bDMARD (Anti-TNF) Patients [N = 2063]				Tofacitinib Patients [N = 361]			Unadjusted Hazard Ratio (95% CI)	Adjusted ² Hazard Ratio (95% CI)
	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)		

3 Following 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). Note: Number of first events and rates of first events may also change following this sensitivity analysis.

4 "On drug" corresponds to secondary analysis using the "censor at switch" approach. Refer to [Section 9.3.1.](#) for cohort definitions.

10.5. Other Analyses

10.5.1. Sensitivity Analysis Restricting the bDMARD Comparator Cohort

Sensitivity analyses were conducted that restricted the bDMARD comparator cohort to patients who were never exposed to tofacitinib or other non-biologic advanced therapies (e.g. baricitinib (Olmiant) and upadacitinib (Rinvoq) and compared the characteristics of those bDMARD patients ever and never exposed to tofacitinib or other non-biologic advanced therapies ([Section 9.9.4.1](#)). These sensitivity analysis results were presented as summary statistics of those without and with previous tofacitinib use or other non-biologic advanced therapies.

Overall, stratification by this treatment history indicates that none of the bDMARD (anti-TNF) cohort were ever exposed to tofacitinib or other non-biologically advanced therapies.



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
Gender	Male	506	24.5%		0	-	-
	Female	1557	75.5%		0	-	-
	Missing	0	0.0%		0	-	-
Age in Years	Male	506	58.8	11.2	0	-	-
	Female	1557	56.6	13.3	0	-	-
	Total	2063	57.1	12.9	0	-	-
	Missing	0	0.0%		0	-	-
Ethnicity	White	1438	94.5%		0	-	-
	Black African/Caribbean/Black British/Black Other	23	1.5%		0	-	-
	Asian/Asian British	51	3.4%		0	-	-
	Mixed/multiple ethnic groups	<10	<0.7%		0	-	-
	Other ethnic groups	<5	-		0	-	-
	Missing	542	26.3%		0	-	-
	Total	1555	165.4	9.5	0	-	-
Height (cm)	Male	376	175.2	7.7	0	-	-
	Female	1179	162.3	7.8	0	-	-
	Missing	508	24.6%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
Weight (kg)	Male	468	88.7	20.2	0	-	-
	Female	1419	75.3	19.0	0	-	-
	Total	1887	78.6	20.1	0	-	-
	Missing	176	8.5%		0	-	-
BMI ≥30 kg/m2	Yes	548	35.7%		0	-	-
	No	987	64.3%		0	-	-
	Missing	528	25.6%		0	-	-
Systolic blood pressure	Male	455	137.9	18.1	0	-	-
	Female	1346	135.4	20.6	0	-	-
	Total	1801	136.0	20.0	0	-	-
	Missing	262	12.7%		0	-	-
Diastolic blood pressure	Male	454	81.9	11.0	0	-	-
	Female	1345	79.1	11.1	0	-	-
	Total	1799	79.9	11.2	0	-	-
	Missing	264	12.8%		0	-	-
Smoking status	Current	355	18.8%		0	-	-
	Previous	767	40.7%		0	-	-
	Never	764	40.5%		0	-	-
	Missing	177	8.6%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olmiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
Herpes Zoster vaccination	Yes	11	61.1%		0	-	-
	No	7	38.9%		0	-	-
	Missing	2045	99.1%		0	-	-
Year of diagnosis	1945-1959	<5	-		0	-	-
	1960-1979	45	2.2%		0	-	-
	1980-1999	350	17.4%		0	-	-
	2000-2019	1607	80.0%		0	-	-
	2020-2025	<10	<0.5%		0	-	-
	Missing	53	2.6%		0	-	-
Years since diagnosis	Male	488	7.9	8.2	0	-	-
	Female	1522	9.1	9.5	0	-	-
	Total	2010	8.8	9.2	0	-	-
	Missing	53	2.6%		0	-	-
Rheumatoid factor status	Positive	1115	62.5%		0	-	-
	Negative	670	37.5%		0	-	-
	Missing	278	13.5%		0	-	-
ACPA (anti-CCP) positive RA	Yes	577	69.1%		0	-	-
	No	258	30.9%		0	-	-
	Missing	1228	59.5%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olmiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
HAQ	Male	468	1.3	0.8	0	-	-
	Female	1448	1.6	0.8	0	-	-
	Total	1916	1.5	0.8	0	-	-
	Missing	147	7.1%		0	-	-
DAS28	Male	505	5.9	1.1	0	-	-
	Female	1553	6.0	1.0	0	-	-
	Total	2058	5.9	1.0	0	-	-
	Missing	5	0.2%		0	-	-
Tender Joint Count	Male	474	14.3	7.5	0	-	-
	Female	1475	14.5	7.1	0	-	-
	Total	1949	14.4	7.2	0	-	-
	Missing	114	5.5%		0	-	-
Swollen Joint Count	Male	474	8.9	5.2	0	-	-
	Female	1473	8.4	5.0	0	-	-
	Total	1947	8.5	5.0	0	-	-
	Missing	116	5.6%		0	-	-
ESR	Male	369	30.9	26.9	0	-	-
	Female	1160	30.3	24.2	0	-	-
	Total	1529	30.5	24.9	0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
CRP	Missing	534	25.9%		0	-	-
	Male	281	26.6	32.3	0	-	-
	Female	868	20.9	27.0	0	-	-
	Total	1149	22.3	28.4	0	-	-
Global Health VAS	Missing	914	44.3%		0	-	-
	Male	463	71.7	20.3	0	-	-
	Female	1432	73.8	19.9	0	-	-
	Total	1895	73.3	20.0	0	-	-
EuroQol Five Dimensions Questionnaire (EQ-5D)	Missing	168	8.1%		0	-	-
	Male	468	0.5	0.3	0	-	-
	Female	1424	0.4	0.3	0	-	-
	Total	1892	0.4	0.3	0	-	-
Use of csDMARDs prior to or at baseline	Missing	171	8.3%		0	-	-
	Yes	2055	99.6%		0	-	-
	No	8	0.4%		0	-	-
	Missing	0	0.0%		0	-	-
Biologically naïve at registration	Yes	2063	100%		0	-	-
	No	0	0.0%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
	Missing	0	0.0%		0	-	-
Previous use of ADA, ETA, or INF	Yes	0	0.0%		0	-	-
	No	2063	100.0%		0	-	-
	Missing	0	0.0%		0	-	-
Previous use of other biologics or biosimilars	Yes	0	0.0%		0	-	-
	No	2063	100.0%		0	-	-
	Missing	0	0.0%		0	-	-
Previous use of other targeted synthetic (tsDMARDs)	Yes	0	0.0%		0	-	-
	No	2063	100.0%		0	-	-
	Missing	0	0.0%		0	-	-
On steroids at registration	Yes	465	22.5%		0	-	-
	No	1598	77.5%		0	-	-
	Missing	0	0.0%		0	-	-
History of TB	Yes	79	3.8%		0	-	-
	No	1984	96.2%		0	-	-
	Missing	0	0.0%		0	-	-
History of diabetes mellitus	Yes	166	8.0%		0	-	-
	No	1897	92.0%		0	-	-

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Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
	Missing	0	0.0%		0	-	-
History of hypertension	Yes	585	28.4%		0	-	-
	No	1478	71.6%		0	-	-
	Missing	0	0.0%		0	-	-
History of angina	Yes	94	4.6%		0	-	-
	No	1969	95.4%		0	-	-
	Missing	0	0.0%		0	-	-
History of MI	Yes	62	3.0%		0	-	-
	No	2001	97.0%		0	-	-
	Missing	0	0.0%		0	-	-
History of stroke	Yes	44	2.1%		0	-	-
	No	2019	97.9%		0	-	-
	Missing	0	0.0%		0	-	-
History of malignancy	Yes	91	4.4%		0	-	-
	No	1972	95.6%		0	-	-
	Missing	0	0.0%		0	-	-
History of liver disease	Yes	54	2.6%		0	-	-
	No	2009	97.4%		0	-	-
	Missing	0	0.0%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
History of renal disease	Yes	38	1.8%		0	-	-
	No	2025	98.2%		0	-	-
	Missing	0	0.0%		0	-	-
History of asthma	Yes	304	14.7%		0	-	-
	No	1759	85.3%		0	-	-
	Missing	0	0.0%		0	-	-
History of chronic bronchitis/emphysema (COPD)	Yes	135	6.5%		0	-	-
	No	1928	93.5%		0	-	-
	Missing	0	0.0%		0	-	-
History of epilepsy	Yes	22	1.1%		0	-	-
	No	2041	98.9%		0	-	-
	Missing	0	0.0%		0	-	-
History of demyelination	Yes	7	0.3%		0	-	-
	No	2056	99.7%		0	-	-
	Missing	0	0.0%		0	-	-
History of depression	Yes	437	21.2%		0	-	-
	No	1626	78.8%		0	-	-
	Missing	0	0.0%		0	-	-



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD
History of peptic ulcer	Yes	71	3.4%		0	-	-
	No	1992	96.6%		0	-	-
	Missing	0	0.0%		0	-	-
History of hyperthyroidism	Yes	73	3.5%		0	-	-
	No	1990	96.5%		0	-	-
	Missing	0	0.0%		0	-	-
History of Knee or hip replacement	Yes	240	12.0%		0	-	-
	No	1768	88.0%		0	-	-
	Missing	55	2.7%		0	-	-
History of Shoulder/Elbow/Wrist/Hand/Ankle/Foot/Neck joint surgery	Yes	244	12.1%		0	-	-
	No	1767	87.9%		0	-	-
	Missing	52	2.5%		0	-	-
Number of comorbidities	0	1018	49.3%		0	-	-
	1	656	31.8%		0	-	-
	2+	389	18.9%		0	-	-
	Missing	0	0.0%		0	-	-

Abbreviations: N, number; SD, Standard Deviation; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score 28; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive Protein; VAS, Visual Analog Scale.



Table 11. Characteristics of patients in the bDMARD (anti-TNF) comparator cohort: (a) not exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq) or filgotinib (Jyseleca)) and (b) exposed to JAK inhibitors.

		(a) bDMARD (Anti-TNF) patients not exposed to JAK inhibitors [N = 2063]			(b) bDMARD (Anti-TNF) patients exposed to JAK inhibitors [N = 0]		
		N	Mean or %	SD	N	Mean	SD

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. To prevent back-calculation of non-zero frequencies < 5, the second lowest frequency is also suppressed.

For categorical variables percentage is included in the "Mean" column.

"Total" represents the statistics for continuous variables without stratification by gender.

Percentage of missing values refers to the percentage of missing values from the number of total possible observations in each cohort.

Data for "Ethnicity" has not been collected between 2019 and 2024.

Data for "Knee or hip replacement" and "Joint surgery " is available until August 2024.

Number of comorbidities represents the total for the history of high blood pressure, ischemic heart disease [angina/MI], stroke, epilepsy, asthma, COPD, renal disease, liver disease, demyelination, diabetes and cancer.

Refer to [Section 9.3.1.](#) for cohort definitions.

10.5.2. Sensitivity Analysis for Confounding by Non-Tofacitinib JAK Inhibitor History

[Table 12](#) and [13](#) describe sensitivity analyses ([Section 9.9.4.2](#)) to evaluate potential confounding by prior use of non-tofacitinib JAK inhibitors.

In [Table 12](#) , in the tofacitinib treated cohort, 313 (86.7%) of 361 patients had no prior use of non-tofacitinib JAK inhibitors ([Table 12](#)); no patients in the bDMARD naïve (csDMARD; n=2831) and bDMARD (anti-TNF;n=2063) treated cohorts had a history of use of non-tofacitinib JAK inhibitors. Among the tofacitinib treated cohort without ([Table 12](#)) prior use of non-tofacitinib JAK inhibitors, rates could not be estimated for safety endpoints for events with zero occurrences; among the safety endpoints that could be estimated, no substantial differences in rates were observed in the tofacitinib treated cohort with prior use of non-tofacitinib JAK inhibitors ([Table 10](#) and [11](#); n=361) and in those without prior use of non-tofacitinib JAK inhibitors ([Table 12](#) ; n=313).



Table 12. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with no prior non-tofacitinib JAK inhibitors.

Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Total serious infection	31	713	43.5 (30.6, 61.8)	446	12806	34.8 (31.7, 38.2)	34.7 (31.6, 38.2)	193	5501	35.1 (30.5, 40.4)	39.1 (33.8, 45.2)
Pneumonia	16	730	21.9 (13.4, 35.8)	267	13270	20.1 (17.8, 22.7)	19.8 (17.5, 22.3)	91	5691	16.0 (13.0, 19.6)	18.6 (15.1, 22.9)
<i>Non-opportunistic</i>	15	730	20.6 (12.4, 34.1)	262	13284	19.7 (17.5, 22.3)	19.4 (17.1, 21.9)	90	5701	15.8 (12.8, 19.4)	18.3 (14.8, 22.6)
<i>Opportunistic</i>	<5	747	1.3 (0.2, 9.5)	10	13796	0.7 (0.4, 1.3)	0.7 (0.4, 1.2)	6	5779	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)
Septicaemia	<5	747	2.7 (0.7, 10.7)	35	13776	2.5 (1.8, 3.5)	2.5 (1.8, 3.5)	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.6)
<i>Non-opportunistic</i>	<5	747	2.7 (0.7, 10.7)	35	13776	2.5 (1.8, 3.5)	2.5 (1.8, 3.5)	10	5783	1.7 (0.9, 3.2)	1.9 (1.0, 3.6)
<i>Opportunistic</i>	0	747	-	<5	13815	0.1 (0.0, 0.5)	0.1 (0.0, 0.5)	0	5793	-	-
Bone/Joint infection	<5	745	4.0 (1.3, 12.5)	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	15	5783	2.6 (1.6, 4.3)	2.9 (1.7, 4.9)
<i>Non-opportunistic</i>	<5	745	4.0 (1.3, 12.5)	37	13719	2.7 (2.0, 3.7)	2.7 (2.0, 3.8)	15	5783	2.6 (1.6, 4.3)	2.9 (1.7, 4.9)
<i>Opportunistic</i>	0	747	-	0	13816	-	-	0	5793	-	-
Herpes Zoster	<5	747	1.3 (0.2, 9.5)	<5	13807	0.1 (0.0, 0.6)	0.1 (0.0, 0.5)	0	5793	-	-
<i>Non-opportunistic</i>	<5	747	1.3 (0.2, 9.5)	<5	13807	0.1 (0.0, 0.6)	0.1 (0.0, 0.5)	0	5793	-	-
<i>Opportunistic</i>	0	747	-	0	13816	-	-	0	5793	-	-
Other serious infection	19	728	26.1 (16.7, 40.9)	205	13320	15.4 (13.4, 17.6)	15.7 (13.7, 18.0)	108	5600	19.3 (16.0, 23.3)	21.0 (17.4, 25.5)
<i>Non-opportunistic</i>	19	728	26.1 (16.7, 40.9)	203	13322	15.2 (13.3, 17.5)	15.5 (13.5, 17.8)	105	5609	18.7 (15.5, 22.7)	20.6 (16.9, 25.0)

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Table 12. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with no prior non-tofacitinib JAK inhibitors.

Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
<i>Opportunistic</i>	0	747	-	<5	13809	0.2 (0.1, 0.7)	0.2 (0.1, 0.7)	<5	5784	0.7 (0.3, 1.8)	0.6 (0.2, 1.7)
TB	0	747	-	0	13816	-	-	<5	5792	0.3 (0.1, 1.4)	0.3 (0.1, 1.4)
Serious Hepatic Dysfunction/Failure[#]	0	747	-	0	13816	-	-	0	5793	-	-
Fractures[#]	5	736	6.8 (2.8, 16.3)	134	13459	10.0 (8.4, 11.8)	10.1 (8.5, 11.9)	39	5733	6.8 (5.0, 9.3)	8.2 (5.9, 11.2)
Malignancies except NMSC	10	1736	5.8 (3.1, 10.7)	265	14219	18.6 (16.5, 21.0)	18.4 (16.3, 20.8)	112	13494	8.3 (6.9, 10.0)	9.1 (7.5, 11.0)
Total malignant events	22	1703	12.9 (8.5, 19.6)	358	13880	25.8 (23.3, 28.6)	25.5 (23.0, 28.4)	148	13347	11.1 (9.4, 13.0)	12.4 (10.5, 14.6)
Lymphoproliferative	<5	1749	1.1 (0.3, 4.6)	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	11	13754	0.8 (0.4, 1.4)	0.9 (0.5, 1.6)
<u>Lymphoma (NHL, Hodgkins)</u>	0	1751	-	24	14670	1.6 (1.1, 2.4)	1.6 (1.1, 2.4)	9	13761	0.7 (0.3, 1.3)	0.7 (0.4, 1.4)
<i>NHL[#]</i>	0	1751	-	11	14699	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)	<5	13780	0.1 (0.0, 0.5)	0.1 (0.0, 0.7)
<i>Hodgkin[#]</i>	0	1751	-	<5	14721	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)	0	13784	-	-
<u>Myeloma</u>	0	1751	-	6	14717	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	0	13784	-	-
<u>Leukaemia</u>	<5	1749	1.1 (0.3, 4.6)	9	14723	0.6 (0.3, 1.2)	0.6 (0.3, 1.1)	<5	13778	0.1 (0.0, 0.6)	0.2 (0.0, 0.7)
<i>CLL[#]</i>	0	1751	-	5	14726	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0	13784	-	-
Non-melanoma skin cancer	12	1718	7.0 (4.0, 12.3)	118	14358	8.2 (6.9, 9.8)	8.1 (6.8, 9.8)	38	13631	2.8 (2.0, 3.8)	3.3 (2.4, 4.5)

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Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Other malignant solid tumours	8	1739	4.6 (2.3, 9.2)	230	14301	16.1 (14.1, 18.3)	15.9 (13.9, 18.1)	101	13524	7.5 (6.1, 9.1)	8.2 (6.7, 10.0)
Brain neoplasms	0	1751	-	<5	14732	0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0	13784	-	-
Of which, Glioblastoma	0	1751	-	<5	14732	0.1 (0.0, 0.5)	0.1 (0.0, 0.5)	0	13784	-	-
Lung cancer [#]	<5	1749	1.1 (0.3, 4.6)	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	9	13781	0.7 (0.3, 1.3)	0.8 (0.4, 1.5)
Melanoma [#]	0	1751	-	8	14698	0.5 (0.3, 1.1)	0.5 (0.3, 1.1)	<5	13765	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)
Total cardiac disorders	8	735	10.9 (5.4, 21.8)	217	13312	16.3 (14.3, 18.6)	15.8 (13.8, 18.1)	55	5714	9.6 (7.4, 12.5)	11.0 (8.4, 14.4)
Serious CHF (new or worsening)	0	747	-	45	13762	3.3 (2.4, 4.4)	3.0 (2.3, 4.1)	6	5788	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)
Myocardial infarction	<5	746	4.0 (1.3, 12.5)	78	13618	5.7 (4.6, 7.2)	5.6 (4.4, 7.0)	18	5752	3.1 (2.0, 5.0)	3.7 (2.3, 5.9)
Acute Coronary Syndrome [#]	<5	745	1.3 (0.2, 9.5)	5	13798	0.4 (0.2, 0.9)	0.3 (0.1, 0.8)	0	5793	-	-
MACE (including MI) [#]	<5	746	5.4 (2.0, 14.3)	163	13447	12.1 (10.4, 14.1)	11.7 (10.1, 13.7)	37	5726	6.5 (4.7, 8.9)	7.4 (5.3, 10.3)
Other cardiac events	6	736	8.2 (3.7, 18.2)	123	13522	9.1 (7.6, 10.9)	8.9 (7.4, 10.6)	35	5755	6.1 (4.4, 8.5)	7.0 (5.0, 9.7)
Venous Thromboembolic Events (VTE)	<5	745	4.0 (1.3, 12.5)	50	13698	3.7 (2.8, 4.8)	3.5 (2.7, 4.7)	11	5781	1.9 (1.1, 3.4)	2.2 (1.2, 4.1)
DVT [#]	0	747	-	14	13780	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)	<5	5791	0.3 (0.1, 1.4)	0.4 (0.1, 1.8)
PE [#]	<5	747	1.3 (0.2, 9.5)	30	13745	2.2 (1.5, 3.1)	2.1 (1.5, 3.0)	6	5789	1.0 (0.5, 2.3)	1.1 (0.5, 2.6)

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Table 12. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with no prior non-tofacitinib JAK inhibitors.

Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Total haematologic events	<5	745	1.3 (0.2, 9.5)	69	13666	5.0 (4.0, 6.4)	4.9 (3.9, 6.3)	20	5776	3.5 (2.2, 5.4)	4.4 (2.8, 6.8)
Aplastic anaemia	0	747	-	0	13816	-	-	0	5793	-	-
Pancytopenia	0	747	-	9	13799	0.7 (0.3, 1.3)	0.7 (0.3, 1.3)	<5	5787	0.5 (0.2, 1.6)	0.6 (0.2, 2.0)
Agranulocytosis	0	747	-	<5	13810	0.1 (0.0, 0.6)	0.1 (0.0, 0.6)	<5	5789	0.3 (0.1, 1.4)	0.3 (0.1, 1.4)
Other dyscrasia	<5	745	1.3 (0.2, 9.5)	61	13679	4.5 (3.5, 5.7)	4.3 (3.4, 5.6)	17	5781	2.9 (1.8, 4.7)	3.8 (2.3, 6.1)
Serious Neutropenia [#]	0	747	-	10	13792	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)	6	5791	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)
Serious haemorrhage [#]	0	747	-	0	13816	-	-	0	5793	-	-
CNS Disorders	<5	743	5.4 (2.0, 14.3)	115	13534	8.5 (7.1, 10.2)	8.3 (6.9, 9.9)	49	5718	8.6 (6.5, 11.3)	8.9 (6.7, 11.9)
Central Demyelination	0	747	-	0	13816	-	-	<5	5792	0.3 (0.1, 1.4)	0.3 (0.1, 1.1)
Peripheral neuropathy	<5	743	1.3 (0.2, 9.5)	15	13779	1.1 (0.7, 1.8)	1.1 (0.6, 1.8)	<5	5792	0.2 (0.0, 1.2)	0.1 (0.0, 1.0)
Cerebrovascular accident	0	747	-	44	13703	3.2 (2.4, 4.3)	3.2 (2.3, 4.2)	10	5777	1.7 (0.9, 3.2)	1.9 (1.0, 3.5)
Other CNS	<5	747	4.0 (1.3, 12.5)	62	13669	4.5 (3.5, 5.8)	4.4 (3.4, 5.7)	37	5733	6.5 (4.7, 8.9)	6.7 (4.8, 9.4)
Optic Neuritis [#]	0	747	-	0	13816	-	-	<5	5791	0.2 (0.0, 1.2)	0.2 (0.0, 1.4)
Progressive Multifocal Leukoencephalopathy (PML)[#]	0	1297	-	0	13816	-	-	0	10972	-	-

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Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
GI perforation	<5	747	1.3 (0.2, 9.5)	5	13812	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	6	5790	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	747	-	0	13816	-	-	0	5793	-	-
Pregnancy (female only)	0	569	-	10	10410	1.0 (0.5, 1.8)	0.8 (0.4, 1.5)	15	4334	3.5 (2.1, 5.7)	2.1 (1.3, 3.5)
Death (on drug²)	11	770	14.3 (7.9, 25.8)	445	14733	30.2 (27.5, 33.1)	29.1 (26.5, 31.9)	54	5891	9.2 (7.0, 12.0)	11.0 (8.4, 14.4)
Death (ever exposed)	30	1751	17.1 (12.0, 24.5)	445	14733	30.2 (27.5, 33.1)	29.3 (26.7, 32.2)	159	13784	11.5 (9.9, 13.5)	13.6 (11.6, 15.9)
Hepatitis B Reactivation[#]	0	747	-	0	13816	-	-	0	5793	-	-
Serious Infusion/Immunologic Reaction [#]	0	747	-	0	13816	-	-	0	5793	-	-
Serious Hypersensitivity Reaction [#]	<5	745	1.3 (0.2, 9.5)	17	13771	1.2 (0.8, 2.0)	1.3 (0.8, 2.0)	5	5792	0.9 (0.4, 2.1)	1.0 (0.4, 2.5)
Serious Lupus/Lupus-Like Illness [#]	0	747	-	0	13816	-	-	0	5793	-	-
Serious Skin Reaction [#]	0	747	-	0	13816	-	-	0	5793	-	-
Interstitial Lung Disease [#]	<5	747	1.3 (0.2, 9.5)	25	13774	1.8 (1.2, 2.7)	1.8 (1.2, 2.7)	9	5786	1.6 (0.8, 3.0)	1.9 (1.0, 3.7)

Data cut at 7 years after start of therapy.

[#] Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

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Table 12. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with no prior non-tofacitinib JAK inhibitors.

Serious Adverse Events	Tofacitinib Patients [N=313]			bDMARD Naïve (csDMARD) Patients [N=2831]				bDMARD (Anti-TNF) Patients [N=2063]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classed as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1](#) for cohort definitions.

[Table 13](#) also describes sensitivity analyses ([Section 9.9.4.2](#)) to evaluate potential confounding by prior use of non-tofacitinib JAK inhibitors. Among the tofacitinib treated cohort with prior use of non-tofacitinib JAK inhibitors, rates could not be estimated for many of the safety endpoints on account of zero event counts; among the safety endpoints that could be estimated, no substantial differences in rates were observed in either group (i.e. tofacitinib patients with prior use of non-tofacitinib JAKs (n=48) and the tofacitinib treated cohort with prior use of non-tofacitinib JAK inhibitors (presented in [Table 10](#) and [11](#); n=361)).



Table 13. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with at least one non-tofacitinib JAK inhibitor.

Serious Adverse Events	Tofacitinib Patients [N=48]			bDMARD Naïve (csDMARD) Patients [N=0]				bDMARD (Anti-TNF) Patients [N=0]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Total serious infection	5	93	53.5 (22.3, 128.6)	NA	-	-	-	NA	-	-	-
Pneumonia	<5	96	20.9 (5.2, 83.6)	NA	-	-	-	NA	-	-	-
<i>Non-opportunistic</i>	<5	96	20.9 (5.2, 83.6)	NA	-	-	-	NA	-	-	-
<i>Opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
Septicaemia	0	98	-	NA	-	-	-	NA	-	-	-
<i>Non-opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
<i>Opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
Bone/Joint infection	0	98	-	NA	-	-	-	NA	-	-	-
<i>Non-opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
<i>Opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
Herpes Zoster	0	98	-	NA	-	-	-	NA	-	-	-
<i>Non-opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
<i>Opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
Other serious infection	<5	96	31.3 (10.1, 97.0)	NA	-	-	-	NA	-	-	-
<i>Non-opportunistic</i>	<5	96	31.3 (10.1, 97.0)	NA	-	-	-	NA	-	-	-
<i>Opportunistic</i>	0	98	-	NA	-	-	-	NA	-	-	-
TB	0	98	-	NA	-	-	-	NA	-	-	-
Serious Hepatic Dysfunction/Failure[#]	0	98	-	NA	-	-	-	NA	-	-	-

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Table 13. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with at least one non-tofacitinib JAK inhibitor.

Serious Adverse Events	Tofacitinib Patients [N=48]			bDMARD Naïve (csDMARD) Patients [N=0]				bDMARD (Anti-TNF) Patients [N=0]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Fractures [#]	0	98	-	NA	-	-	-	NA	-	-	-
Malignancies except NMSC	<5	241	4.2 (0.6, 29.5)	NA	-	-	-	NA	-	-	-
Total malignant events	<5	233	17.2 (6.5, 45.8)	NA	-	-	-	NA	-	-	-
Lymphoproliferative	0	246	-	NA	-	-	-	NA	-	-	-
<u>Lymphoma (NHL, Hodgkins)</u>	0	246	-	NA	-	-	-	NA	-	-	-
<u>NHL</u> [#]	0	246	-	NA	-	-	-	NA	-	-	-
<u>Hodgkin</u> [#]	0	246	-	NA	-	-	-	NA	-	-	-
<u>Myeloma</u>	0	246	-	NA	-	-	-	NA	-	-	-
<u>Leukaemia</u>	0	246	-	NA	-	-	-	NA	-	-	-
<u>CLL</u> [#]	0	246	-	NA	-	-	-	NA	-	-	-
Non-melanoma skin cancer	<5	234	17.1 (6.4, 45.6)	NA	-	-	-	NA	-	-	-
Other malignant solid tumours	<5	241	4.2 (0.6, 29.5)	NA	-	-	-	NA	-	-	-
<u>Brain neoplasms</u>	0	246	-	NA	-	-	-	NA	-	-	-
<u>Of which, Glioblastoma</u>	0	246	-	NA	-	-	-	NA	-	-	-
<u>Lung cancer</u> [#]	0	246	-	NA	-	-	-	NA	-	-	-
<u>Melanoma</u> [#]	0	246	-	NA	-	-	-	NA	-	-	-
Total cardiac disorders	<5	97	41.3 (15.5, 109.9)	NA	-	-	-	NA	-	-	-

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Table 13. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients with at least one non-tofacitinib JAK inhibitor.

Serious Adverse Events	Tofacitinib Patients [N=48]			bDMARD Naïve (csDMARD) Patients [N=0]				bDMARD (Anti-TNF) Patients [N=0]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Serious CHF (new or worsening)	<5	97	10.3 (1.4, 72.9)	NA	-	-	-	NA	-	-	-
Myocardial infarction	<5	98	10.2 (1.4, 72.6)	NA	-	-	-	NA	-	-	-
Acute Coronary Syndrome [#]	0	98	-	NA	-	-	-	NA	-	-	-
MACE (including MI) [#]	<5	96	41.5 (15.6, 110.6)	NA	-	-	-	NA	-	-	-
Other cardiac events	<5	98	20.5 (5.1, 81.8)	NA	-	-	-	NA	-	-	-
Venous Thromboembolic Events (VTE)	0	98	-	NA	-	-	-	NA	-	-	-
DVT [#]	0	98	-	NA	-	-	-	NA	-	-	-
PE [#]	0	98	-	NA	-	-	-	NA	-	-	-
Total haematologic events	0	98	-	NA	-	-	-	NA	-	-	-
Aplastic anaemia	0	98	-	NA	-	-	-	NA	-	-	-
Pancytopenia	0	98	-	NA	-	-	-	NA	-	-	-
Agranulocytosis	0	98	-	NA	-	-	-	NA	-	-	-
Other dyscrasia	0	98	-	NA	-	-	-	NA	-	-	-
Serious Neutropenia [#]	0	98	-	NA	-	-	-	NA	-	-	-
Serious haemorrhage [#]	0	98	-	NA	-	-	-	NA	-	-	-
CNS Disorders	<5	97	20.6 (5.1, 82.3)	NA	-	-	-	NA	-	-	-
Central Demyelination	0	98	-	NA	-	-	-	NA	-	-	-

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Serious Adverse Events	Tofacitinib Patients [N=48]			bDMARD Naïve (csDMARD) Patients [N=0]				bDMARD (Anti-TNF) Patients [N=0]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Peripheral neuropathy	0	98	-	NA	-	-	-	NA	-	-	-
Cerebrovascular accident	<5	97	10.3 (1.4, 73.0)	NA	-	-	-	NA	-	-	-
Other CNS	<5	98	10.2 (1.4, 72.4)	NA	-	-	-	NA	-	-	-
Optic Neuritis [#]	0	98	-	NA	-	-	-	NA	-	-	-
Progressive Multifocal Leukoencephalopathy (PML)[#]	0	194	-	NA	-	-	-	NA	-	-	-
GI perforation	0	98	-	NA	-	-	-	NA	-	-	-
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	98	-	NA	-	-	-	NA	-	-	-
Pregnancy (female only)	0	73	-	NA	-	-	-	NA	-	-	-
Death (on drug²)	<5	101	29.8 (9.6, 92.6)	NA	-	-	-	NA	-	-	-
Death (ever exposed)	6	246	24.4 (11.0, 54.3)	NA	-	-	-	NA	-	-	-
Hepatitis B Reactivation[#]	0	98	-	NA	-	-	-	NA	-	-	-
Serious Infusion/Immunologic Reaction [#]	0	98	-	NA	-	-	-	NA	-	-	-
Serious Hypersensitivity Reaction [#]	0	98	-	NA	-	-	-	NA	-	-	-
Serious Lupus/Lupus-Like Illness [#]	0	98	-	NA	-	-	-	NA	-	-	-
Serious Skin Reaction [#]	0	98	-	NA	-	-	-	NA	-	-	-

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Serious Adverse Events	Tofacitinib Patients [N=48]			bDMARD Naïve (csDMARD) Patients [N=0]				bDMARD (Anti-TNF) Patients [N=0]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Interstitial Lung Disease [#]	0	98	-	NA		-		NA		-	

Data cut at 7 years after start of therapy.

[#] Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events; NA No participants were present in this group for iNon-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1](#). for cohort definitions.

10.5.3. Sensitivity Analyses Employing a 90-Day Extension To Risk Windows

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. Findings from this sensitivity analysis are presented in [Table 9](#) and [Table 10](#), respectively:

- Comparing tofacitinib to bDMARD naïve (csDMARD) patients:



- aHRs were not estimable for: MI, VTE, herpes zoster, PML, and gastrointestinal perforation
- MACE: aHR=0.60 (0.26, 1.41)
- Total serious infections (aHR=1.13 (0.71, 1.80)),
- Comparing tofacitinib to bDMARD (anti-TNF) patients:
 - aHRs were not estimable for: MI, VTE, herpes zoster, PML, and gastrointestinal perforation
 - MACE: aHR=0.99 (0.36, 2.77)
 - Total serious infections (aHR=0.96 (0.60, 1.53))

Overall, the adjusted HRs estimated by sensitivity analysis methods did not appreciably alter the aHRs obtained by Cox proportional hazards multivariable modeling.

10.5.4. Subgroup Analyses for Age-Dependent Rate Events of Interest

Table 14 and 15 describe the number of events and IRs with 95% CIs for each treatment cohort stratified by patients aged ≥ 65 years (Table 14) and < 65 years of age (Table 15). Overall, rates across safety endpoints were higher for patients ≥ 65 years old for all three patient cohorts, when qualitatively compared to patients < 65 . Total serious infections were the most common safety endpoint in both the ≥ 65 -year- (Table 14) and < 65 -year-old age groups (Table 15), with pneumonia being the most frequent infection in both age groups. The rate of *other serious infections* was higher in the tofacitinib treated cohort compared to bDMARD naïve (csDMARD) and bDMARD (anti-TNF) treated cohorts; this was consistent in both age groups (Table 14 and 15). In the ≥ 65 -year-old age group, the rates of death (both on drug and ever exposed) were lower in the tofacitinib treatment group compared to the bDMARD naïve (csDMARD) treated group, and higher than the bDMARD (anti-TNF) treated group (Table 14). In the < 65 -year-old age group, < 5 events of death (on drug) were observed in the tofacitinib group and the incidence of death in the ever-exposed group was lower in the tofacitinib treated group compared to the bDMARD naïve (csDMARD) treated group but higher compared to the bDMARD (anti-TNF) treated group (Table 15). In the < 65 patient group, most safety endpoints had frequencies < 5 events across the three treatment cohorts (Table 15).



Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Total serious infection	22	316	69.7 (45.9, 105.9)	270	4730	57.1 (50.7, 64.3)	57.0 (50.5, 64.2)	93	1502	61.9 (50.5, 75.9)	61.9 (50.5, 75.9)
Pneumonia	12	329	36.5 (20.7, 64.2)	173	4938	35.0 (30.2, 40.7)	34.7 (29.9, 40.3)	53	1565	33.9 (25.9, 44.3)	33.9 (25.9, 44.4)
<i>Non-opportunistic</i>	12	329	36.5 (20.7, 64.2)	172	4942	34.8 (30.0, 40.4)	34.4 (29.7, 40.0)	53	1566	33.8 (25.9, 44.3)	33.9 (25.9, 44.3)
<i>Opportunistic</i>	0	337	-	<5	5252	0.8 (0.3, 2.0)	0.7 (0.3, 1.9)	<5	1613	1.2 (0.3, 5.0)	1.2 (0.3, 5.0)
Septicaemia	<5	337	5.9 (1.5, 23.7)	28	5234	5.3 (3.7, 7.7)	5.4 (3.7, 7.8)	5	1610	3.1 (1.3, 7.5)	3.1 (1.3, 7.5)
<i>Non-opportunistic</i>	<5	337	5.9 (1.5, 23.7)	28	5234	5.3 (3.7, 7.7)	5.4 (3.7, 7.8)	5	1610	3.1 (1.3, 7.5)	3.1 (1.3, 7.5)
<i>Opportunistic</i>	0	337	-	<5	5259	0.2 (0.0, 1.4)	0.2 (0.0, 1.4)	0	1614	-	-
Bone/Joint infection	0	337	-	17	5222	3.3 (2.0, 5.2)	3.2 (2.0, 5.2)	7	1605	4.4 (2.1, 9.1)	4.4 (2.1, 9.1)
<i>Non-opportunistic</i>	0	337	-	17	5222	3.3 (2.0, 5.2)	3.2 (2.0, 5.2)	7	1605	4.4 (2.1, 9.1)	4.4 (2.1, 9.1)
<i>Opportunistic</i>	0	337	-	0	5259	-	-	0	1614	-	-
Herpes Zoster	<5	337	3.0 (0.4, 21.1)	<5	5250	0.4 (0.1, 1.5)	0.4 (0.1, 1.5)	0	1614	-	-
<i>Non-opportunistic</i>	<5	337	3.0 (0.4, 21.1)	<5	5250	0.4 (0.1, 1.5)	0.4 (0.1, 1.5)	0	1614	-	-
<i>Opportunistic</i>	0	337	-	0	5259	-	-	0	1614	-	-
Other serious infection	13	323	40.2 (23.4, 69.3)	120	5016	23.9 (20.0, 28.6)	24.5 (20.5, 29.4)	49	1551	31.6 (23.9, 41.8)	31.5 (23.8, 41.7)

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Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
<i>Non-opportunistic</i>	13	323	40.2 (23.4, 69.3)	120	5016	23.9 (20.0, 28.6)	24.5 (20.5, 29.4)	49	1551	31.6 (23.9, 41.8)	31.5 (23.8, 41.7)
<i>Opportunistic</i>	0	337	-	<5	5254	0.2 (0.0, 1.4)	0.2 (0.0, 1.4)	<5	1614	0.6 (0.1, 4.4)	0.6 (0.1, 4.4)
TB	0	337	-	0	5259	-	-	<5	1613	0.6 (0.1, 4.4)	0.6 (0.1, 4.4)
Serious Hepatic Dysfunction/Failure[#]	0	337	-	0	5259	-	-	0	1614	-	-
Fractures[#]	<5	331	9.1 (2.9, 28.1)	90	5010	18.0 (14.6, 22.1)	18.4 (15.0, 22.6)	25	1579	15.8 (10.7, 23.4)	15.8 (10.7, 23.4)
Malignancies except NMSC	7	770	9.1 (4.3, 19.1)	155	5341	29.0 (24.8, 34.0)	28.3 (24.1, 33.1)	58	3888	14.9 (11.5, 19.3)	14.4 (11.1, 18.7)
Total malignant events	20	737	27.1 (17.5, 42.1)	216	5104	42.3 (37.0, 48.4)	41.3 (36.1, 47.3)	82	3780	21.7 (17.5, 26.9)	21.0 (16.9, 26.1)
Lymphoproliferative	<5	779	2.6 (0.6, 10.3)	20	5553	3.6 (2.3, 5.6)	3.5 (2.2, 5.4)	5	3996	1.3 (0.5, 3.0)	1.3 (0.5, 3.0)
<u>Lymphoma (NHL, Hodgkins)</u>	0	781	-	10	5573	1.8 (1.0, 3.3)	1.7 (0.9, 3.2)	<5	4002	1.0 (0.4, 2.7)	1.0 (0.4, 2.7)
<i>NHL[#]</i>	0	781	-	<5	5585	0.7 (0.3, 1.9)	0.7 (0.3, 1.9)	<5	4007	0.2 (0.0, 1.8)	0.3 (0.0, 1.9)
<i>Hodgkin[#]</i>	0	781	-	<5	5589	0.2 (0.0, 1.3)	0.1 (0.0, 1.0)	0	4012	-	-
<u>Myeloma</u>	0	781	-	<5	5579	0.7 (0.3, 1.9)	0.7 (0.2, 1.8)	0	4012	-	-
<u>Leukaemia</u>	<5	779	2.6 (0.6, 10.3)	6	5586	1.1 (0.5, 2.4)	1.1 (0.5, 2.4)	<5	4006	0.2 (0.0, 1.8)	0.3 (0.0, 1.9)

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Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
<i>CLL</i> [#]	0	781	-	<5	5588	0.7 (0.3, 1.9)	0.7 (0.3, 1.9)	0	4012	-	-
Non-melanoma skin cancer	14	744	18.8 (11.1, 31.8)	81	5333	15.2 (12.2, 18.9)	14.9 (12.0, 18.6)	26	3897	6.7 (4.5, 9.8)	6.6 (4.5, 9.8)
Other malignant solid tumours	5	773	6.5 (2.7, 15.5)	138	5376	25.7 (21.7, 30.3)	25.0 (21.2, 29.7)	53	3904	13.6 (10.4, 17.8)	13.1 (10.0, 17.1)
<i>Brain neoplasms</i>	0	781	-	<5	5592	0.4 (0.1, 1.4)	0.4 (0.1, 1.6)	0	4012	-	-
<i>Of which, Glioblastoma</i>	0	781	-	<5	5592	0.2 (0.0, 1.3)	0.2 (0.0, 1.4)	0	4012	-	-
<i>Lung cancer</i> [#]	<5	779	2.6 (0.6, 10.3)	33	5577	5.9 (4.2, 8.3)	5.9 (4.2, 8.3)	<5	4010	1.0 (0.4, 2.7)	1.0 (0.4, 2.7)
<i>Melanoma</i> [#]	0	781	-	6	5565	1.1 (0.5, 2.4)	1.1 (0.5, 2.4)	<5	4000	0.5 (0.1, 2.0)	0.4 (0.1, 1.7)
Total cardiac disorders	8	330	24.2 (12.1, 48.5)	139	4981	27.9 (23.6, 33.0)	27.3 (23.2, 32.3)	28	1586	17.7 (12.2, 25.6)	17.7 (12.2, 25.6)
Serious CHF (new or worsening)	<5	336	3.0 (0.4, 21.1)	38	5222	7.3 (5.3, 10.0)	7.1 (5.2, 9.8)	<5	1613	2.5 (0.9, 6.6)	2.5 (0.9, 6.6)
Myocardial infarction	<5	336	5.9 (1.5, 23.8)	50	5152	9.7 (7.4, 12.8)	9.5 (7.2, 12.6)	11	1598	6.9 (3.8, 12.4)	6.9 (3.8, 12.4)
Acute Coronary Syndrome [#]	<5	335	3.0 (0.4, 21.2)	<5	5246	0.8 (0.3, 2.0)	0.7 (0.3, 2.0)	0	1614	-	-
MACE (including MI) [#]	5	335	14.9 (6.2, 35.9)	114	5051	22.6 (18.8, 27.1)	22.1 (18.4, 26.6)	22	1591	13.8 (9.1, 21.0)	13.2 (8.6, 20.2)
Other cardiac events	5	331	15.1 (6.3, 36.3)	75	5103	14.7 (11.7, 18.4)	14.4 (11.5, 18.1)	17	1599	10.6 (6.6, 17.1)	10.6 (6.6, 17.1)

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Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Venous Thromboembolic Events (VTE)	<5	337	5.9 (1.5, 23.8)	33	5200	6.3 (4.5, 8.9)	6.3 (4.4, 8.8)	7	1607	4.4 (2.1, 9.1)	4.4 (2.1, 9.1)
DVT [#]	0	337	-	7	5237	1.3 (0.6, 2.8)	1.4 (0.6, 2.9)	<5	1613	1.2 (0.3, 5.0)	1.2 (0.3, 4.9)
PE [#]	<5	337	3.0 (0.4, 21.1)	22	5228	4.2 (2.8, 6.4)	4.1 (2.7, 6.2)	<5	1613	1.9 (0.6, 5.8)	1.9 (0.6, 5.8)
Total haematologic events	0	337	-	42	5186	8.1 (6.0, 11.0)	8.0 (5.9, 10.9)	15	1603	9.4 (5.6, 15.5)	9.4 (5.6, 15.5)
Aplastic anaemia	0	337	-	0	5259	-	-	0	1614	-	-
Pancytopenia	0	337	-	6	5245	1.1 (0.5, 2.5)	1.2 (0.5, 2.6)	<5	1612	1.2 (0.3, 5.0)	1.2 (0.3, 5.0)
Agranulocytosis	0	337	-	0	5259	-	-	<5	1614	0.6 (0.1, 4.4)	0.6 (0.1, 4.4)
Other dyscrasia	0	337	-	38	5194	7.3 (5.3, 10.1)	7.2 (5.3, 10.0)	13	1605	8.1 (4.7, 14.0)	8.1 (4.7, 14.0)
Serious Neutropenia [#]	0	337	-	5	5251	1.0 (0.4, 2.3)	0.9 (0.4, 2.3)	<5	1613	2.5 (0.9, 6.6)	2.5 (0.9, 6.6)
Serious haemorrhage [#]	0	337	-	0	5259	-	-	0	1614	-	-
CNS Disorders	5	332	15.0 (6.3, 36.1)	73	5106	14.3 (11.4, 18.0)	14.1 (11.2, 17.8)	20	1596	12.5 (8.1, 19.4)	12.5 (8.1, 19.4)
Central Demyelination	0	337	-	0	5259	-	-	0	1614	-	-
Peripheral neuropathy	<5	333	3.0 (0.4, 21.3)	6	5243	1.1 (0.5, 2.5)	1.1 (0.5, 2.4)	0	1614	-	-
Cerebrovascular accident	<5	336	3.0 (0.4, 21.1)	32	5185	6.2 (4.4, 8.7)	6.1 (4.3, 8.6)	<5	1611	2.5 (0.9, 6.6)	2.5 (0.9, 6.6)
Other CNS	<5	337	8.9 (2.9, 27.6)	38	5194	7.3 (5.3, 10.1)	7.3 (5.3, 10.0)	16	1599	10.0 (6.1, 16.3)	10.0 (6.1, 16.3)

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Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Optic Neuritis [#]	0	337	-	0	5259	-	-	<5	1612	0.6 (0.1, 4.4)	0.6 (0.1, 4.4)
Progressive Multifocal Leukoencephalopathy (PML) [#]	0	592	-	0	5259	-	-	0	3179	-	-
GI perforation	<5	337	3.0 (0.4, 21.1)	<5	5256	0.4 (0.1, 1.5)	0.4 (0.1, 1.6)	<5	1613	2.5 (0.9, 6.6)	2.5 (0.9, 6.6)
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	337	-	0	5259	-	-	0	1614	-	-
Pregnancy (female only)	0	254	-	0	3816	-	-	0	1214	-	-
Death (on drug ²)	10	346	28.9 (15.6, 53.7)	336	5593	60.1 (54.0, 66.9)	59.2 (53.2, 65.9)	35	1642	21.3 (15.3, 29.7)	21.3 (15.3, 29.7)
Death (ever exposed)	25	781	32.0 (21.6, 47.3)	336	5593	60.1 (54.0, 66.9)	58.2 (52.3, 64.9)	105	4012	26.2 (21.6, 31.7)	25.8 (21.3, 31.3)
Hepatitis B Reactivation [#]	0	337	-	0	5259	-	-	0	1614	-	-
Serious Infusion/Immunologic Reaction [#]	0	337	-	0	5259	-	-	0	1614	-	-
Serious Hypersensitivity Reaction [#]	0	337	-	13	5222	2.5 (1.4, 4.3)	2.5 (1.5, 4.4)	<5	1614	1.9 (0.6, 5.8)	1.9 (0.6, 5.8)
Serious Lupus/Lupus-Like Illness [#]	0	337	-	0	5259	-	-	0	1614	-	-
Serious Skin Reaction [#]	0	337	-	0	5259	-	-	0	1614	-	-
Interstitial Lung Disease [#]	0	337	-	14	5239	2.7 (1.6, 4.5)	2.7 (1.6, 4.5)	5	1608	3.1 (1.3, 7.5)	3.1 (1.3, 7.5)

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Table 14. Number of first events and rates of first of safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, among patients ≥65.

Serious Adverse Events	Tofacitinib Patients [N=147]			bDMARD Naïve (csDMARD) Patients [N=1,056]				bDMARD (Anti-TNF) Patients [N=629]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classed as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1](#) for cohort definitions.

Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Total serious infection	14	491	28.5 (16.9, 48.1)	176	8076	21.8 (18.8, 25.3)	21.6 (18.6, 25.1)	100	4000	25.0 (20.6, 30.4)	25.5 (20.9, 31.1)

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Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Pneumonia	6	497	12.1 (5.4, 26.9)	94	8331	11.3 (9.2, 13.8)	10.8 (8.8, 13.3)	38	4126	9.2 (6.7, 12.7)	9.4 (6.8, 12.9)
<i>Non-opportunistic</i>	5	497	10.1 (4.2, 24.2)	90	8342	10.8 (8.8, 13.3)	10.4 (8.4, 12.8)	37	4135	8.9 (6.5, 12.3)	9.0 (6.5, 12.5)
<i>Opportunistic</i>	<5	508	2.0 (0.3, 14.0)	6	8543	0.7 (0.3, 1.6)	0.6 (0.3, 1.4)	<5	4167	1.0 (0.4, 2.6)	1.1 (0.4, 2.9)
Septicaemia	0	508	-	7	8542	0.8 (0.4, 1.7)	0.7 (0.3, 1.5)	5	4173	1.2 (0.5, 2.9)	1.2 (0.5, 2.8)
<i>Non-opportunistic</i>	0	508	-	7	8542	0.8 (0.4, 1.7)	0.7 (0.3, 1.5)	5	4173	1.2 (0.5, 2.9)	1.2 (0.5, 2.8)
<i>Opportunistic</i>	0	508	-	0	8557	-	-	0	4179	-	-
Bone/Joint infection	<5	506	5.9 (1.9, 18.4)	20	8497	2.4 (1.5, 3.6)	2.4 (1.5, 3.7)	8	4177	1.9 (1.0, 3.8)	2.0 (1.0, 4.1)
<i>Non-opportunistic</i>	<5	506	5.9 (1.9, 18.4)	20	8497	2.4 (1.5, 3.6)	2.4 (1.5, 3.7)	8	4177	1.9 (1.0, 3.8)	2.0 (1.0, 4.1)
<i>Opportunistic</i>	0	508	-	0	8557	-	-	0	4179	-	-
Herpes Zoster	0	508	-	0	8557	-	-	0	4179	-	-
<i>Non-opportunistic</i>	0	508	-	0	8557	-	-	0	4179	-	-
<i>Opportunistic</i>	0	508	-	0	8557	-	-	0	4179	-	-
Other serious infection	9	500	18.0 (9.4, 34.6)	85	8304	10.2 (8.3, 12.7)	10.3 (8.3, 12.8)	59	4049	14.6 (11.3, 18.8)	14.8 (11.5, 19.1)
<i>Non-opportunistic</i>	9	500	18.0 (9.4, 34.6)	83	8306	10.0 (8.1, 12.4)	10.0 (8.1, 12.5)	56	4058	13.8 (10.6, 17.9)	14.0 (10.8, 18.3)
<i>Opportunistic</i>	0	508	-	<5	8555	0.2 (0.1, 0.9)	0.2 (0.1, 1.0)	<5	4170	0.7 (0.2, 2.2)	0.7 (0.2, 2.2)
TB	0	508	-	0	8557	-	-	<5	4178	0.2 (0.0, 1.7)	0.2 (0.0, 1.7)

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Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Serious Hepatic Dysfunction/Failure [#]	0	508	-	0	8557	-	-	0	4179	-	-
Fractures [#]	<5	503	4.0 (1.0, 15.9)	44	8449	5.2 (3.9, 7.0)	4.9 (3.6, 6.5)	14	4153	3.4 (2.0, 5.7)	3.5 (2.1, 6.0)
Malignancies except NMSC	<5	1207	3.3 (1.2, 8.8)	110	8879	12.4 (10.3, 14.9)	12.4 (10.3, 15.0)	54	9605	5.6 (4.3, 7.3)	5.9 (4.5, 7.8)
Total malignant events	6	1199	5.0 (2.2, 11.1)	142	8776	16.2 (13.7, 19.1)	16.2 (13.7, 19.1)	66	9567	6.9 (5.4, 8.8)	7.2 (5.7, 9.3)
Lymphoproliferative	0	1216	-	19	9092	2.1 (1.3, 3.3)	2.1 (1.3, 3.3)	6	9758	0.6 (0.3, 1.4)	0.6 (0.3, 1.4)
<u>Lymphoma (NHL, Hodgkins)</u>	0	1216	-	14	9097	1.5 (0.9, 2.6)	1.6 (0.9, 2.6)	5	9759	0.5 (0.2, 1.2)	0.5 (0.2, 1.3)
<u>NHL[#]</u>	0	1216	-	7	9115	0.8 (0.4, 1.6)	0.8 (0.4, 1.6)	0	9773	-	-
<u>Hodgkin[#]</u>	0	1216	-	<5	9132	0.3 (0.1, 1.0)	0.3 (0.1, 1.1)	0	9773	-	-
<u>Myeloma</u>	0	1216	-	<5	9138	0.2 (0.1, 0.9)	0.2 (0.1, 1.0)	0	9773	-	-
<u>Leukaemia</u>	0	1216	-	<5	9137	0.3 (0.1, 1.0)	0.3 (0.1, 0.9)	<5	9772	0.1 (0.0, 0.7)	0.1 (0.0, 0.6)
<u>CLL[#]</u>	0	1216	-	<5	9137	0.1 (0.0, 0.8)	0.1 (0.0, 0.7)	0	9773	-	-
Non-melanoma skin cancer	<5	1207	1.7 (0.4, 6.6)	37	9025	4.1 (3.0, 5.7)	4.1 (2.9, 5.6)	12	9734	1.2 (0.7, 2.2)	1.3 (0.7, 2.3)
Other malignant solid tumours	<5	1207	3.3 (1.2, 8.8)	92	8925	10.3 (8.4, 12.6)	10.3 (8.4, 12.7)	48	9620	5.0 (3.8, 6.6)	5.3 (4.0, 7.0)
<u>Brain neoplasms</u>	0	1216	-	<5	9139	0.2 (0.1, 0.9)	0.2 (0.1, 0.9)	0	9773	-	-

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Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
<i>Of which, Glioblastoma</i>	0	1216	-	0	9140	-	-	0	9773	-	-
<i>Lung cancer[#]</i>	0	1216	-	15	9127	1.6 (1.0, 2.7)	1.7 (1.0, 2.8)	5	9771	0.5 (0.2, 1.2)	0.6 (0.3, 1.5)
<i>Melanoma[#]</i>	0	1216	-	<5	9133	0.2 (0.1, 0.9)	0.2 (0.1, 1.0)	<5	9766	0.2 (0.1, 0.8)	0.2 (0.1, 0.9)
Total cardiac disorders	<5	502	8.0 (3.0, 21.2)	78	8331	9.4 (7.5, 11.7)	9.1 (7.3, 11.4)	27	4129	6.5 (4.5, 9.5)	6.8 (4.7, 10.0)
Serious CHF (new or worsening)	0	508	-	7	8540	0.8 (0.4, 1.7)	0.7 (0.3, 1.5)	<5	4175	0.5 (0.1, 1.9)	0.5 (0.1, 2.0)
Myocardial infarction	<5	508	3.9 (1.0, 15.8)	28	8466	3.3 (2.3, 4.8)	3.3 (2.2, 4.7)	7	4155	1.7 (0.8, 3.5)	1.7 (0.8, 3.7)
Acute Coronary Syndrome [#]	0	508	-	<5	8551	0.1 (0.0, 0.8)	0.1 (0.0, 0.7)	0	4179	-	-
MACE (including MI) [#]	<5	508	5.9 (1.9, 18.3)	49	8396	5.8 (4.4, 7.7)	5.7 (4.3, 7.6)	16	4135	3.9 (2.4, 6.3)	4.0 (2.5, 6.6)
Other cardiac events	<5	502	6.0 (1.9, 18.5)	48	8420	5.7 (4.3, 7.6)	5.6 (4.2, 7.5)	18	4156	4.3 (2.7, 6.9)	4.6 (2.9, 7.2)
Venous Thromboembolic Events (VTE)	<5	506	2.0 (0.3, 14.0)	17	8498	2.0 (1.2, 3.2)	1.9 (1.2, 3.1)	<5	4174	1.0 (0.4, 2.6)	1.0 (0.4, 2.6)
DVT [#]	0	508	-	7	8543	0.8 (0.4, 1.7)	0.7 (0.3, 1.5)	0	4179	-	-
PE [#]	0	508	-	8	8517	0.9 (0.5, 1.9)	1.0 (0.5, 2.0)	<5	4175	0.7 (0.2, 2.2)	0.7 (0.2, 2.2)
Total haematologic events	<5	507	2.0 (0.3, 14.0)	27	8480	3.2 (2.2, 4.6)	3.1 (2.1, 4.5)	5	4173	1.2 (0.5, 2.9)	1.3 (0.5, 3.1)
Aplastic anaemia	0	508	-	0	8557	-	-	0	4179	-	-
Pancytopenia	0	508	-	<5	8553	0.4 (0.1, 1.1)	0.4 (0.1, 1.1)	<5	4175	0.2 (0.0, 1.7)	0.2 (0.0, 1.7)

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Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Agranulocytosis	0	508	-	<5	8552	0.2 (0.1, 0.9)	0.2 (0.1, 0.9)	<5	4175	0.2 (0.0, 1.7)	0.2 (0.0, 1.7)
Other dyscrasia	<5	507	2.0 (0.3, 14.0)	23	8485	2.7 (1.8, 4.1)	2.6 (1.7, 4.0)	<5	4176	1.0 (0.4, 2.6)	1.1 (0.4, 2.9)
Serious Neutropenia [#]	0	508	-	5	8542	0.6 (0.2, 1.4)	0.6 (0.3, 1.5)	<5	4178	0.5 (0.1, 1.9)	0.5 (0.1, 2.0)
Serious haemorrhage [#]	0	508	-	0	8557	-	-	0	4179	-	-
CNS Disorders	<5	508	2.0 (0.3, 14.0)	42	8428	5.0 (3.7, 6.7)	4.8 (3.6, 6.6)	29	4121	7.0 (4.9, 10.1)	7.0 (4.9, 10.1)
Central Demyelination	0	508	-	0	8557	-	-	<5	4178	0.5 (0.1, 1.9)	0.5 (0.1, 1.9)
Peripheral neuropathy	0	508	-	9	8537	1.1 (0.5, 2.0)	1.1 (0.6, 2.1)	<5	4178	0.2 (0.0, 1.7)	0.2 (0.0, 1.7)
Cerebrovascular accident	0	508	-	12	8517	1.4 (0.8, 2.5)	1.4 (0.8, 2.5)	6	4166	1.4 (0.6, 3.2)	1.5 (0.7, 3.4)
Other CNS	<5	508	2.0 (0.3, 14.0)	24	8475	2.8 (1.9, 4.2)	2.7 (1.8, 4.1)	21	4134	5.1 (3.3, 7.8)	4.9 (3.2, 7.6)
Optic Neuritis [#]	0	508	-	0	8557	-	-	0	4179	-	-
Progressive Multifocal Leukoencephalopathy (PML)[#]	0	899	-	0	8557	-	-	0	7793	-	-
GI perforation	0	508	-	<5	8557	0.4 (0.1, 1.1)	0.4 (0.1, 1.2)	<5	4178	0.5 (0.1, 1.9)	0.5 (0.1, 2.0)
Serious Lower GI Ulcer/Bleed/Perforation [#]	0	508	-	0	8557	-	-	0	4179	-	-
Pregnancy (female only)	0	388	-	10	6594	1.5 (0.8, 2.8)	1.4 (0.8, 2.6)	15	3120	4.8 (2.9, 8.0)	3.6 (2.2, 5.9)
Death (on drug²)	<5	525	7.6 (2.9, 20.3)	109	9140	11.9 (9.9, 14.4)	11.4 (9.4, 13.8)	19	4249	4.5 (2.9, 7.0)	4.9 (3.1, 7.6)

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Table 15. Number of first events and rates of first safety endpoint events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF cohorts), among patients <65 yrs.

Serious Adverse Events	Tofacitinib Patients [N=214]			bDMARD Naïve (csDMARD) Patients [N=1,775]				bDMARD (Anti-TNF) Patients [N=1,434]			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
Death (ever exposed)	11	1216	9.0 (5.0, 16.3)	109	9140	11.9 (9.9, 14.4)	11.8 (9.7, 14.2)	54	9773	5.5 (4.2, 7.2)	6.1 (4.7, 8.0)
Hepatitis B Reactivation [#]	0	508	-	0	8557	-	-	0	4179	-	-
Serious Infusion/Immunologic Reaction [#]	0	508	-	0	8557	-	-	0	4179	-	-
Serious Hypersensitivity Reaction [#]	<5	506	2.0 (0.3, 14.0)	<5	8549	0.5 (0.2, 1.2)	0.5 (0.2, 1.3)	<5	4178	0.5 (0.1, 1.9)	0.5 (0.1, 2.0)
Serious Lupus/Lupus-Like Illness [#]	0	508	-	0	8557	-	-	0	4179	-	-
Serious Skin Reaction [#]	0	508	-	0	8557	-	-	0	4179	-	-
Interstitial Lung Disease [#]	<5	508	2.0 (0.3, 14.0)	11	8535	1.3 (0.7, 2.3)	1.3 (0.7, 2.3)	<5	4178	1.0 (0.4, 2.6)	1.1 (0.4, 2.9)

Data cut at 7 years after start of therapy.

[#] Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other serious infection" includes other serious infections that are not classed as pneumonia, septicaemia, bone/joint infection, or herpes zoster.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

"Other dyscrasia" includes other serious dyscrasia that are not classed as aplastic anaemia, pancytopenia, or agranulocytosis.

"Other CNS" includes other serious CNS events that are not classed as central demyelination, peripheral neuropathy or cerebrovascular accident.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

2 "On drug" corresponds to secondary analysis using the "censor at switch" approach.

Refer to [Section 9.3.1.](#) for cohort definitions.



10.5.5. Subgroup Analyses Evaluating Risk Factors and Time Periods

Tables 16 through 20 present findings from the described subgroup analyses in [Section 9.9.5](#). In the tofacitinib, bDMARD naïve (csDMARD), and bDMARD (anti-TNF) treated cohorts with no VTE risk factors, 0, 8, and <5 patients had a VTE safety event, respectively (Table 16). Within patients with at least 1 VTE risk factor <5 patients experienced a VTE event in the tofacitinib treated cohort, specifically PE events, compared to 42 and 10 VTE events in the bDMARD naïve (csDMARD) and bDMARD (anti-TNF) treated cohorts, respectively (Table 16).

Table 16. Incidence rates of VTE events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by type of VTE event and risk factor indicator (≥1 VTE risk factor versus no VTE risk factor).

Safety Endpoints	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
No VTE Risk Factor											
Number of patients	127			982				917			
VTE	0	317	-	8	4802	1.7 (0.8, 3.3)	1.9 (0.9, 3.8)	<5	2735	0.4 (0.1, 2.6)	0.2 (0.0, 1.8)
DVT [#]	0	317	-	<5	4830	0.4 (0.1, 1.7)	0.4 (0.1, 1.9)	0	2737	-	-
PE [#]	0	317	-	5	4809	1.0 (0.4, 2.5)	1.3 (0.5, 3.1)	<5	2735	0.4 (0.1, 2.6)	0.2 (0.0, 1.8)
At Least 1 VTE Risk Factor											
Number of patients	234			1849				1146			
VTE	<5	526	5.7 (1.8, 17.7)	42	8897	4.7 (3.5, 6.4)	4.8 (3.6, 6.5)	10	3046	3.3 (1.8, 6.1)	3.5 (1.9, 6.6)

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Table 16. Incidence rates of VTE events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by type of VTE event and risk factor indicator (≥1 VTE risk factor versus no VTE risk factor).

Safety Endpoints	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)	Events	Person year	Rate/1000 pyrs (95% CI)	Standard ¹ Rate/1000 pyrs (95% CI)
DVT [#]	0	528	-	12	8950	1.3 (0.8, 2.4)	1.3 (0.7, 2.3)	<5	3054	0.7 (0.2, 2.6)	0.8 (0.2, 3.2)
PE [#]	<5	528	1.9 (0.3, 13.4)	25	8936	2.8 (1.9, 4.1)	2.9 (2.0, 4.3)	5	3053	1.6 (0.7, 3.9)	1.6 (0.6, 4.0)

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

The following VTE risk factors were evaluated at baseline: Age (≥65 years versus <65 years), History of major surgery ("History of Knee or hip replacement" or "History of Shoulder/Elbow/Wrist/Hand/Ankle/Foot/Neck joint surgery"), History of MI, History of malignancy, History of diabetes, and History of hypertension.

Refer to [Section 9.3.1](#) for cohort definitions.

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 were also conducted (i.e., period prior to 31 January 2020 vs. period after 31 January 2020) ([Table 17](#)). As shown in Table 17, changes to the SmPC for tofacitinib use corresponded to a low frequency of VTE events reported across all three treatment cohorts.

In the period prior to 31 January 2020, VTE events were observed across all cohorts. The age and sex standardised incidence rate in the tofacitinib cohort was 4.5 (1.5, 14.0) per 1,000 person-years, compared with 3.7 (2.8, 4.9) per 1000 person-years in the bDMARD naïve (csDMARD) cohort and 2.4 (1.3, 4.4) per 1000 person-years in the bDMARD (anti-TNF) cohort.



In the period after 31 January 2020, no VTE events were observed across the tofacitinib, and bDMARD (anti-TNF) cohorts. Additionally, there were no patients observed for bDMARD naïve (csDMARD) cohort during this time period.

Table 17. Incidence rates of VTE events among all patients and patients with VTE risk factors initiating tofacitinib and all patients and patients with VTE risk factors registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Before 31 January 2020											
Number of patients	258			2831				2045			
Venous Thrombotic Event (VTE)	<5	666	4.5 (1.5, 14.0)	50	13698	3.7 (2.8, 4.8)	3.7 (2.8, 4.9)	11	5755	1.9 (1.1, 3.5)	2.4 (1.3, 4.4)
DVT [#]	0	669	-	14	13780	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	<5	5765	0.3 (0.1, 1.4)	0.5 (0.1, 2.1)
PE [#]	<5	669	1.5 (0.2, 10.6)	30	13745	2.2 (1.5, 3.1)	2.3 (1.6, 3.3)	6	5762	1.0 (0.5, 2.3)	1.2 (0.5, 2.7)
On or after 31 January 2020											
Number of patients	103			0				18			
Venous Thrombotic Event (VTE)	0	176	-	NA	-	-	-	0	27	-	-
DVT [#]	0	176	-	NA	-	-	-	0	27	-	-
PE [#]	0	176	-	NA	-	-	-	0	27	-	-

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Table 17. Incidence rates of VTE events among all patients and patients with VTE risk factors initiating tofacitinib and all patients and patients with VTE risk factors registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
With at Least 1 VTE Risk Factor and Before 31 January 2020											
Number of patients	177			1849				1137			
Venous Thrombotic Event (VTE)	<5	431	7.0 (2.2, 21.6)	42	8897	4.7 (3.5, 6.4)	4.8 (3.6, 6.6)	10	3035	3.3 (1.8, 6.1)	3.5 (1.9, 6.6)
DVT [#]	0	434	-	12	8950	1.3 (0.8, 2.4)	1.3 (0.8, 2.4)	<5	3043	0.7 (0.2, 2.6)	0.8 (0.2, 3.2)
PE [#]	<5	434	2.3 (0.3, 16.4)	25	8936	2.8 (1.9, 4.1)	2.9 (2.0, 4.3)	5	3042	1.6 (0.7, 3.9)	1.6 (0.6, 4.0)
With at Least 1 VTE Risk Factor and On or after 31 January 2020											
Number of patients	57			0				9			
Venous Thrombotic Event (VTE)	0	95	-	NA	-	-	-	0	11	-	-
DVT [#]	0	95	-	NA	-	-	-	0	11	-	-
PE [#]	0	95	-	NA	-	-	-	0	11	-	-

Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events; NA No participants were present in this group for analysis. Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up. Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).



Table 17. Incidence rates of VTE events among all patients and patients with VTE risk factors initiating tofacitinib and all patients and patients with VTE risk factors registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)

Only serious adverse events are included.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

Refer to [Section 9.3.1.](#) for cohort definitions.

The following VTE risk factors were evaluated at baseline: Age (≥ 65 years versus < 65 years), History of major surgery ("History of Knee or hip replacement" or "History of Shoulder/Elbow/Wrist/Hand/Ankle/Foot/Neck joint surgery"), History of MI, History of malignancy, History of diabetes, and History of hypertension.

Refer to [Section 9.3.1.](#) for cohort definitions.

For the safety endpoints of cardiac disorders (overall and stratified by subtype), incidence rates were stratified by patients with ≥ 1 CV risk factors versus no CV risk factors ([Table 18](#))

Among patients without baseline CV risk factors, < 5 MI and < 5 MACE events were observed in the tofacitinib cohort during the primary risk window (end of treatment plus 90 days; see [Section 9.9.2.2.1](#)), whereas a small number of events were observed in both comparator cohorts. Incidence rates in comparator cohorts were low in this subgroup.

Among patients with at least one baseline CV risk factor, MI and MACE events were observed across all cohorts. In this subgroup, incidence rates for MI were broadly comparable across cohorts, with crude incidence rates of 6.7 per 1,000 PY in the tofacitinib cohort, 8.6 per 1,000 PY in the bDMARD naïve (csDMARD) cohort, and 6.0 per 1,000 PY in the bDMARD (anti-TNF) cohort.

Among patients with at least one baseline CV risk factor, MACE incidence rates were 13.4 per 1,000 PY tofacitinib cohort, 18.8 per 1,000 PY in the bDMARD naïve (csDMARD) cohort, and 11.7 per 1,000 PY in the bDMARD (anti-TNF) cohort, although confidence intervals were wide.



Table 18. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by indicator of CV risk factors (≥1 CV risk factor versus no CV risk factor).

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
No CV Risk Factor											
Number of patients	159			1236				1045			
Total Cardiac Disorders	<5	389	5.1 (1.3, 20.6)	37	5920	6.2 (4.5, 8.6)	6.2 (4.5, 8.7)	13	3064	4.2 (2.5, 7.3)	4.6 (2.6, 8.2)
CHF (new or worsening)	0	395	-	<5	6017	0.7 (0.2, 1.8)	0.6 (0.2, 1.8)	<5	3082	0.3 (0.046, 2.3)	0.3 (0.0, 2.1)
Myocardial infarction	<5	395	2.5 (0.4, 18.0)	12	5987	2.0 (1.1, 3.5)	1.9 (1.0, 3.4)	<5	3079	0.6 (0.2, 2.6)	0.4 (0.1, 1.6)
Acute Coronary Syndrome [#]	0	395	-	0	6025	-	-	0	3085	-	-
MACE (including MI) [#]	<5	395	5.1 (1.3, 20.3)	22	5962	3.7 (2.4, 5.6)	3.7 (2.4, 5.8)	6	3071	2.0 (0.9, 4.3)	1.5 (0.7, 3.4)
Other cardiac events	<5	389	2.6 (0.4, 18.2)	24	5952	4.0 (2.7, 6.0)	4.1 (2.7, 6.2)	10	3072	3.3 (1.8, 6.0)	3.9 (2.0, 7.4)
At Least 1 CV Risk Factor											
Number of patients	202			1595				1018			
Total Cardiac Disorders	10	443	22.6 (12.1, 41.9)	180	7392	24.3 (21.0, 28.2)	24.8 (21.3, 28.9)	42	2650	15.8 (11.7, 21.4)	16.1 (11.7, 22.1)
CHF (new or worsening)	<5	450	2.2 (0.3, 15.8)	41	7745	5.3 (3.9, 7.2)	5.6 (4.1, 7.7)	5	2705	1.8 (0.8, 4.4)	2.2 (0.9, 5.3)
Myocardial infarction	<5	449	6.7 (2.2, 20.7)	66	7631	8.6 (6.8, 11.0)	8.9 (6.9, 11.5)	16	2673	6.0 (3.7, 9.8)	6.0 (3.6, 10.2)

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Table 18. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by indicator of CV risk factors (≥1 CV risk factor versus no CV risk factor).

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Acute Coronary Syndrome [#]	<5	448	2.2 (0.3, 15.8)	5	7773	0.6 (0.3, 1.5)	0.7 (0.3, 1.6)	0	2708	-	-
MACE (including MI) [#]	6	448	13.4 (6.0, 29.8)	141	7485	18.8 (16.0, 22.2)	19.4 (16.4, 23.0)	31	2655	11.7 (8.2, 16.6)	11.8 (8.1, 17.2)
Other cardiac events	7	444	15.8 (7.5, 33.1)	99	7570	13.1 (10.7, 15.9)	13.0 (10.6, 15.9)	25	2683	9.3 (6.3, 13.8)	9.6 (6.3, 14.5)

Data cut at 7 years after start of therapy.

[#] Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

The following CV risk factors were evaluated at baseline: Age (patients ≥65 years versus <65 years), History of diabetes, History of renal disease, History of hypertension, History of MI, History of angina.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

Refer to [Section 9.3.1](#) for cohort definitions.

Stratification of the incidence rates by time period (i.e. before and after June 2021) was conducted to account for changes in the SmPC for CV events (i.e. MACE and MI) ([Table 19](#))

In the period prior to 01 Jun 2021, CV events were observed across all cohorts. The crude MI incidence rate in the tofacitinib cohort was 3.8 per 1000 person-years, compared with 5.7 per 1000 person-years in the bDMARD naïve (csDMARD) cohort and 3.1 per



Table 18. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by indicator of CV risk factors (≥1 CV risk factor versus no CV risk factor).

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)

1000 person-years in the bDMARD (anti-TNF) cohort; the crude MACE incidence rates were 7.6, 12.1, and 6.5 per 1,000 PY, respectively.

In the period after 01 Jun 2021, <5 CV events were observed in the tofacitinib cohort during the risk window (end of treatment plus 90 days; see [Section 9.9.2.2.1](#)), whereas no events were observed in the bDMARD naïve (csDMARD) and bDMARD (anti-TNF) cohorts.

Table 19. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Before 01 June 2021											
Number of patients	324			2831				2052			
Total Cardiac Disorders	10	783	12.8 (6.9, 23.7)	217	13312	16.3 (14.3, 18.6)	16.4 (14.3, 18.7)	55	5701	9.6 (7.4, 12.6)	11.2 (8.5, 14.6)



Table 19. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
CHF (new or worsening)	<5	795	1.3 (0.2, 8.9)	45	13762	3.3 (2.4, 4.4)	3.2 (2.4, 4.3)	6	5775	1.0 (0.5, 2.3)	1.3 (0.6, 2.9)
Myocardial infarction	<5	795	3.8 (1.2, 11.7)	78	13618	5.7 (4.6, 7.2)	5.8 (4.6, 7.2)	18	5740	3.1 (2.0, 5.0)	3.8 (2.4, 6.1)
Acute Coronary Syndrome [#]	<5	793	1.3 (0.2, 8.9)	5	13798	0.4 (0.2, 0.9)	0.3 (0.1, 0.8)	0	5780	-	-
MACE (including MI) [#]	6	793	7.6 (3.4, 16.8)	163	13447	12.1 (10.4, 14.1)	12.2 (10.5, 14.2)	37	5713	6.5 (4.7, 8.9)	7.7 (5.5, 10.7)
Other cardiac events	7	784	8.9 (4.3, 18.7)	123	13522	9.1 (7.6, 10.9)	9.1 (7.6, 10.9)	35	5742	6.1 (4.4, 8.5)	7.0 (5.0, 9.8)
On or after 01 June 2021											
Number of patients	37			0				11			
Total Cardiac Disorders	<5	49	40.6 (10.2, 162.4)	NA	-	-	-	0	13	-	-
CHF (new or worsening)	0	50	-	NA	-	-	-	0	13	-	-
Myocardial infarction	<5	49	20.2 (2.8, 143.4)	NA	-	-	-	0	13	-	-
Acute Coronary Syndrome [#]	0	50	-	NA	-	-	-	0	13	-	-
MACE (including MI) [#]	<5	49	40.4 (10.1, 161.6)	NA	-	-	-	0	13	-	-
Other cardiac events	<5	49	20.2 (2.8, 143.4)	NA	-	-	-	0	13	-	-

Data cut at 7 years after start of therapy.



Table 19. Incidence rates of CV events among patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)

Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events; NA No participants were present in this group for analysis.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

"Other cardiac events" includes other serious cardiac events that are not classed as CHF or myocardial infarction.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

Refer to [section 9.3.1](#) for cohort definitions.

Stratification of the incidence rates by time period (i.e. before and after the regulatory signal valuation of June 2021) was conducted to account for changes in the SmPC for malignant events (i.e. malignancy excluding NMSC, lung cancer, lymphoma) ([Table 20](#)).

In the period prior to June 2021, events were observed across all cohorts, with generally similar or lower incidence rates in the tofacitinib cohort, qualitatively compared to both comparator cohorts. For example, the crude incidence rate of malignancies excluding NMSC were 4.8 per 1000 person-years in the tofacitinib cohort, compared with 18.6 per 1000 person-years in the bDMARD naïve (csDMARD) cohort and 8.3 per 1000 person-years in the bDMARD (anti-TNF) cohort.

After 01 Jun 2021, <5 events were observed in the tofacitinib cohort, with a zero case occurrence for the majority of subtypes. No crude incidence rates were estimable for comparator cohorts, due either to having a sample size of 0 (i.e. in the bDMARD naïve (csDMARD) cohort post 01 Jun 2021) or zero case count (i.e. in the bDMARD anti-TNF cohort post 01 Jun 2021).



Table 20. Number of first and rates of first malignancy events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Before 01 June 2021											
Number of patients	324			2831				2052			
Malignancies except NMSC	9	1877	4.8 (2.5, 9.2)	265	14219	18.6 (16.5, 21.0)	18.6 (16.5, 21.0)	112	13469	8.3 (6.9, 10.0)	9.3 (7.7, 11.2)
Total malignant event	24	1835	13.1 (8.8, 19.5)	358	13880	25.8 (23.3, 28.6)	25.8 (23.2, 28.6)	148	13323	11.1 (9.5, 13.1)	12.5 (10.6, 14.8)
Lymphoproliferative	<5	1894	0.5 (0.1, 3.7)	39	14645	2.7 (1.9, 3.6)	2.6 (1.9, 3.6)	11	13730	0.8 (0.4, 1.4)	0.9 (0.5, 1.6)
Lymphoma (NHL, Hodgkins)	0	1894	-	24	14670	1.6 (1.1, 2.4)	1.6 (1.1, 2.4)	9	13736	0.7 (0.3, 1.3)	0.7 (0.4, 1.4)
NHL [#]	0	1894	-	11	14699	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)	<5	13755	0.1 (0.0, 0.5)	0.1 (0.0, 0.7)
Hodgkin [#]	0	1894	-	<5	14721	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)	0	13760	-	-
Myeloma	0	1894	-	6	14717	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)	0	13760	-	-
Leukaemia	<5	1894	0.5 (0.1, 3.7)	9	14723	0.6 (0.3, 1.2)	0.6 (0.3, 1.1)	<5	13753	0.1 (0.0, 0.6)	0.2 (0.0, 0.7)
CLL [#]	0	1894	-	5	14726	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0	13760	-	-
Non-melanoma Skin Cancer	16	1849	8.7 (5.3, 14.1)	118	14358	8.2 (6.9, 9.8)	8.2 (6.8, 9.9)	38	13607	2.8 (2.0, 3.8)	3.3 (2.4, 4.6)
Other malignant solid tumours	8	1877	4.3 (2.1, 8.5)	230	14301	16.1 (14.1, 18.3)	16.1 (14.1, 18.3)	101	13500	7.5 (6.2, 9.1)	8.3 (6.8, 10.2)

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Table 20. Number of first and rates of first malignancy events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Brain neoplasms	0	1894	-	<5	14732	0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0	13760	-	-
Of which, Glioblastoma	0	1894	-	<5	14732	0.1 (0.0, 0.5)	0.1 (0.0, 0.5)	0	13760	-	-
Lung cancer [#]	<5	1892	1.1 (0.3, 4.2)	48	14703	3.3 (2.5, 4.3)	3.3 (2.5, 4.4)	9	13756	0.7 (0.3, 1.3)	0.8 (0.4, 1.5)
Melanoma [#]	0	1894	-	8	14698	0.5 (0.3, 1.1)	0.6 (0.3, 1.1)	<5	13741	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)
On or after 01 June 2021											
Number of patients	37			0				11			
Malignancies except NMSC	<5	101	19.8 (5.0, 79.4)	NA	-	-	-	0	24	-	-
Total malignant events	<5	101	19.8 (5.0, 79.4)	NA	-	-	-	0	24	-	-
Lymphoproliferative	<5	101	9.9 (1.4, 70.4)	NA	-	-	-	0	24	-	-
Lymphoma (NHL, Hodgkins)	0	103	-	NA	-	-	-	0	24	-	-
NHL [#]	0	103	-	NA	-	-	-	0	24	-	-
Hodgkin [#]	0	103	-	NA	-	-	-	0	24	-	-
Myeloma	0	103	-	NA	-	-	-	0	24	-	-
Leukaemia	<5	101	9.9 (1.4, 70.4)	NA	-	-	-	0	24	-	-
CLL [#]	0	103	-	NA	-	-	-	0	24	-	-
Non-melanoma Skin Cancer	0	103	-	NA	-	-	-	0	24	-	-

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Table 20. Number of first and rates of first malignancy events in patients initiating tofacitinib and patients registered in the bDMARD Naïve (csDMARD) and bDMARD (anti-TNF) cohorts, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoint	Tofacitinib Patients			bDMARD Naïve (csDMARD) Patients				bDMARD (Anti-TNF) Patients			
	Events	Person year	Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)	Events	Person year	Rate (95% CI)	Standard ¹ Rate (95% CI)
Other malignant solid tumours	<5	103	9.7 (1.4, 68.9)	NA	-	-	-	0	24	-	-
Brain neoplasms	0	103	-	NA	-	-	-	0	24	-	-
Of which, Glioblastoma	0	103	-	NA	-	-	-	0	24	-	-
Lung cancer [#]	0	103	-	NA	-	-	-	0	24	-	-
Melanoma [#]	0	103	-	NA	-	-	-	0	24	-	-

Data cut at 7 years after start of therapy.

Coded using MedDRA SMQs and PTs provided by Pfizer; - Rate (95% CI) not generated for zero events; NA No participants were present in this group for analysis.

Non-zero frequencies <5 are not reported, in line with General Data Protection Regulation requirements. Subcategory (e.g., five infection subcategories) counts may exceed the overall total of main category (e.g., Total serious infection) because patients were counted once in the overall time-to-first-event analysis, but could contribute one event to multiple subcategories during follow-up.

Categories and subcategories were coded using two systems as indicated (Manchester Template and MedDRA codes provided by Pfizer).

Only serious adverse events are included.

1 Age-sex standardised rate (direct standardisation approach using the age-sex distribution of person-time in the tofacitinib treated cohort).

Refer to [Section 9.3.1.](#) for cohort definitions.

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

11. DISCUSSION

11.1. Key results

This final study report describes the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV, MACE, MI, VTE (DVT and PE) and other specified outcomes, including fractures, among patients with RA in an existing UK based register who initiate tofacitinib.

Compared to the bDMARD naïve (csDMARD) treated patient cohort, adjusted analyses suggest that the tofacitinib treated cohort had a statistically significant reduced risk of several safety endpoints, including total malignant events (ever or on drug), malignancies (except NMSC), solid tumours, and death (ever exposed). The relative hazard was higher among tofacitinib treated as compared with bDMARD naïve (csDMARD) treated patients for total serious infections, other serious infections (i.e. not pre-specified), and NMSC, but these differences were no longer statistically significant after multivariable adjustment. Results from the sensitivity analyses demonstrated no change in the effect estimates.

Compared to the bDMARD (anti-TNF) cohort, findings suggest that there was an increased crude risk for NMSC (ever or on drug) and death (ever exposed) for the tofacitinib treated cohort, but that after confounder adjustment in a multivariable model the elevated association was no longer statistically significant. No statistically significant differences were observed for rates of safety endpoints between bDMARD (anti-TNF) treated and tofacitinib treated cohorts; no changes were observed following sensitivity analyses for select safety endpoints.

Overall, incidence rates across safety endpoints were qualitatively higher for patients ≥ 65 years old for all three patient cohorts, compared to patients < 65 . Total serious infections were the most common safety endpoint in both the ≥ 65 -year- and < 65 -year-old age groups, with pneumonia being the most frequent infection in both age groups. The rate of *other serious infections* was higher in the tofacitinib treated cohort compared to bDMARD naïve (csDMARD) and bDMARD (anti-TNF) treated cohorts; this was consistent in both age groups. In the < 65 -year-old age group, < 5 events of death on drug were observed in the tofacitinib group and the incidence of death in the ever-exposed group was lower in the tofacitinib treated group compared to the bDMARD naïve (csDMARD) treated group but higher compared to the bDMARD (anti-TNF) treated group.

11.2. Limitations

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing the BSRBR-RA, a well-established UK 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 biases, endpoint misclassification, residual confounding and generalizability are of concern when comparing incidence rates.

As a new therapy in the EU RA treatment options, 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 increased risk for safety events of interest events. Biases resulting from channeling may present as increased rates of safety events of interest. Comparison to internal comparators illuminate such channeling. Stratification on key indicators of disease severity, patient characteristics and past therapies was done for contextualization.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing these events. The rates of events of interest and their distribution among patient types may have changed over time. The 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.

Certain patient characteristics to help define baseline risk are not captured or are subject to high levels of missing and may limit data interpretation; such characteristics include alcohol consumption, duration of previous therapy, history of some comorbidities (e.g. serious or opportunistic infections, herpes zoster, fractures, history of malignancy type, history of chronic kidney disease, history of statin use, history of coronary heart disease), characteristics which may influence VTE outcomes (e.g. previous VTE, previous major surgery, MI within previous 3 months prior to index date, current or recent use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (likely to be missing in database), inherited coagulation disorders), or characteristics which may influence CV risk (e.g. history of coronary artery procedures). Further, baseline data for history of VTE and history of heart failure will be missing for all registry patients that were registered prior to February 2021, and it will not be possible to obtain this data retrospectively. Data for ethnicity will be missing for registry patients registered between 2019 and 2024.

Prior to 2016, NHS England data was used to validate cancer and death reports in the BSRBR-RA data from the hospital, but this process was not possible after this date due to restrictions and access controls in relation to Data Sharing Agreements. As the Xeljanz (Tofacitinib) cohort included in this report was recruited from 2017 onwards, the lack of availability of national linkage data from the death and cancer registers hosted by NHS England would have affected the number of some events included in this report and caution in interpretation is advised, particularly in comparing the rate of malignant events and death in the Xeljanz (Tofacitinib) cohort to the bDMARD naïve (csDMARD) cohort (with 100% of recruitment prior to 2016) and the bDMARD (anti-TNF) cohort (with 70% of recruitment included in this analyses prior to 2016).

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials and different durations of data collection. For instance, if data collection duration for PML is different than that for malignancies and death, it might impact extent of outcome ascertainment. While the BSRBR-RA 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. Further, when the COVID-19 pandemic hit in 2020, many NHS sites prioritised COVID-19 vaccine studies and paused existing clinical research studies, which could have also resulted in the events not being reported to the BSRBR-RA.

This study followed patients for a period of 7-years but conclusions may not be generalizable outside of the 7-year period since initiation of therapy.

11.3. Interpretation

Study findings are generally consistent with the known safety profile of tofacitinib. There were elevated incidence rates for NMSC, death, total serious infections, and other serious infections (NMSC and serious infections are important identified risks in the EU RMP) in the tofacitinib cohort relative to bDMARD patients. However, after adjustment for multiple confounders, these were no longer statistically significant. The meta-analysis of the four tofacitinib PASS (details provided in [Appendix 8](#) and in [Appendix 4 SAP](#)) compared tofacitinib and bDMARD cohorts and demonstrated a pooled estimate of aHR=1.03 (0.75, 1.41) for all-cause death (using the on drug approach); a pooled estimate of aHR=2.08 (1.55, 2.79) for NMSC (using the on drug approach); no pooled estimates were available for total or serious infections. 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 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.

11.4. Generalizability

This study uses data from the BSRBR-RA which collects data from patients with RA living in the UK. Generalizability to patients with RA who are not enrolled in the register is maximised by encouraging physicians to enroll each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history. Therefore, in the 7-year study observation period, the study findings are likely to be generalizable to all tofacitinib treated patients with RA in the UK.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

In summary, results are generally consistent with known safety profile of tofacitinib. This final report describes the occurrence of pre-defined safety endpoints in UK patients with RA and included data on 361, 2831, and 2063 respective tofacitinib, csDMARD, and anti-TNF treated patients from marketing of tofacitinib until 14 September 2025. After adjusting for several confounders, findings suggest that there is no statistically significant increased risk of study safety endpoints, when comparing the tofacitinib cohort to the bDMARD (anti-TNF) and bDMARD naïve (csDMARD) cohorts. Overall, the findings here presented should be

interpreted with caution considering the limitation of the study and the limited power for some of the outcomes.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

Document Approval Record

Document Name:	Clean A3921312_Final Report BODY_v1.0_27JUL2026 clean
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 British Society For Rheumatology Biologics Register-rheumatoid Arthritis (bsrbr-ra)

Signed By:	Date(GMT)	Signing Capacity
Asomaning, Kofi	29-Jul-2026 13:31:44	Final Approval
De Bernardi, Barbara	03-Aug-2026 07:51:08	EUQPPV Approval

APPENDIX 1. SIGNATURES

PROTOCOL NUMBER:

A3921312

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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBRA).

STUDY REPORT VERSION:

V 1.0

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.

Pfizer NI study lead/LIS1 study lead

Cherise Wong

Signature:



Date: 27 Jul 2026

Professor of Epidemiology, The University of Manchester
Kimme Hyrich, MD, PhD FRCPC

Signature:



Date: 27/07/2026



NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	An Active Surveillance, PostAuthorization 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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA).
Protocol Number	A3921312
Protocol Version Identifier	v 7.1
Date	15 April 2026
EU Post Authorisation Study (PAS) Register Number	EUPAS31126
Active Substance	L04AA29 Tofacitinib
Medicinal Product	Xeljanz® (tofacitinib)
Product Reference	EMA/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 special interest in RA

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	patients treated with tofacitinib in relation to other new advanced targeted therapies? Objectives: To evaluate the rates of serious infections, malignancy (overall, excluding non-melanoma skin cancer), subtypes of lymphoma, lung cancer, cardiovascular events, MACE, MI, VTE (DVT and PE), and other specified outcomes, including fractures, among patients with RA in United Kingdom (UK)-based register who initiate tofacitinib. Rates will also be estimated among RA patients who initiate tumour necrosis factor inhibitor (TNFi) drugs (ie, patients receiving Humira (adalimumab) (ADA), Enbrel (etanercept) (ETA), or Remicade (infliximab) (INF)) 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 methods to adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities and other potential confounders.
Country of study	United Kingdom
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	adalimumab (Humira)
AE	adverse event
bDMARD	biologic disease modifying antirheumatic drug
BID	bis in die (Twice a day)
BP	blood pressure
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
BSRBR-RA	British Society for Rheumatology Biologics Register- Rheumatoid Arthritis
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	Cardiovascular
CVD	cardiovascular disease
DAS	Disease activity score
DMARD	disease modifying antirheumatic drug
DMEC	Data Monitoring and Ethics Committee
DVT	Deep venous thrombosis
EBV	Epstein Barr Virus
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPITT	European Pharmacovigilance Issues Tracking Tool
EQ-5D	EuroQol Five Dimensions Questionnaire
ESR	erythrocyte sedimentation rate
ETA	etanercept (Enbrel)
EU	European Union
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	health assessment questionnaire
HLT	high level term
HMA-EMA	Heads of Medicines Agencies-European Medicines Agency
ICD	International classification of diseases
IEC	independent ethics committee
IL	Interleukin
INF	infliximab (Remicade)

Abbreviation	Definition
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
LLT	Low level term
LTE	long term extension
MACE	major adverse cardiovascular events
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial infarction
MTX	Methotrexate
NDA	New Drug Application
NEC	Not elsewhere classifiable
NHL	non-Hodgkin's lymphoma
NI	non-interventional
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
N	No
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	Post-authorization study
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PV	pharmacovigilance
PY	person-years
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance and Epidemiology End Results
SIR	standardised incidence ratio
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
TB	Tuberculosis
TBD	to be determined

Abbreviation	Definition
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
UK	United Kingdom
VTE	Venous thromboembolism
Y	Yes

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA).

Version: Final Protocol (v 7.1).

Date: 15 April 2026
Michelle Iannacone, PhD
Methods Lead
Safety Surveillance Research
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 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 endpoints of special 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 in BSRBR-RA.

Research question: Research Question: What are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies

Objectives: To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, cardiovascular events, major adverse cardiovascular events (MACE), myocardial infarction (MI), venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]) and other specified outcomes, including fractures, among patients with RA in a United Kingdom (UK)-based register who initiate tofacitinib. Rates will also be estimated among RA patients who initiate other tumour necrosis factor (TNF) inhibitor (TNFi) drugs (ie, patients receiving Humira (adalimumab) (ADA), Enbrel (etanercept) (ETA), or Remicade (infliximab) (INF)) to provide context for rates observed on tofacitinib. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and MACE have been added as study endpoints (MI and lymphoma (overall) were already included as a study endpoints). Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

Study design: This active surveillance study uses data from the existing BSRBR-RA, 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.

Population: The study population will comprise all patients with RA enrolled within BSRBR-RA who receive tofacitinib following EU approval and marketing, through the end of the study period. Two comparator cohorts of patients within BSRBR with active RA at cohort entry will be used for risk characterization purposes. The first comparator cohort consists of RA patients who are biologic naïve at recruitment receiving conventional synthetic DMARDs (csDMARDs), the second consists of RA patients initiating adalimumab (ADA), etanercept (ETA), or infliximab (INF) as their first bDMARD..

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), cardiovascular events (including MACE), and VTE (DVT and PE).

Data sources: BSRBR collects core baseline data, including patient demographics and disease characteristics, will be collected by the recruiting clinician using a standardised form. In addition, some BSRBR personal and medical information are obtained directly from each patient recruited (eg, smoking history).

Study size: This is an active surveillance descriptive study without prespecified statistical hypotheses; therefore, there is no minimum sample size requirement. The targeted sample size for tofacitinib treated patients is 500, though enrolment will not be capped and continue throughout the study period. Over 3600 biologic naïve and 2100 biologic exposed patients are currently enrolled in the register.

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

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

5. AMENDMENTS AND UPDATES

Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	September 2021	Substantial	Title Page	Updated to replace old Pfizer logo with new one Updated to include EU PAS Register Number Updated objectives to align with changes in protocol. Updated contact information for protocol author. Updated contact information for the MAH Contact Person	Editorial change Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor
	September 2021		Section 2	Updated to include new abbreviations	Editorial change
	September 2021		Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principle investigator.
	September 2021		Section 4	Revised version and date. Updated Objective and Variables to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated Data Analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes.	Pharmacovigilance Risk Assessment Committee (PRAC) request and clarification.
	September 2021		Section 7	Updated to include information on changes to protocol resulting from June 2021 signal evaluation procedures. Also 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		Section 8	Updated objectives to include lymphoproliferative malignancy subtypes,	PRAC request and clarifications

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				lung cancer and MACE as additional safety endpoints. Updated objective to include estimation of event rates in the elderly aged 65 years and older.	
	September 2021		Section 9.2.4	Updated Risk Window to include sensitivity analysis for the 90-extension period.	PRAC request and clarification.
	September 2021		Section 9.3.1	Updated to include CV risk factors	PRAC request and clarifications
	September 2021		Section 9.3.2	Updated to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated to include fracture as additional safety endpoint. Updated to include all-cause mortality as a safety endpoint.	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk Editorial Change.
	September 2021		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		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		Section 11	Minor clarifications to safety reporting language	Editorial change

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
	September 2021		Annex 2	Author name changed. Signature and signature date updated	Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author.
	September 2021		Appendix 1	Updated to include definitions for additional endpoints.	PRAC request and clarifications
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		Section 2	Updated to include new abbreviations	Editorial change
	February 2022		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. Updated the Milestones to remove reference to the	Editorial change PRAC request and clarification PRAC request and clarification

Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				reports provide to MAH every 6 months.	
	February 2022		Section 7	Updated the Cardiovascular Disease section to remove MACE as an “important identified risk”.	PRAC request and clarification
	February 2022		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		Section 9.3.1	Updated Baseline Data to include additional CV risk factors	PRAC request and clarification
	February 2022		Section 9.3.2	Updated the Endpoints to replace the term ‘lymphoproliferative malignancy’ with ‘lymphoma’. Update the abbreviations for DVT and PE.	PRAC request and clarification Editorial change
	February 2022		Section 9.7	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
	February 2022		Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
	February 2022		All sections where applicable	Replaced term ‘lymphoproliferative malignancy’ with ‘lymphoma’.	PRAC request and clarification

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
	February 2022		Annex 2	Signature date updated	Editorial change.
3.0	March 2025	Substantial	Title Page	Updated Author information and MAH Contact	Editorial change.
	March 2025		Section 2	Added abbreviation for Heads of Medicines Agencies-European Medicines Agency	Editorial change.
	March 2025		Section 6	Updated name of EMA register.	Editorial change
	March 2025		Section 9.2.2	Added exclusion two exclusion criterion including to 1) exclude anyone that doesn't meet the inclusion criteria and 2) 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.
	March 2025		Section 9.7	Added sensitivity analysis for the final report to assess potential confounding by prior non-tofacitinib JAKi	To assess potential confounding via stratification (since excluding patients with prior use would reduce sample size substantially)
4.0	July 2025	Substantial	Title Page	Product Reference and Procedure Number was updated	Editorial change to align with IRIS requirements
	July 2025		Title Page	MAH Contact Person Information was Updated	Editorial change
	July 2025		Section 9.2.2	Removed exclusion criteria to exclude patients with prior history of the specific safety event of interest being analyzed. Included statement "There are no exclusion criteria for this study."	Per PRAC request. prior history will be accounted for using model adjustment for baseline comorbidities. Editorial change to match MAH protocol template instructions.
	July 2025		Section 9.2.4	To align with amendment to section 9.2.2, removed	Editorial change.

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				word “/exclusion” from the last sentence that now reads as follows “Patients switching therapies are eligible to move between cohorts if inclusion criteria are met.”	
	July 2025		Annex 2	Signature date updated.	Editorial change.
5.0	December 2025	Substantial	Section 4	Revised Abstract by: - Updating description of second comparator cohort. - Updating text regarding the availability of characteristics captured at baseline. - Updating the biologic naïve (non-biologic control cohort) sample size available for analysis.	- To align with Section 9.2.1 Inclusion Criteria. - To align with amendments made to Section 9.3.1. - The Registry provided an update on the sample size available for the biologic naïve control cohort.
	December 2025		Section 9.2	In Study Population section, updated the biologic naïve (non-biologic control cohort) sample size.	The Registry provided an update on the sample size available for the biologic naïve control cohort.
	December 2025		Section 9.3.1	Removing baseline characteristics that are not collected by Registry: The following details under Diagnosis: ‘(including the presence or absence of those features listed in 1987 American College of Rheumatology (ACR) criteria for RA)’	Reason for removal of baseline characteristics: - BSRBR-RA only includes patients with “consultant rheumatologist diagnosis of rheumatoid arthritis (RA)” as eligible for inclusion in the study cohorts - BSRBR-RA standardized form at baseline does not collect information

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				- Year of recalled symptom onset or year of diagnosis - Duration of previous therapy recorded as start/month/year - History of NMSC, history of lymphoma, and history of lung cancer - Undergoing major surgery from date of hospital admission to one month after date of discharge (<i>if feasible</i>) - Ever use at baseline of combined hormonal contraceptives or hormone replacement therapy (<i>if feasible</i>) - Inpatient care because of RA (i.e., RA as main diagnostic listing; from date of admission to date after discharge) - History of chronic kidney disease, statin use, as proxy for history of hypercholesterolemia, coronary heart disease - Current working status (patient form) Updated description of baseline characteristics:	- on years of symptom onset or year of diagnosis - BSRBR-RA standardized form used at baseline does not include dates of previous therapy exposure to inform duration of use prior to index date - BSRBR-RA standardized form used at baseline does not include information on the history of NMSC, lymphoma, or lung cancer - BSRBR-RA standardized form used at baseline does not collect information on the history of any major surgeries undergone during hospital admission - BSRBR-RA standardized form used at baseline does not include information on ever use at baseline of combined hormonal contraceptives or hormone replacement therapy - BSRBR-RA standardized form used at baseline does not include information on inpatient care because of RA - BSRBR-RA standardized form

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				- Updated “oral steroid use” to “steroid use” - Updated “MI within previous 3 months prior to index date” to MI - Updated malignancy events by removing “(i.e., history of malignancies excluding NMSC, and specifically history of NMSC) - Added History of Renal Disease - Updated vaccination to “Herpes Zoster Vaccination”	used at baseline does not include information on history of chronic kidney disease, hypercholesterolemia, or coronary heart disease - BSRBR-RA standardized form used at baseline does not include information on current working status Reason for updating the description of the baseline characteristics: - BSRBR-RA standardized form used at baseline does not include information on type of administration of steroid use - BSRBR-RA standardized form used at baseline does not include information on date of comorbidity. Therefore, it is not possible to identify MI within 3 months of the index date - BSRBR-RA standardized form used at baseline does not include information on type/site of malignancy - BSRBR-RA standardized form used at baseline collects information on history of renal

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
					disease, which was added since chronic kidney disease information is not collected Vaccination status refers only to vaccination to herpes zoster
	December 2025		Section 9.4	Updated information under <i>Baseline</i> description of data source regarding information collected at baseline.	To align with amendments made to Section 9.3.1.
	December 2025		Section 9.9	Updated Limitations to Research Methods to include limitations in data capture of baseline characteristics that may limit data interpretation.	To provide clarity of potential limitations in interpretation of study findings due to missing baseline data leading to inability to adjust for potential differences in distribution across study cohorts.
	December 2025		Section 9.9	Updated Limitations to Research Methods to include limitations in data capture by enrollment date of registry patient.	Baseline data for history of VTE, history of heart failure, and history of angina will be missing for all registry patients that were registered prior to February 2021. Data for ethnicity will be missing for registry patients registered between 2019 and 2024.
	December 2025		Annex 2	Signature date updated.	Editorial change.
6.0	March 2026	Substantial	Section 9.3.1	Added variable “year of RA diagnosis” to Baseline Data.	PRAC Request
	March 2026		Section 9.9	Updated Limitations Section by removing “and history of angina” from paragraph 4, line 11. This change was made following confirmation from BSRBR that	PRAC Request

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Amendment number	Date	Amendment Type (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				information on history of angina is available prior to February 2021 and will be included in the Final Report.	
	March 2026		Annex 2	Signature date updated	Editorial change
7.0	April 2026	Administrative	Table of Contents and Corresponding Sections of Document Body	The Table of Contents was updated to correct the section numbers to match the most recent version of the internal Pfizer CT-24 protocol template for secondary data collection.	Editorial change
	April 2026		Annex 2	Signature date updated	Editorial change

6. MILESTONES

Milestone	Planned date
Registration in the HMA-EMA Catalogues	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

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 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.^{16,31} Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA).¹⁷ 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.

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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. To enable assessment of safety endpoints of special interest including rare events and endpoints with long latency periods, Pfizer will implement a postapproval, active surveillance study of tofacitinib exposed patients using actively collected prospective data in BSRBR-RA. Long term morbidity and mortality event tracking of these cohorts over 7-years is an appropriate method for evaluating the risk associated with these treatments.

There is an increased risk of premature mortality, serious infection and lymphoma in patients with RA and other connective tissue diseases, independent of the treatment they have received.²¹ Thus, the patients on newly approved therapies without a well-established record of safety are already at increased background risk of premature mortality, infection and malignancy-. Additionally, following the result of the June 2021 signal evaluation procedure (EPITT 19382) to assess the increased incidence rate of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients treated with tofacitinib for rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma 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 BSRBR register, is designated as a 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 ³⁶⁵ 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.^{5,10} 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,^{4,8,10,24} however studies looking at TNFi treated- cohorts over time have shown that rates of serious infection decline over time.^{3,28} 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.²⁸

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.^{2,6,7}

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.^{15,27,30,33}

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.^{22,27} 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.

Cardiovascular Disease

Patients with RA have higher rates of CVD than the general population.²³ 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.

Other Safety Events of Interest

The BSRBR-RA register collects data on other safety events of interest in the RA population including central nervous system (CNS) events, fractures, pregnancy and mortality. These events will also be analyzed to identify new safety signals.

8. RESEARCH QUESTION AND OBJECTIVES

This study asks what are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies.

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 outcomes, including fractures, among patients with RA in an existing UK based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients treated with TNFi therapies to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested in this descriptive study. Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, and MI, VTE, and other event rates, including fractures, 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. 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 endpoint). 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 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 has the primary aim to study the safety of new therapies for RA during routine post-marketed clinical use.

This study will estimate the incidence rates of safety events of interest among patients starting tofacitinib. Rates will also be estimated among (1) an existing cohort of patients starting originator TNFi (ADA, ETA and INF) since 2010 and (2) an existing historic cohort of patients with active RA who had not started a targeted therapy (recruited between 2002 and 2008) but are on csDMARD. No hypotheses will be tested. Data capture and follow-up methods are the same for all cohorts within the BSRBR-RA. Pending adequate sample size to permit adjustment for important variables for comparative analyses, multivariate statistical methods adjusting for potential confounders will be determined a priori and documented in a statistical analysis plan (SAP).

9.2. Setting

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. For the first 78 years the main focus was on the study of the safety profile of the first three TNFi agents (ie, ADA, ETA and INF) as a class and as individual therapies. With the exception of the risk of developing tuberculosis, data within the BSRBR-RA has not demonstrated any clear differences in AE profile between these agents. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.⁹ Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections,¹⁰ and malignancies.^{19,25} All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

External validity, ie, generalizability to RA patients who are not enrolled in the register, is maximised by encouraging physicians to enrol each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

Within the BSRBR-RA there are 2 comparator cohorts. These represent cohorts of patients exposed to agents which have been studied:

- The first is a cohort of patients with prevalent active RA (guide DAS >4.2) on csDMARD recruited between 2001 and 2008 for whom follow-up data are already available. No new data are being collected for this cohort as the 7-year follow-up period since last subject first visit has been surpassed. This cohort consists of patients who were either being treated before the advent of approved targeted therapies for RA or for whom biologics were not needed or desired. Some of these patients will have subsequently progressed to a biologic or other new therapy, been lost to follow up or died. For the purpose of analysis (see below), their follow-up will be censored at the time of the first of these events, thus they will only contribute patient months of follow-up to the first cohort up to the first event. Patients initially enrolled in the first cohort who later initiate a targeted therapy are eligible for subsequent enrolment in the corresponding cohort, eg, biologic or tofacitinib.
- The second is a cohort of TNFi exposed patients with active RA registered within 6 months of starting ADA, ETA or INF as their first biologic. Recruitment to this cohort started in 2010 and is ongoing. Patients enrolled in the TNFi cohort who later initiate tofacitinib are eligible for subsequent enrolment in the tofacitinib exposed cohort. Per

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national prescribing restrictions, patients will not be prescribed TNFi and tofacitinib concurrently. All comparisons will be made with the overall TNFi class rather than individual therapies.

The greatest concern in using the BSRBR-RA cohorts is the potential lack of comparability between the newly approved therapy, ie, tofacitinib, and the comparison cohorts in relation to their underlying risk of endpoint development. If there is a significant imbalance between key confounders between the groups then this could reduce the validity of comparisons. The key confounders to be measured at baseline include details of disease severity, including symptom duration, current health assessment questionnaire (HAQ), current significant comorbidities and relevant previous therapies. Analyses undertaken to date comparing the established TNFi cohorts with the csDMARD group have not revealed any serious imbalance that cannot be adjusted for in subsequent analyses.¹⁹

Study Population

The active surveillance population includes rheumatoid arthritis patients already enrolled in the register who met the criteria for the cohorts as defined in [Section 9.3.2](#) as well as patients with rheumatoid arthritis, newly treated with tofacitinib following EMA approval and UK launch of the product (fully available January 2018) and registered with the BSRBR-RA. Over 3600 biologic naïve and 2100 biologic exposed patients are currently enrolled in the register. Some tofacitinib exposed- patients will be newly enrolled in the register, having been recruited to the BSRBR-RA within 6 months of their first dose. -Others will already have been enrolled in the BSRBR-RA as prior biologic disease modifying antirheumatic drug (bDMARD) initiators but will switch to tofacitinib during follow up. Key clinical data at time of switch are requested. For patients enrolled during the 6-month period after initiation, the baseline date will be reported as the drug start date rather than the date of registration. The first postbaseline visit occurs at 6 months after tofacitinib initiation, regardless of date of enrolment.

9.2.1. Inclusion Criteria

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

9.2.1.1. Inclusion Criteria: Tofacitinib Exposed Cohort

1. Eligible for BSRBR-RA.
2. Initiation of tofacitinib, regardless of prior therapy (within 6 months of register enrolment).

9.2.1.2. Inclusion Criteria: bDMARD Exposed Cohort

1. Eligible for BSRBR-RA.
2. Initiation of ADA, ETA or INF as their first bDMARD within 6 months of register enrolment.

9.2.1.3. Inclusion Criteria: bDMARD Naïve Cohort

1. Eligible for BSRBR-RA.
2. Active RA (guide DAS >4.2 (to ensure comparable disease activity to tofacitinib and bDMARD initiators).
3. Prevalent use of csDMARD (prevalent use) without bDMARD or tofacitinib.
4. Enrolled in register between 2001-2008.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.2.3. Index Date

The index date for the tofacitinib cohort is the date the first tofacitinib dose was taken. Similarly, the date for the second comparator cohort (TNFi-exposed) corresponds to the date of the first dose of ETA, ADA, or INF, which ever therapy was taken first. For the first comparator cohort, the index date is the date of entry into the register. This cohort is based on prevalent active RA treated with csDMARD.

9.2.4. Risk Window

Within each cohort each patient will be evaluated for safety events of interest and accrue person time from the cohort index date until the first occurrence of the event of interest, initiation of biologic (comparator cohort 1), discontinuation of biologic (comparator cohort 2), discontinuation of tofacitinib (tofacitinib exposed cohort), death, loss to follow up, exit from the register or after 7-years of follow up. Differences in duration of therapy will be examined (similar to censoring patterns). Interim reports will not censor the existing comparison cohorts to match the tofacitinib cohort. The final report will censor all patients at 7-years after the first tofacitinib exposed patient enters the register. Follow-up will be uniquely determined for each safety endpoint of interest.

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)).¹ 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 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

¹ 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.

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, excluding NMSC, 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 cancers (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.^{18,19,31,28} 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.^{18,19,31,28} Additional analyses will be conducted to evaluate potential confounders and the impact of different latency assumptions as will be described in the SAP. Sensitivity analyses will be conducted that restrict the bDMARD comparator cohort to patients who were never exposed to tofacitinib or other non-biologic advanced therapies and compare the characteristics of those bDMARD patients ever and never exposed to tofacitinib.

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

Of note, several studies compared a once-exposed approach to a time on drug and other approaches and found similar rates of malignancy using an on-drug and ever-exposed approach.^{18,19,31}

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.

Treatment/Event pattern	Once-exposed always at risk		Censoring at Switch	
	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

- Patients continue to be followed after index exposure discontinuation if they do not initiate another systemic therapy in a different class.
- 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.

Patients switching therapies are eligible to move between cohorts if inclusion criteria are met.

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

9.3.1. Baseline Data

Baseline data are derived from BSRBR information reported by the recruiting clinician (or patient where noted), using a standardised form:

1. Diagnosis of RA by rheumatologist and year of RA diagnosis;
2. Age at treatment start, gender;
3. Ethnicity (patient form);
4. Previous drug history of immunosuppressive csDMARDs and biologics, biosimilar or other new advanced therapy;
5. Co-morbidity (e.g., history of diabetes mellitus, history of MI, history of hypertension, and ever for malignancy events))
(ie, <http://bsrbr.org/hospitals/data-collection/>);
6. All current therapy;
7. Findings necessary to calculate the DAS28;
8. HAQ and EuroQol Five Dimensions Questionnaire (EQ-5D);
9. Height, weight, single blood pressure (BP) measurement at baseline;
10. Steroid use (baseline and ever exposure);
11. Smoking history (current, past, never – patient form);
12. Herpes Zoster Vaccination.

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 below:

- Age
- Previous VTE (*if feasible*)
- MI
- Heart failure
- Malignancy
- Diabetes
- Hypertension

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)
- History of diabetes
- History of renal disease
- History of hypertension
- History of previous MI
- History of stable angina pectoris

9.3.2. Endpoints

The BSRBR-RA is an existing, efficient data collection system for evaluating a range of safety outcomes associated with therapies used to treat RA including cancers,^{19,25} cardiovascular events,¹² and serious infections.¹⁰ The endpoints collected in BSRBR-RA are events associated with RA itself and therapies used to treat moderate- to -severe disease. The endpoints of interest are listed below:

1. Aplastic Anaemia, Pancytopenia, Serious Neutropenia;
2. Cerebrovascular Accident;
3. Death;
4. Demyelination, Optic Neuritis;

5. Fractures;
6. Hepatitis B Reactivation;
7. Malignancy (overall, excluding NMSC);
8. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia);
9. Lung Cancer;
10. NMSC;
11. Myocardial Infarction/Acute Coronary Syndrome;
12. Major Adverse Cardiac Events (MACE)
13. Pregnancy;
14. Progressive Multifocal Leukoencephalopathy (PML);
15. Pulmonary Embolism;
16. Serious Congestive Heart Failure;
17. Serious Infusion/Immunologic Reaction;
18. Serious Hypersensitivity Reaction;
19. Serious Infection;
20. Herpes Zoster;
21. Serious Hepatic Dysfunction/Failure;
22. Serious Lower Gastrointestinal Ulcer/Bleed/Perforation;
23. Serious Lupus/ Lupus Like Illness;
24. Serious Skin Reaction (eg, Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis);
25. Serious Haemorrhage;
26. Tuberculosis;
27. Venous thromboembolic events (DVT and PE);
28. All-cause mortality.

Given the age dependent rate events of interest, analyses will be conducted in elderly patients aged ≥ 65 years.

9.4. Data Sources

Baseline

BSRBR is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardised form. In addition, some BSRBR personal and medical information reflect data obtained directly from each patient recruited (eg, on smoking history).

Follow-up

BSRBR data are the source of information on antirheumatic treatment, updated every 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the DAS28 is also collected.

BSRBR data include reports from patients contacted every 6 months for the first three years of their follow up period and asked to complete a patient diary which includes data about hospital admissions and new hospital referrals. Data collection instruments are distributed by post to patients and their physicians according to schedule. One attempt is made to follow-up nonresponders. Nonresponders at one follow up point are (unless further follow up is refused) contacted again at the next follow up point and all follow-up data since the last completed study follow-up is requested. Patients lost to follow up continue to be followed for death and cancer endpoints through the respective registers.

Endpoints

BSRBR data include reports of serious morbidity, either by subject or enrolling physician during regularly scheduled assessments, and the referring physician is immediately contacted by the BSRBR-RA and asked to provide further details, where available. For specific morbidities of interest certain specific details are requested. All serious morbidities reported to BSRBR are coded by a trained nurse using the Medical Dictionary for Regulatory Activities (MedDRA).

BSRBR uses the UK national death and cancer registers allow the “flagging” of individuals such that if they die or are entered in a cancer register, the BSRBR-RA learns of the event and obtain death certificate details or cancer register details. By law, deaths due to natural causes are to be registered within 5 days. However, the lag time between cancer incidence and registration in the national cancer database takes longer depending on confirmatory diagnoses, tests, national cancer register requirements and local resources. BSRBR-RA downloads which patients have been flagged for incident cancer or death once per year based on personal identifiers.

9.5. Study Size

This active surveillance descriptive study is not intended to test a prespecified statistical hypothesis; therefore no minimum sample size is required. The study enrolment goal is 500 patients in the tofacitinib arm, but success depends largely on use of tofacitinib in UK. Enrolment will not be capped at 500 but continue throughout the study period.

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

Table 1 and Table 2 below describe the power to detect a 2-fold difference in event rates between tofacitinib- initiators and bDMARD initiators- assuming the following:

- $\alpha=0.05$;
- 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 events (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 1 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 2 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.¹⁰

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 1), 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 1). 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 1) 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 11100 bDMARD patients would only provide 40% power to detect a 2-fold difference (Table 2).

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

Table 1. 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, 5Year 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	0.99
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 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	0.18	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 12 months of enrolment of tofacitinib exposed patients in BSRBR, 110 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

In BSRBR-RA data are collected via the hospital (at 6 monthly intervals for three years and annually thereafter) and patient questionnaires (at 6 monthly intervals for three years). Patient and physician assessments are sent via post to the study team at the University of Manchester who then enter the data into the study database.

9.7. Data Analysis

All statistical analyses will be performed by BSRBR using Stata. The semi-annual analyses will consist of comparisons in baseline status between the individuals in the different cohorts. All serious and non-serious safety events of interest will be provided.

The initial analyses will consist of descriptive comparisons of baseline status and crude event rates between the different cohorts.

Analyses will be undertaken at 6 monthly intervals following the initial analyses and will include recruitment details, baseline characteristics and crude event rates. Semiannual reports are delivered in July and January. Such analyses can act as a guide to the ultimate levels of recruitment and length of follow-up required. The need for continued recruitment and follow-up can only be taken in light of results from such analyses.

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

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.

The feasibility of conducting a final comparative study will be evaluated at 7 years of follow up based on statistical power and suitable overlap in patient populations in the exposure groups. 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 methods. For these analyses, the exposure cohorts will be analyzed overall, previous biologics use and monotherapy and combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs). Increased risk of malignancy (excluding NMSC), MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events, as well as an increase in mortality, in patients treated with a combination therapy with MTX specifically will be described, if sample sizes are sufficient, in the interim and final reports. These and potentially other agreed upon strata will be determined a priori and included in SAP filed with Sponsor. The general analytic approach will be descriptive and include rates of events of interest within stratified treatment cohorts. Data will be presented as number of events, crude and age/sex standardized incidence rates. -Such analyses will be performed by and at the direction of BSRBR. The approved SAP will also describe the a priori determined common set of MedDRA codes and MedDRA version to define serious infections, GI perforations, herpes zoster, fractures, and CV events (eg, MACE). The codes will be harmonised with other registers conducting similar analysis. A draft set of MedDRA codes is included in [Appendix 1](#). Any such comparisons will be made with the overall TNFi class rather than individual therapies. 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.

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. 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. The rates of safety events of interest, including infections, MACE, MI, VTE, and malignancies excluding NMSC, will also be evaluated within the elderly aged ≥ 65 years.

Descriptive data will be presented in the interim reports. 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).

Decisions as to the timing of scientific publications are made independently by the British Society of Rheumatology (BSR) and the academic teams who oversee the BSRBR-RA. A Data Monitoring and Ethics Committee (DMEC) has been established by the BSR. The DMEC is independent of the principal investigators and also of any of the pharmaceutical companies involved and has the power to request interim analyses and advise on the timing and nature of any publications. The DMEC includes at least one epidemiologist and one statistician.

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 priori and described in an approved SAP.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (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.

9.8. Quality Control

Data used in this study are secondary use of data collected as part of the existing BSRBR, which has established quality control practices.

9.9. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing the BSRBR-RA, a well-established UK 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 biases, endpoint misclassification, residual confounding and generalizability are of concern when comparing event rates.

As a new therapy in the EU 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 increased risk for safety events of interest events. Biases resulting from channeling may present as increased rates of safety events of interest. 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 over time.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing these events. The rates of events of interest and their distribution among patient types may have changed over time. The 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.

Certain patient characteristics to help define baseline risk are not captured at all or are subject to high levels of missing and may limit data interpretation; such characteristics include ACR criteria for diagnosis RA, alcohol consumption, duration of previous therapy (including previous csDMARD, biological and biosimilar therapies), steroid administration type (i.e. intravenous, subcutaneous or oral), history of comorbidities (e.g. serious or opportunistic infections, herpes zoster, fractures, history of malignancy type (including history of NMSC, lymphoma and lung cancers), history of chronic kidney disease), characteristics which may influence VTE outcomes (e.g. previous VTE, previous major surgery from the date of hospital admission to one month after the date of discharge, MI within previous 3 months prior to index date, current or recent use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (likely to be missing in database), inherited coagulation disorders), or characteristics which may influence CV risk (e.g. history of coronary heart disease and coronary artery procedures and history of statin use). Further, baseline data for history of VTE and history of heart failure will be missing for all registry patients that were registered prior to February 2021, and it will not be possible to obtain this data retrospectively. Data for ethnicity will be missing for registry patients registered between 2019 and 2024.

Additionally, stratified analyses by time periods after January 2020 will be limited to the RA patients receiving tofacitinib as the registry is no longer recruiting new patients receiving TNF and DMARD therapy regimens. Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the BSRBR-RA 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.

This study will include patients followed for a period of 7-years after the first tofacitinib patient is enrolled in the register. 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 PARTICIPANTS

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 or any other personal identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The tofacitinib PASS will use fully anonymized data from the existing BSRBR-RA, therefore patient consent is not applicable.

10.2. Patient Consent

As this study involves deidentified/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; planned analyses use data from secondary data sources that do not include patient identifiers.

10.4. Institutional Review Board (IRB)/ Ethics Committee (EC)

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.

The analyses for the tofacitinib PASS will be completed using fully anonymised data. The data will not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

The BSRBR-RA protocols are approved by the North West 5 Research Ethics Committee (REC 00/8/053 with most recent approval amendment (#27) approval date of 06-Dec-2018).

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), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (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

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 investigator 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.

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. A final dataset, to include 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 as appropriate. Data may be used in regulatory communications external to the UK 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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14. LIST OF TABLES

Table 1. 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, 5Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm.....37

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.....38

15. LIST OF FIGURES

Not applicable.

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16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

Not applicable.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, PostAuthorization 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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR-RA)

EU PAS Register® number: EUPAS31126
Study reference number (if applicable): A3921312

<u>Section 1: Milestones</u>	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ²	☒	☐	☐	6
1.1.2 End of data collection ³	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
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:

Secondary database study

<u>Section 2: Research question</u>	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 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.

³ Date from which the analytical dataset is completely available.

<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
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 <i>a priori</i> hypothesis?	☒	☐	☐	8

Comments:

<u>Section 3: Study design</u>	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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.

<u>Section 4: Source and study populations</u>		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
4.2.2	Age and sex	☒	☐	☐	9.2
4.2.3	Country of origin	☒	☐	☐	9.2
4.2.4	Disease/indication	☒	☐	☐	9.2
4.2.5	Duration of follow-up	☒	☐	☐	9.4
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

Comments:

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<u>Section 5: Exposure definition and measurement</u>		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?	☐	☐	☒	
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.

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Appendix 1
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)	☒	☐	☐	Appendix 1
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:

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.2

Comments:

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

<u>Section 8: Effect measure modification</u>	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

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<u>Section 9: Data sources</u>	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))	☒	☐	☐	Appendix 1

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<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.3.3 Covariates and other characteristics?	☒	☐	☐	Appendix 1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.2.4

Comments:

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

<u>Section 11: Data management and quality control</u>	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:

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<u>Section 12: Limitations</u>	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)	☒	☐	☐	8.0, 9.5, 9.7

Comments:

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<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.5
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

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

Comments:

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<u>Section 15: Plans for communication of study results</u>	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:

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Name of the main author of the protocol:	Michelle Iannacone		
Date: 15 April 2026			
Signature:			

18. ANNEX 3. ADDITIONAL INFORMATION

See [Appendix 1](#).

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Appendix 1. 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.

Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
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.
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	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147 Brain 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

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
		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% [15]. 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.	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;

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

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

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			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 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.	10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheo-oesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
		Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients.	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, nonobstructive; 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;

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			10034649 Peritoneal abscess; 10034674 Peritonitis; 10038073 Rectal perforation; 10038975 Retroperitoneal abscess; 10041103 Small intestinal perforation; 10046274 Upper gastrointestinal 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;

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			10062065 Perforated ulcer; 10062070 Peritonitis bacterial; 10062570 Enterovesical fistula; 10065713 Gastric fistula; 10065879 Gastrointestinal anastomotic leak; 10066870 Aorto-oesophageal fistula; 10066892 Rectourethral fistula; 10067091 Gastrophrenic 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).

Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
Lung Cancer	Identified through the Cancer Register. ICD-7: 162.1		High level terms (HLT): 10038723 Respiratory tract and pleural neoplasms malignant cell type unspecified, not elsewhere classifiable (NEC); 10024973 Lower respiratory tract neoplasms. Low level term (LLT): 10023292 Kaposi's sarcoma, lung; Exclude preferred terms (PT): 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	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

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
		an estimated coverage greater than 95%	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; Non-Hodgkin's lymphoma unspecified histology indolent stage IV 10029625; Hodgkin's disease 10020206; Hodgkin's disease lymphocyte depletion stage I site unspecified 10020208;

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			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 refractory 10020216; 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;

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Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			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 disease mixed cellularity stage I supradiaphragmatic 10020237; Hodgkin's disease mixed cellularity stage II subdiaphragmatic 10020238; Hodgkin's disease mixed cellularity stage II

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

Event	ARTIS		BIOBADASER, BSRBR, RABBIT
	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
			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 Lumbar spine/pelvis: S32 Shoulder/humerus: S42 Forearm: S52 Wrist/hand: S62	The positive predictive value (PPV) for fractures in the Swedish NPR is extremely high: a validation of 647 patient charts the PPV of fracture in Swedish	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 delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner

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

A3921312

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 British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR RA)

Statistical Analysis Plan

(SAP)

Version: 3.0

Author: Iannacone, Michelle (Pfizer, Inc., USA) and Azadbakht, Narges (BSRBR RA, United Kingdom)

Date: 23-APR-2026

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Adalimumab (Humira)
AE	Adverse event
bDMARD	Biologic disease modifying antirheumatic drug
BID	Bis in die (Twice a day)
BP	Blood pressure
BSRBR-RA	British Society for Rheumatology Biologics Register- Rheumatoid Arthritis
CHF	Congestive heart failure
CI	Confidence interval
csDMARD	Conventional synthetic disease modifying antirheumatic drug
CV	Cardiovascular
CVD	Cardiovascular disease
DAS	Disease activity score
DMARD	Disease modifying antirheumatic drug
DVT	Deep venous thrombosis
EMA	European Medicines Agency
EQ-5D	EuroQol Five Dimensions Questionnaire
ESR	Erythrocyte sedimentation rate
ETA	Etanercept (Enbrel)
EU	European Union
GI	Gastrointestinal
HAQ	Health assessment questionnaire
ICD	International classification of diseases
INF	Infliximab (Remicase)
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-interventional
NICE	National Institute for Health and Clinical Excellence
NMSC	Non-melanoma skin cancer
NSAIDs	Non-steroidal anti-inflammatory drugs
OI	Opportunistic infection
PAS	Post-authorization study
PASS	Post-authorization safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PML	Progressive multifocal leukoencephalopathy
PPV	Positive predictive value
PRAC	Pharmacovigilance risk Assessment Committee
PT	Preferred term
PV	Pharmacovigilance
PY	Person-years
RA	Rheumatoid arthritis

Abbreviation	Definition
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEER	Surveillance and Epidemiology End Results
SIR	Standardized incidence ratio
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
TB	Tuberculosis
TBD	To be determined
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom
VTE	Venous thromboembolism

2. RATIONALE AND BACKGROUND

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 disease-modifying antirheumatic drugs (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 Janus Kinase (JAK).[16,31] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[17] 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 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. 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.

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 in British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA). This study is designated as a PASS and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

3. STUDY OBJECTIVES AND HYPOTHESES

The objective of this descriptive study is to evaluate the rates of serious infections, malignancy (overall, excluding non-melanoma skin cancer (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 PE (pulmonary embolism)) and other specified outcomes, including fractures, among patients with RA in an existing UK-based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients treated with TNFi therapies to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested because this is a descriptive study.

Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, and MI, VTE, and other event rates, including fractures, 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.

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 endpoint). 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.

4. RESEARCH METHODS

4.1. Study design

This is 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 has the primary aim to study the safety of new therapies for RA during routine post-marketed clinical use.

This study will estimate the incidence rates of safety events of interest among patients starting tofacitinib. Rates will also be estimated among (1) an existing cohort of patients starting originator TNFi (ADA, ETA and INF) since 2010 and (2) an existing historic cohort of patients with active RA who had not started a targeted therapy (recruited between 2002 and 2008) but are on csDMARD.

No hypotheses will be tested.

Following a decision to treat with biologics, patients are recruited by their rheumatologist to participate in the BSRBR-RA and are asked to provide informed written consent, after which their data are extracted from their medical record, including the drug start date, and provided to the BSRBR-RA. The date these data are received by the team in Manchester is the registration date. For the purpose of analyses in this report, all exposure time will be calculated from the registration date or the date of drug start, whichever came later.

4.2. Study population

The active surveillance population includes rheumatoid arthritis patients already enrolled in the register who met the criteria for the cohorts as defined in Section 9.2.1 (in the protocol, Version 6.0) as well as patients with rheumatoid arthritis, newly treated with tofacitinib following EMA approval and UK launch of the product (fully available January 2018) and registered with the BSRBR-RA. In the BSRBR-RA, there are two comparison cohorts readily available which include the csDMARD comparison cohort containing 3600 biologic-naïve patients and the anti-TNF comparison cohort containing 2100 biologic-exposed patients. Some tofacitinib-exposed patients will be newly enrolled in the register, having been recruited to the BSRBR-RA within 6 months of their first dose. Others will already have been enrolled in the BSRBR-RA as prior biologic disease modifying antirheumatic drug (bDMARD) initiators, but will switch to tofacitinib during follow up. Key clinical data at time of switch are requested. For patients enrolled during the 6 month period after initiation, the baseline date will be reported as the drug start date rather than the date of registration. The first post-baseline visit occurs 6 months after tofacitinib initiation, regardless of date of enrolment.

4.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study. The inclusion criteria for eligibility for inclusion in the BSRBR-RA include 1) willingness to give informed consent to participate in the study with access to medical records, 2) aged over 16 years, and 3) consultant RA diagnosis.

Treated with Tofacitinib RA Cohort

- *Eligible for BSRBR-RA.*
- *Initiation of tofacitinib, regardless of prior therapy (within 6 months of register enrolment)*

Treated with bDMARD RA Cohort

- *Eligible for BSRBR-RA.*
- *Initiation of ADA, ETA, or INF as their first bDMARD, regardless of prior therapy, within 6 months of register enrolment*

bDMARD Naïve RA Cohort

- *Eligible for BSRBR-RA*
- *Active RA (guide DAS >4.2 (to ensure comparable disease activity to tofacitinib and bDMARD initiators)*
- *Prevalent use of csDMARD (prevalent use) without bDMARD or tofacitinib*
- *Enrolled in register between 2001-2008.*

4.2.2. Exclusion Criteria

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

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

To be eligible for inclusion in the ***Tofacitinib Exposed Cohort***, patients must be included in BSRBR and initiate tofacitinib. The index date for the tofacitinib cohort is the date of register entry or the date of drug start, whichever came later. Entry will be defined as date of treatment start from 01 May 2017 through 14 September 2025. Patients with prior use of bDMARDs or other therapies (e.g., other JAK inhibitors) during the baseline period will not be excluded. All exposure time will be calculated from the registration date or the date of drug start, whichever came later.

4.2.4. Comparator Cohorts

- To be eligible for the ***bDMARD Exposed Cohort***, patients must be included in BSRBR-RA, initiate ADA, ETA, or INF as their first bDMARD within 6 months of register enrollment. The index date for comparator cohort is the date of register entry or the date of drug start, whichever came later. All exposure time will be calculated from the registration date or the date of drug start, whichever came later.
- To be eligible for the ***bDMARD Naïve Cohort***, patients must be included in BSRBR-RA, enrolled during 2001-2008, have active RA (defined as DAS > 4.2), and prevalent use of csDMARD (patients needed to be receiving at least one csDMARD at registration) without bDMARD or tofacitinib. The index date for comparator cohort is the date of register entry or the date of drug start, whichever came later. All exposure time will be calculated from the registration date or the date of drug start, whichever came later.

4.3. Variables

4.3.1. Exposure Variables

This study will include three cohorts of interest, defined by their treatment for RA. Table 1 includes the medications used to treat RA for each cohort. At baseline, hospitals are asked for details of previous RA therapies. For biologics, drug and start/stop dates are requested. For csDMARDs and steroids, it is only asked if they have ever received it.

Table 1. Classification of Medications for the Treatment of RA by cohort

Tofacitinib	bDMARD	csDMARD
Xeljanz	Adalimumab	Methotrexate
	Etanercept	Azathioprine
	Infliximab	Cyclophosphamide
		Leflunomide
		Cyclosporine

4.3.2. 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](#).

1. Serious infection (overall) and by subtype:
 - Pneumonia (non-opportunistic and opportunistic)
 - Septicaemia (non-opportunistic and opportunistic)
 - Bone/join infection (non-opportunistic and opportunistic)
2. Herpes zoster (including hospitalized and non-hospitalized events). (non-opportunistic and opportunistic)
 - Other serious infection (non-opportunistic and opportunistic); not classified as pneumonia, septicaemia, bone/joint infection, or herpes zoster
 - Tuberculosis (TB)
3. Serious Hepatic Dysfunction/Failure
4. Fractures
5. Malignancies (overall, excluding NMSC)
 - Lymphoma (overall) and independently by subtype:

- Non-Hodgkin lymphoma
 - Hodgkin lymphoma
 - Chronic lymphatic leukemia
 - Myeloma
 - Leukaemia
 - Lung cancer
 - Malignant solid tumours
 - Melanoma
 - Brain neoplasms
 - Glioblastoma
6. NMSC
7. Cardiac disorders (total) and by subtype:
- Myocardial infarction /Acute Coronary Syndrome
 - Serious Congestive Heart failure (new or worsening of condition associated with treatment)
8. MACE (including MI, stroke, and death due to cardiovascular events)
- Other serious cardiac events not classified as MI or heart failure
9. Thromboembolic events (VTE) and its components separately:
- Deep vein thrombosis (DVT)
 - Pulmonary embolism (PE).
10. Hematologic disorders:
- Aplastic Anaemia
 - Pancytopenia
 - Argranulocytosis

- Other dyscrasia (includes other serious dyscrasia for serious haematologic events that are not classes as aplastic anaemia, pancytopenia, or agranulocytosis)
- Serious Neutropenia
- Serious Haemorrhage

11. Disorders of the nervous system:

- Cerebrovascular Accident
- Demyelination
- Peripheral neuropathy
- Other CNS (other serious CNS events that are not classed as central demyelination or peripheral neuropathy)
- Optic Neuritis

12. Progressive multifocal leukoencephalopathy (PML)

13. Gastrointestinal (GI) issues:

- Serious Lower Gastrointestinal Ulcer/Bleed/Perforation

14. Pregnancy Occurrence

15. All-cause Mortality.

16. Hepatitis B Reactivation

17. Serious Infusion/Immunologic Reaction

18. Serious Hypersensitivity Reaction

19. Serious Lupus/Lupus-Like Illness

20. Serious Skin Reaction (e.g., Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis)

Given the age-dependent rate events of interest, analyses will also be conducted in elderly patients aged ≥ 65 years. (See [Section 4.7](#) for additional details).

Rates of these endpoints of interest and their 95% CI will be reported for tofacitinib exposed and comparator cohorts every six months. These endpoints will be defined as described in [Table 2. Safety Endpoint Definitions](#) below.

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
Serious infections (overall)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Pneumonia (non-opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Pneumonia (opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Septicaemia (non-opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Septicaemia (opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Bone or joint infections (non-opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Bone or joint infections (opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Herpes zoster (hospitalized or non-hospitalized) (non-opportunistic)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Herpes zoster (hospitalized) (opportunistic)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Other serious infections (opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Other serious infections (non-opportunistic)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Tuberculosis (TB)	Outcome (primary endpoint)	MedDRA codes as described in Manchester Template
Serious Hepatic Dysfunction/Failure	Outcome (primary endpoint)	MedDRA HLGT 10001708 LLT10020751
Fractures	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
Malignancies (excluding non-melanoma skin cancers)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template SMQ Narrow Malignancy related conditions SMQ Narrow Malignancy related therapeutic and diagnostic procedures SMQ Narrow Malignant or unspecified tumours SMQ Narrow Tumour markers
Lymphoma (overall and independently by subtype)	Outcome (secondary endpoint)	Manchester Template/As described in Appendix 1 of Protocol Version 6.0.
<i>Non-Hodgkin lymphoma</i>	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
<i>Hodgkin lymphoma</i>	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
<i>Chronic lymphatic leukemia</i>	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
Lymphoproliferative malignancy	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Myeloma	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Leukaemia	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Lung cancer	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
Other malignant solid tumours (overall and by subtype)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
<i>Melanoma</i>	Outcome (secondary endpoint)	PT 10025650
<i>Brain neoplasms</i>	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
<i>Glioblastoma</i>	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
NMSC, including basal cell cancer	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
Cardiac disorders (total)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Myocardial infarction / Acute Coronary Syndrome	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0. PT Myocardial infarction 10028596 PT Acute Coronary syndrome 10051592
Serious Congestive Heart Failure (new or worsening)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Major Adverse Cardiovascular Events (MACE), including MI	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
Other cardiac events	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Venous Thromboembolic Events (DVT/PE)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template SMQ Narrow Embolic and thrombotic events, venous
DVT	Outcome (secondary endpoint)	PT 10051055
PE	Outcome (secondary endpoint)	PT 10037377

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
Hematologic Disorders (overall and by subtype)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Aplastic Anemia		MedDRA codes as described in Manchester Template
Pancytopenia	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Argranulocytosis	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Other dyscrasia	OutcomeT (secondary endpoint)	MedDRA codes as described in Manchester Template
Serious Neutropenia	Outcome (secondary endpoint)	MedDRA codes for "Serious "Decrease in Neutrophil Counts and Neutropenia". PT 10029354
Serious Haemorrhage	Outcome (secondary endpoint)	MedDRA codes for "Serious Haemorrhage" PT 10055798
Disorders of the nervous system (overall and by subtype)	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Cerebrovascular Accident	Outcome (secondary endpoint)	MedDRA codes as described in Appendix 1 of PASS Protocol Version 6.0.
Demyelination	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Peripheral neuropathy	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Other CNS disorders (other serious CNS events that are not classes as 'central demyelination' or 'peripheral neuropathy')	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
Optic Neuritis	Outcome (secondary endpoint)	PT 10030942
Progressive multifocal leukoencephalopathy (PML)	Outcome (secondary endpoint)	PT Progressive multifocal

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
		leukoencephalopathy MedDRA PT 10036807
Gastrointestinal (GI) perforations	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template SMQ Narrow Gastrointestinal perforation PT Abscess bacterial PT Abscess rupture PT Appendicectomy PT Appendicitis PT Biliary abscess PT Colitis PT Diverticulitis PT Diverticulum PT Gallbladder abscess PT Liver abscess PT Pancreatic abscess PT Pelvic abscess PT Perihepatic abscess PT Postoperative abscess PT Pyloric abscess PT Rectovaginal septum abscess PT Splenic abscess PT Subdiaphragmatic abscess
Serious lower gastrointestinal ulcer / bleed / perforation		PT 10050953 PT 10061975
Pregnancy Occurrence	Outcome (secondary endpoint)	MedDRA codes as described in Manchester Template
All-cause mortality	Outcome (secondary endpoint)	MedDRA Death PT 10011906.
Interstitial lung disease, pending feasibility	Outcome (secondary endpoint)	SMQ Broad and Narrow Interstitial lung disease LLT 10022611
Hepatitis B Reactivation	Outcome (secondary endpoint)	MedDRA PT 10058827
Serious Infusion/Immunologic Reaction	Outcome (secondary endpoint)	MedDRA PT (Infusion related reaction) 10051792

Table 2. Safety Endpoint Definitions

Variable	Role	Operational definition
Serious Hypersensitivity Reaction	Outcome (secondary endpoint)	MedDRA PT 10020751 HLGT Allergic conditions HLT Allergic conditions NEC HLT Allergies to foods, food additives, drugs and other chemicals HLT Anaphylactic and anaphylactoid responses HLT Angioedemas HLT Atopic disorders HLT Urticarias
Serious Lupus/Lupus-Like Illness	Outcome (secondary endpoint)	MedDRA PT 10042945
Serious Skin Reaction (e.g., Stevens Johnson Syndrome, erythema multiforme, toxic epidermal necrosis)	Outcome (secondary endpoint)	Skin reaction PT10040914, Stevens Johnson syndrome PT 10042033, Erythema multiforme PT 10015218, Epidermal necrosis PT 10059284

*Infection severity is based on judgment of rheumatologist.

Note: Across all 'serious' medical terms, seriousness is determined based on seriousness criteria.

This list may be extended with a reasonable number of additional sub-diagnoses or new health related outcomes as agreed to by BSRBR researchers and Sponsor before the final analysis and safety report.

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 be adjusted for in comparative analysis.

4.3.3. Covariates

The following baseline data (Table 3) were derived from BSRBR information reported by the recruiting clinician (or patient where noted), using a standardized form. Medication History and Comorbidities were identified from the Clinical Baseline Form at registration.

The data captured include, but are not restricted to, the following: disease severity, 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 including NMSC, history of lymphoma), and history of therapeutic procedures.

At baseline, data corresponding to comorbidities is collected by asking whether the patient has “ever” had any comorbidities (listed and other).

Table 3. Definitions of baseline patient characteristics

Variable	Operational definition
Age at start of treatment	Calculated using the date of birth and the date of the start of treatment. Categories: 16-18 19-34 35-44 45-54 55-64 65-74 75+
Year of Diagnosis	Calendar year of diagnosis presented in 5-year groups
RA Disease Duration	Mean (SD) Estimated using the number of years since diagnosis.
Sex	Categories: Male/Female
<i>Ethnicity</i>	Categories when available (data collection began August 2024): Asian/Asian British, Black African/Caribbean/Black British/Black Other, Missing, Mixed/multiple ethnic groups, Other ethnic group, and White.
<i>Previous use of csDMARDs</i>	Categories: Yes/No

Table 3. Definitions of baseline patient characteristics

Variable	Operational definition
<i>Biologically naïve at registration</i>	Categories: Yes/No
<i>Previous use of ADA, ETA, or INF</i>	Categories: Yes/No
<i>Previous use of other biologics or biosimilars</i>	Categories: Yes/No
<i>Previous use of other targeted synthetic (tsDMARDs)</i>	Categories: Yes/No
<i>On steroids at registration</i>	Categories: Yes/No
<i>History of TB</i>	Categories: Yes/No
<i>History of VTE</i>	Categories: Yes/No
<i>History of diabetes mellitus</i>	Categories: Yes/No
<i>History of hypertension</i>	Categories: Yes/No
<i>History of MI</i>	Categories: Yes/No
<i>History of Stroke</i>	Categories: Yes/No
<i>History of malignancy events (incl. NMSC)</i>	Categories: Yes/No
<i>Number of comorbidities (includes: high blood pressure, ischemic heart disease (angina/MI), stroke, epilepsy, asthma, COPD, renal disease, liver disease, demyelination, diabetes and previous cancer.)</i>	Counts
<i>Smoking (current/previous/never)</i>	Categories: current/previous/ never

Table 3. Definitions of baseline patient characteristics

Variable	Operational definition
<i>Height</i>	Centimeters
<i>Weight</i>	Kilograms
<i>BMI</i>	BMI ≥ 30 kg/m ² Categories: Yes/No
<i>Blood pressure (BP)</i>	Systolic/Diastolic
<i>Herpes zoster vaccination (Y/N)</i>	Categories: Yes/No
<i>DAS28 score</i>	Calculated by: 28 counts of swollen and tender joints, ESR in mm/1h, patient global health numeric rating score (NRS) (0-10). Mean (SD)
<i>HAQ</i>	Median (IQR)
<i>EuroQol Five Dimensions Questionnaire (EQ-5D)</i>	Mean (SD)
<i>Global Health VAS (median (IQR)) (range: 0 to 10)</i>	Median (IQR) Range: 0 to 10
<i>28 Tender Joint Count</i>	Mean (SD)
<i>28 Swollen Joint Count</i>	Mean (SD)
<i>C-reactive protein (CRP)</i>	mg/liter
<i>Erythrocyte sedimentation rate (ESR)</i>	mm/1h
<i>ACPA (anti-CCP) positive RA</i>	Categories: Yes/No
<i>Rheumatoid factor positive</i>	Categories: RF+/RF-

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 below:

Table 4. Definitions of VTE Risk Factors

Variable	Role	Data source(s)	Operational definition (ICD-10)
Age at start of follow-up (≥65 years versus <65 years)	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Calculated using the date of birth and the date of the start of treatment.
Previous VTE	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Categories: Yes/No
Ever had major surgery	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	History of Total knee replacement Total hip replacement Total shoulder replacement Total elbow replacement Wrist/hand/ankle/foot surgery Neck surgery At registration.
History of MI at registration	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion	Categories: Yes/No

Table 4. Definitions of VTE Risk Factors

Variable	Role	Data source(s)	Operational definition (ICD-10)
		of the “Clinical Baseline Form”.	
History of heart failure	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Categories: Yes/No
History of malignancy	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Categories: Yes/No
History of diabetes mellitus	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Categories: Yes/No
History of hypertension	Baseline characteristic and potential confounder	Data recorded by the hospital healthcare team via the completion of the “Clinical Baseline Form”.	Categories: Yes/No

To facilitate the evaluation of the safety endpoints of MI and MACE, the following CV risk factors will also be evaluated at baseline:

Table 5. Definitions of CV risk factors

Variable	Operational definition
<i>History of diabetes</i>	Categories: Yes/No
<i>History of renal disease</i>	Categories: Yes/No
<i>History of hypertension</i>	Categories: Yes/No
<i>History of previous MI</i>	Categories: Yes/No
<i>History of angina</i>	Categories: Yes/No

4.4. Data sources

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. For the first 7-8 years the main focus was on the study of the safety profile of the first three TNFi agents (ie, ADA, ETA and INF) as a class and as individual therapies. With the exception of the risk of developing tuberculosis, data within the BSRBR-RA has not demonstrated any clear differences in AE profile between these agents. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.[2] Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections,[3] and malignancies.[4,5] All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

External validity, i.e., generalizability to RA patients who are not enrolled in the register, is maximised by encouraging physicians to enroll each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

The greatest concern in using the BSRBR-RA cohorts is the potential lack of comparability between the newly approved therapy, ie, tofacitinib, and the comparison cohorts in relation to their underlying risk of endpoint development. If there is a significant imbalance between key confounders between the groups then this could reduce the validity of comparisons. The key confounders to be measured at baseline include details of disease severity, including symptom duration, current health assessment questionnaire (HAQ), current significant comorbidities and relevant previous therapies. Analyses undertaken to date comparing the established TNFi cohorts with the csDMARD group have not revealed any serious imbalance that cannot be adjusted for in subsequent analyses.[4]

Baseline

BSRBR is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardized form. In addition, some BSRBR personal and medical information reflect data obtained directly from each patient recruited (eg, on smoking history, alcohol consumption, and work status).

Follow up

BSRBR data are the source of information on anti-rheumatic treatment, updated every 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the DAS 28 is also collected.

BSRBR data include reports from patients contacted every 6 months for the first three years of their follow up period and asked to complete a patient diary which includes data about hospital admissions and new hospital referrals. Data collection instruments are distributed by post to patients and their physicians according to schedule. One attempt is made to follow-up non-responders. Non-responders at one follow up point are (unless further follow up is refused) contacted again at the next follow up point and all follow-up data since the last completed study follow-up is requested. Patients lost to follow up continue to be followed for death and cancer endpoints through the respective registers.

Endpoints

BSRBR data include reports of serious morbidity, either by subject or enrolling physician during regularly scheduled assessments, and the referring physician is immediately contacted by the BSRBR-RA and asked to provide further details, where available. For specific morbidities of interest certain specific details are requested. All serious morbidities reported to BSRBR are coded by a trained nurse using the Medical Dictionary for Regulatory Activities (MedDRA).

BSRBR uses the UK national death and cancer registers allow the “flagging” of individuals such that if they die or are entered in a cancer register, the BSRBR-RA learns of the event and obtain death certificate details or cancer register details. By law, deaths due to natural causes are to be registered within 5 days. However, the lag-time between cancer incidence and registration in the national cancer database takes longer depending on confirmatory

diagnoses, tests, national cancer register requirements and local resources. BSRBR-RA downloads which patients have been flagged for incident cancer or death once per year based on personal identifiers.

4.5. Sample size and power calculations

This active surveillance descriptive study is not intended to test a pre-specified statistical hypothesis therefore no minimum sample size is required. The study enrolment goal is 500 patients in the tofacitinib arm, but success depends largely on use of tofacitinib in UK. Enrolment will not be capped at 500 but continue throughout the study period.

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

Tables 6 and 7 below describe the power to detect a 2-fold difference in event rates between tofacitinib-initiators and bDMARD-initiators assuming the following:

- $\alpha=0.05$;
- 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, 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 6 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 7 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.[3]

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 11100 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.

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	0.99
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 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 12 months of enrolment of tofacitinib-exposed patients in BSRBR, 110 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.

4.6. Missing Data

For baseline tables, no imputation of missing values is performed and a missing category will be added for patients with missing a characteristic (categorical) of interest. For calculations of event rates, missing baseline covariate data are replaced using multiple imputation. For the multivariable Cox proportional hazard regressions, two models will be provided: 1) a complete case analysis and 2) a missing category analysis.

The database forces entry for dates of treatment start and for dates of occurrence of an event, therefore, no special handling or imputation will be needed for missing drug exposure data.

4.7. Statistical methodology and analyses

The study population will comprise all patients with RA enrolled within BSRBR who receive tofacitinib following European Medicines Agency (EMA) approval and UK launch. For contextualization purposes, the study population will also include BSRBR patients treated with bDMARDs and naïve to bDMARDs (treated with csDMARDs).

4.7.1. Index date, Risk Window, and Follow-up

The **index date** was defined as:

1. Tofacitinib cohort: Date of register entry or the first tofacitinib dose taken, whichever came later

2. bDMARD exposed comparator cohort: Date register entry or the date of the first dose taken of either ETA, ADA, or INF, whichever came later
3. bDMARD naïve cohort: date of entry into the BSRBR register

Patients who switched to a subsequent therapy were eligible for enrollment as an initiator of the subsequent therapy, and the initiation date was defined as the date of initiating the subsequent therapy.

Follow-up definitions:

Follow up data in BSRBR-RA were derived from regular follow-up visits. All patients have six-monthly questionnaires completed by the rheumatology team for the first three years of the study and then annual questionnaires for at least two further years.

For bDMARD naïve cohort, follow-up time starts at entry to study and continues until death, the date of last received follow-up form, the cut-off date for the report, or until patient starts a biologic drug. The report can only include patients for whom at least one follow-up form has been returned.

For Tofacitinib cohort and bDMARD exposed comparator cohort, follow-up time will start at index date. The end of follow-up time depends on the analyses listed below:

Within each cohort each patient will be evaluated for safety events of interest while exposed to the index therapy and accrue person-time from the cohort index date until the first occurrence of the event of interest, initiation of biologic (comparator cohort 1), discontinuation of biologic (comparator cohort 2), discontinuation of tofacitinib (tofacitinib-exposed cohort), death, loss to follow up, exit from the registry or after 7 years of follow up. Interim reports will not censor the existing comparison cohorts to match the tofacitinib cohort on index date or duration of follow up. The final report will censor all patients at 7 years. Follow-up will be uniquely determined for each safety endpoint of interest.

For safety events of special interest, detailed queries are sent out to get more information on the events. Reports of death are sent to the study independent of follow-up forms. All information received on serious adverse events (SAEs) will be reviewed by BSRBR trained clinical staff prior to coding. Reports can arise from the hospital team, patients or the national registers. In order for SAEs to be included in analysis, the following information is required: (i) A legible and recognised disorder/signs and symptoms (ii) The date of the event (iii) Which biologic drug the patient was on at the time of the event. Where this information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the serious adverse event. Where a serious adverse event is patient reported, a request for information is always sent to the hospital for validation. Events that do not fall under the definition of an SAE are not subject to such additional validation. The data undergoes regular validation checks both manually and automatically.

For all SAEs, except malignancy or death but including pregnancy, the risk window begins with the start of Tofacitinib treatment and continues for 90-days after the end of therapy, date of last received follow-up form, death or the cut-off date for the report, whichever comes first, even in cases of subsequent switching to another biologic agent during the 90

days following end of therapy. SAEs, which occur outside of this risk window, will not count for purposes of incidence rate estimation.

For the anti-TNF comparison cohort the risk window begins with the start of anti-TNF treatment (at the point of registration), and continues for 90-days after the end of the generic therapy (i.e. patients can switch to a biosimilar of the registered anti-TNF but not between different anti-TNF therapies), date of last received follow-up form, death or the cut-off date for the report, whichever comes first, even in cases of subsequent switching to another biologic agent during the 90-days following end of therapy. SAEs, which occur outside of this risk window, will not count for purposes of incidence rate estimation.

For csDMARD control patients, follow-up time starts at entry to study and continues until death, the date of last received follow-up form, the cut-off date for the report, or until patient starts a biologic drug. The report can only include patients for whom at least one follow-up form has been returned.

(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,
- Date of last received follow-up form,
- Date of death,
- Loss to follow up,
- Exit from the register,
- End of data collection (cut-off date for the report),
- End of treatment* +90 days (even in cases of subsequent switching to another biologic agent during the 90-days following end of therapy), or
- after 7 years of follow up. (Interim reports will not censor the existing comparison cohorts to match the tofacitinib cohort on index date or duration of follow up. The final report will censor all patients at 7 years.)

*End of treatment was defined as the end of treatment date recorded by the treating rheumatologist. The healthcare team at the hospital will be contacted every 6 months for the first 3 years and then annually thereafter, and asked to complete a standard data form covering any change in treatment over the preceding 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. 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. 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 captured.

(2) Analysis for Malignancy, Progressive multifocal leukoencephalopathy (PML), and All-Cause Mortality outcomes were evaluated using two approaches: 1) an 'ever exposed' analysis as per the primary analysis, meaning a patient once exposed is always considered at risk, and 2) 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,
- Date of last received follow-up form,
- Date of death,
- End of data collection

For analyses of risk of malignancy, the analysis assumes an ever-exposed model of risk assessment and therefore, the **risk window** for the Tofacitinib or anti-TNF cohorts includes all person-time in the register from start of therapy and extends until death or the cut-off date for the report, whichever comes first, even in case of subsequent switching to another biologic agent.

With the **ever exposed** (also known as **always at risk**) approach, follow up for each exposure cohort continued after switching to a new drug or discontinuation of treatment. This approach maximized 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 were double counted if a patient indexed to bDMARD switched to tofacitinib and a malignancy occurred subsequent to tofacitinib exposure. That is, the event was assigned to both the bDMARD and the tofacitinib exposure cohorts as were the corresponding PY from the index date to the respective cohorts. For csDMARD control patients, follow-up time starts at entry to study and continues until death, the cut-off date or patient starts biologic drug. 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 PY 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.[4,6-8]

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

- Event of interest,

- Date of last received follow-up form,
 - Date of death,
 - End of data collection,
 - Date of switch.
1. Tofacitinib cohort: switch to another JAK inhibitor, or switch to a non-JAK-inhibitor based advanced systemic therapy. Follow-up time starts from the tofacitinib start date until tofacitinib stop plus 90-day extension.
 2. bDMARD cohort: switch to tofacitinib or other non-biological advanced systemic therapy (JAK inhibitors, non-TNF bDMARDs, certolizumab and golimumab). Follow-up time starts from bDMARD start date until bDMARD stop date plus 90-day extension.
 3. bDMARD naïve cohort: switch to a non-csDMARD therapy (all b/tsDMARDs for RA). Follow-up time will end when patient starts a biologic drug, so they would not have a 90-day extension.

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).

The schematic in [Table 1](#) 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.

Table 1. Schematic of Examples of Patterns of Event and Treatment Patterns Illustrating Contributions to Rate Calculation in the Once Exposed Always at Risk versus Censoring at Switch

	Once-exposed always at risk		Censoring at Switch	
<i>Treatment/Event pattern</i>	<i>bDMARD rate contribution (events/person years)</i>	<i>Tofacitinib rate contribution (events/person years)</i>	<i>bDMARD rate contribution (events/person years)</i>	<i>Tofacitinib rate contribution (events/person years)</i>
* ~ ~ ~ ^ - - 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 ^b
^ - - - ~ ~ ~ X	0/0 ^c	1/7	0/0 ^c	0/4

- Patients continue to be followed after index exposure discontinuation if they do not initiate another systemic therapy in a different class*
- Patients who switched back to prior bDMARD after tofacitinib treatment will not attribute follow-up time in the prior bDMARD treatment duration.*
- Patients are ineligible for bDMARD cohort index after tofacitinib index*

Please note: In the **interim reports**, the existing comparison cohorts were not censored to match the tofacitinib cohort. However, the **final report** will censor all patients at 7 years after the first tofacitinib exposed patient enters the register. Follow-up was uniquely determined for each safety endpoint of interest.

4.7.2. Registered patients versus switched patients

The term “registered” patient refers to all patients who register with the BSRBR-RA and upon starting their biologic/biosimilar/other targeted therapy and complete a clinical and patient baseline form. If a patient switched from their registered drug to a new biologic/biosimilar/other targeted therapy, they were usually encouraged to re-register prompting the completion of a new baseline form to identify patient and disease characteristics at the start of their new therapy. These patients would also count as “registered” patients.

However, in some cases patients will switch biologic/biosimilar/other targeted therapy and not re-register in the study. These patients are referred to as “switchers”. This is because, whilst BSRBR continues to follow-up them for safety events, BSRBR does not receive new baseline forms with the updated patient and disease characteristics at the point of starting their new therapy. So, for example, if a patient registered in Anti-TNF and switched to Tofacitinib treatment without re-registration, “age” and “disease duration” can be re-calculated for Tofacitinib treatment, “gender” will be carried forward. Other variables will be coded as missing and will be handled as mentioned in [Section 4.6 Missing Data](#).

Baseline characteristics are usually only reported for the “registered” patients. For re-registering/switching patients on a biologic, biosimilar other new targeted therapy who are already participating in the registry, there is a simplified baseline information form which captures a subset of the baseline data most likely to change over time.

4.7.3. Primary analyses

4.7.3.1. Statistical Methods

Descriptive statistics for each of the cohorts ([Appendix A Tables 1-4](#)) will be presented for all baseline characteristics (see [Table 3 Section 4.3.3](#) for baseline covariates). The semi-annual (i.e. interim reports) analyses will consist of comparisons in baseline status between the individuals in the different cohorts. All serious and non-serious safety events of interest will be provided. The initial analyses will consist of descriptive comparisons of baseline status and crude event rates for safety endpoints of interest (see [Section 4.3.2](#) for list of safety endpoints) between the different cohorts.

The final analysis of endpoints will provide the rates of events overall ([Appendix A Table 5](#)), and in subgroups defined by baseline characteristics, including age ≥ 65 ([Appendix A Table 7](#)) and < 65 ([Appendix A Table 8](#)) and sex (male/female) ([Appendix A Table 4](#)).

Crude incidence rates and the number of events will be tabulated for each cohort and safety endpoint of interest, and age/sex-standardized rates will be 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 (CI) follows the methods described in the Rothman *et al.* textbook entitled Modern Epidemiology (p.242)[9]; 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.

4.7.3.2. Statistical Analyses

Crude incidence rates and number of events will be presented by age subgroups (age < 65 vs. ≥ 65 years at cohort entry) ([Appendix A Tables 7-8](#)), and by absence (versus presence) of prior non-tofacitinib JAK inhibitors ([Appendix A Tables 9-10](#)) for all outcomes and all cohorts.

4.7.4. Secondary analyses

4.7.4.1. Statistical Methods

Pending feasibility, adjusted hazard ratios will be estimated with Cox proportional hazards regression using time from index as the time scale ([Appendix A Tables 6 and 6a](#)). The comparisons to be made will be: tofacitinib vs. bDMARD-exposed, and tofacitinib vs. csDMARD-exposed. Models are adjusted using deciles of a propensity score which is calculated using the following variables: 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 at baseline, interactions, variables such as “Year of registration” and “Number of previous DMARDs” can often cause difficulty in calculating propensity score and are usually excluded from calculation of propensity score.

Covariates will be parameterized as described in [Table 3-Table 5 Section 4.3.3](#). Comparison of time to first event will be included in Cox proportional hazards regressions only when a minimum of 10 events across tofacitinib and csDMARDs comparator cohorts has been observed with at least five events in each cohort; When cohort outcome combinations have less than 5 events, only numbers, crude and age/sex-adjusted incidence rates will be estimated.

4.7.4.2. Statistical Analyses

Crude rates will also be estimated (using the primary approach for follow-up) for:

- (1) the outcome of VTE stratified by type of event (DVT and PE) and binary indicator (≥ 1 VTE risk factor versus no VTE risk factor) ([Appendix A Table 11](#))
- (2) the outcomes of CV outcomes stratified by type of event (e.g. MI, MACE, serious congestive heart failure) ([Appendix A Table 13](#))
- (3) the outcome of MACE and MI stratified by binary indicator (≥ 1 CV risk factor versus no CV risk factor) ([Appendix A Table 14](#))
- (4) For lymphoma, incidence rates will be stratified by lymphoma subtypes; not limited but including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphatic leukemia ([Appendix A Table 15](#))

Stata version 14.0 will be used for all analyses.

4.7.5. Sensitivity analyses

4.7.5.1. bDMARD comparator cohort never exposed to tofacitinib or other non-biologic advanced therapies

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 (e.g. baricitinib (Olumiant) and upadacitinib (Rinvoq) and compare the characteristics of those bDMARD patients ever and never exposed to tofacitinib or other non-biologic advanced therapies. These sensitivity analysis results will be presented as summary statistics of those with and without previous tofacitinib use or other non-biologic advanced therapies.

4.7.5.2. MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events

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.

4.7.5.3. Potential confounding by non-tofacitinib JAK inhibitors

To evaluate and account for potential confounding by prior non-tofacitinib JAK inhibitors, a sensitivity analyses with stratified results by the absence versus presence of prior non-tofacitinib JAK inhibitors will be conducted. ([Appendix A Tables 9-10](#))

4.7.6. Additional analyses

Any safety information deemed to be reportable as defined in the protocol will be described.

Given the age-dependent rate events of interest, analysis will be stratified by older adult patients aged ≥ 65 years versus patients under the age of 65. ([Appendix A Tables 7-8](#))

In addition, overall event rates, *the final analysis of endpoints will provide the rates of events 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 (if feasible), MI, heart failure, malignancy, diabetes, hypertension* ([Appendix A Table 11](#)).

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. CV risk factors (evaluated at baseline) are defined as: *age (patients ≥ 65 years versus < 65 years), history of diabetes, history of hypertension, history of previous MI, history of stable angina pectoris* ([Appendix A Table 14](#)).

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 pregnancies.

4.7.7. Post-hoc analyses

Not applicable.

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6. APPENDICES

6.1. Appendix A: Table shells

Table 1: Baseline demographic details of patients initiating Tofacitinib and registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients.

		Tofacitinib Cohort Patients	(a) bDMARD Biologic- naïve*	(b) bDMARD Biologic- experienced*
Cumulative number of registrations				
Cumulative number by gender	Male			
	Female			
Cumulative number by age at registration	16-18			
	19-34			
	35-44			
	45-54			
	55-64			
	65-74			
	75 +			

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Table 2: Baseline characteristics of patients initiating Tofacitinib and registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients.

		Tofacitinib Cohort Patients [N =]			(a) bDMARD Biologic- naïve* [N =]			(b) bDMARD Biologic- experience d* [N =]		
		N	Me an	S D	N	Me an	S D	N	Me an	S D
Gender	Male									
	Female									
Age in Years	Male									
	Female									
	Total									
Ethnicity	White									
	Black African/Caribbea n/Black British/Black Other									
	Asian/Asian British									
	Mixed/multiple ethnic groups									
	Other ethnic group									
Height										
Weight										
BMI ≥30 kg/m2	Yes									
	No									
Blood pressure										
Smoking status	Current									
	Previous									
	Never									
Herpes Zoster vaccination	Yes									
	No									
Years since diagnosis	Male									
	Female									
	Total									
Rheumatoid factor status	Positive									
	Negative									
ACPA (anti-CCP) positive RA	Yes									
	No									
HAQ	Male									

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Data for history of "Heart failure" and "Venous thromboembolism" has been collected since February 2021.

Data for "Knee or hip replacement" and "Joint surgery " is available until August 2024.

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Table 3: Total exposure included in the analysis for patients initiating Tofacitinib and registered in the bDMARD cohort:

(a) biologic-naïve patients and (b) biologic experienced patients.

		Tofacitinib Cohort Patients [N =]		(a) bDMARD Biologic-naïve* [N =]		(b) bDMARD Biologic- experienced* [N =]	
Safety Endpoint		N	Person- years	N	Person- years	N	Person-years
All SAEs except malignancy or death but including pregnancy	Male						
	Female						
	Total						
	<i>Min</i>						
	<i>Mean</i>						
	<i>Median</i>						
	<i>Max[#]</i>						
Death	Male						
	Female						
	Total						
	<i>Min</i>						
	<i>Mean</i>						
	<i>Median</i>						
	<i>Max[#]</i>						
Malignancy	Male						
	Female						
	Total						
	<i>Min</i>						
	<i>Mean</i>						
	<i>Median</i>						
	<i>Max[#]</i>						

Table 4: Baseline characteristics of patients in the bDMARD cohort: (a) never exposed to non-biologics and (b) exposed to biologics (biologic experienced).

		(a) biologic-naïve [N =]			(b) non-biologic- experienced [N =]		
		N	Mean	SD	N	Mean	SD
Gender	Male						
	Female						
Age in Years	Total						
Ethnicity	White						
	Black African/Caribbean/Black British/Black Other						
	Asian/Asian British						
	Mixed/multiple ethnic groups						
	Other ethnic group						
Height							
Weight							
BMI ≥30 kg/m2	Yes						
	No						
Blood pressure							
Smoking status	Current						
	Previous						
	Never						
Herpes Zoster vaccination	Yes						
	No						
Years since diagnosis	Total						
Rheumatoid factor status	Positive						
	Negative						
ACPA (anti-CCP) positive RA	Yes						
	No						

HAQ	Total						
DAS28	Total						
Tender Joint Count	Total						
Swollen Joint Count	Total						
ESR	Total						
CRP	Total						
Global Health VAS	Total						
EuroQol Five Dimensions Questionnaire (EQ-5D)	Total						
Previous use of csDMARDs	Yes						
	No						
Biologically naïve at registration	Yes						
	No						
Previous use of ADA, ETA, or INF	Yes						
	No						
Previous use of other biologics or biosimilars	Yes						
	No						
Previous use of other targeted synthetic (tsDMARDs)	Yes						
	No						
On steroids at registration	Yes						
	No						
History of TB	Yes						
	No						
History of VTE	Yes						
	No						
History of diabetes mellitus	Yes						
	No						
History of hypertension	Yes						
	No						
History of angina	Yes						
	No						

History of MI	Yes						
	No						
History of heart failure	Yes						
	No						
History of stroke	Yes						
	No						
History of malignancy	Yes						
	No						
History of liver disease	Yes						
	No						
History of renal disease	Yes						
	No						
History of asthma	Yes						
	No						
History of chronic bronchitis/emphysema (COPD)	Yes						
	No						
History of epilepsy	Yes						
	No						
History of demyelination	Yes						
	No						
History of depression	Yes						
	No						
History of peptic ulcer	Yes						
	No						
History of hyperthyroidism	Yes						
	No						
History of Knee or hip replacement	Yes						
	No						
History of Shoulder/Elbow/Wrist/Hand/Ankle/Foot/Neck joint surgery	Yes						

	No						
Number of comorbidities							
Charlson Comorbidity Index							

1 Comparing the characteristics of bDMARD comparator cohort patients who were never exposed to JAK inhibitors (tofacitinib (Xeljanz), baricitinib (Olmiant), upadacitinib (Rinvoq) or filgotinib (Juseleca)) to bDMARD patients ever exposed to JAK inhibitors.

Table 5: Number of first events and rates of first safety endpoint events in patients initiating Tofacitinib and registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients; stratified by male and female patients [rates are per 1000 person years]

Safety Endpoint	Tofacitinib Cohort Patients [N =]						bDMARD Biologic-naïve* [N =]						bDMARD Biologic-naïve* [N =]					
	Males		Females		Total		Males		Females		Total		Males		Females		Total	
	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)	Event s	Rat e (95 % CI)
Total serious infection																		
Pneumonia																		
Non-opportunistic																		
Opportunistic																		
Septicaemia																		
Non-opportunistic																		
Opportunistic																		
Bone/Joint infection																		
Non-opportunistic																		
Opportunistic																		
Herpes Zoster																		
Non-opportunistic																		
Opportunistic																		
Other serious infection																		

Non-opportunistic																		
Opportunistic																		
TB																		
Serious Hepatic Dysfunction/Failure																		
Fractures																		
Total malignant events (overall, excluding NMSC)																		
Lymphoproliferative malignancy																		
Lymphoma (NHL, Hodgkins)																		
NHL																		
Hodgkin																		
CLL																		
Myeloma																		
Leukaemia																		
Non-melanoma skin cancer																		
Lung Cancer																		
Solid tumors																		
Melanoma																		
Brain neoplasms																		

Tofacitinib

A3921312 NON-INTERVENTIONAL STUDY STATISTICAL ANALYSIS PLAN FOR SECONDARY DATA COLLECTION STUDY

Version 1.0, 05 December 2025

<i>Of which, Glioblastoma</i>																		
Total cardiac disorders																		
Serious CHF (new or worsening)																		
Myocardial infarction/Acute Coronary Syndrome																		
MACE (including MI)																		
Other cardiac events																		
Venous Thromboembolic Events																		
DVT																		
PE																		
Total haematologic events																		
Aplastic anaemia																		
Pancytopenia																		
Agranulocytosis																		
Other dyscrasia																		
Serious Neutropenia																		
Serious haemorrhage																		
CNS Disorders																		

Tofacitinib

A3921312 NON-INTERVENTIONAL STUDY STATISTICAL ANALYSIS PLAN FOR SECONDARY DATA COLLECTION STUDY

Version 1.0, 05 December 2025

Cerebrovascular accident																		
Central Demyelination																		
Peripheral neuropathy																		
Other CNS																		
Optic Neuritis																		
Progressive Multifocal Leukoencephalopath y (PML)																		
GI perforation																		
Serious Lower GI Ulcer/Bleed/Perforati on																		
Pregnancy Occurrence (female only)																		
All-cause Mortality																		
Hepatitis B Reactivation																		
Serious Infusion/Immunologi c Reaction																		
Serious Hypersensitivity Reaction																		

Serious Lupus/Lupus-Like Illness																		
Serious Skin Reaction																		

Data cut at 7 years after start of therapy.

Table 6: Number of first events and rates of first events in all Tofacitinib and csDMARD treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs csDMARD treatment [rates per 1000 person years]

Serious Adverse Events		csDMARD Patients [N =]		All Tofacitinib Patients [N =]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio Following Sensitivity Analysis ¹ (95% CI)
	N	Rate/1000 pyrs (95% CI)	N	Rate/1000 pyrs (95% CI)			
Total serious infection							
Pneumonia							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Septicaemia							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Bone/Joint infection							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Herpes Zoster							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Other serious infection							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
TB							NA
Serious Hepatic Dysfunction/Failure							NA
Fractures							NA

Total malignant events (overall, excluding NMSC)							NA
Lymphoproliferative malignancy							NA
Lymphoma (overall)							NA
NHL							NA
Hodgkin							NA
CLL							NA
<i>Myeloma</i>							NA
<i>Leukaemia</i>							NA
Non-melanoma skin cancer							NA
Solid tumours							NA
Lung cancer							NA
Melanoma							NA
<i>Brain neoplasms</i>							NA
<i>Of which, Glioblastoma</i>							NA
Total cardiac disorders							NA
CHF (new or worsening)							NA
Myocardial infarction/Acute Coronary Syndrome							
MACE (including MI)							
Other cardiac events							NA
Venous Thrombotic Event (VTE)							
DVT							
PE							
Total haematologic events							NA

Aplastic anaemia							NA
Pancytopenia							NA
Agranulocytosis							NA
Serious Neutropenia							NA
Serious haemorrhage							NA
Other dyscrasia							NA
CNS Disorders							NA
Cerebrovascular accident							NA
Central Demyelination							NA
Peripheral neuropathy							NA
Optic Neuritis							NA
Other CNS							NA
Progressive multifocal leukoencephalopathy (PML)							
GI perforation							
Serious Lower GI Ulcer/Bleed/Perforation							
Pregnancy Occurrence (female only)							NA
All-cause mortality							NA
Hepatitis B Reactivation							NA
Serious Infusion/Immunologic Reaction							NA
Serious Hypersensitivity Reaction							NA
Serious Lupus/Lupus-Like Illness							NA

Serious Skin Reaction						NA
-----------------------	--	--	--	--	--	----

*Data cut at 7 years after start of therapy. *p < 0.05*

¹ Following 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). Note: Number of first events and rates of first events may also change following this sensitivity analysis.

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Table 6a: Number of first events and rates of first events in all Tofacitinib and anti-TNF treated patients, including unadjusted and adjusted hazard ratios for Tofacitinib treatment vs biologic experienced patients [rates per 1000 person years]

Serious Adverse Events		Anti-TNF Patients [N =]		All Tofacitinib Patients [N =]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio Following Sensitivity Analysis ¹ (95% CI)
	N	Rate/1000 pyrs (95% CI)	N	Rate/1000 pyrs (95% CI)			
Total serious infection							
Pneumonia							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Septicaemia							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Bone/Joint infection							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Herpes Zoster							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
Other serious infection							
<i>Non-opportunistic</i>							
<i>Opportunistic</i>							
TB							NA
Serious Hepatic Dysfunction/Failure							NA
Fractures							NA

Total malignant events (overall, excluding NMSC)							NA
Lymphoproliferative malignancy							NA
Lymphoma (NHL, Hodgkins)							NA
NHL							NA
Hodgkin							NA
CLL							NA
<i>Myeloma</i>							NA
<i>Leukaemia</i>							NA
Non-melanoma skin cancer							NA
Solid tumours							NA
Lung cancer							NA
Melanoma							NA
<i>Brain neoplasms</i>							NA
<i>Of which, Glioblastoma</i>							NA
Total cardiac disorders							NA
CHF (new or worsening)							NA
Myocardial infarction/Acute Coronary Syndrome							
MACE (including MI)							
Other cardiac events							NA
Venous Thrombotic Event (VTE)							
DVT							
PE							

Total haematologic events							NA
Aplastic anaemia							NA
Pancytopenia							NA
Agranulocytosis							NA
Serious Neutropenia							NA
Serious haemorrhage							NA
Other dyscrasia							NA
CNS Disorders							NA
Cerebrovascular accident							NA
Central Demyelination							NA
Peripheral neuropathy							NA
Optic Neuritis							NA
Other CNS							NA
Progressive multifocal leukoencephalopathy (PML)							
GI perforation							
Serious Lower Gastrointestinal Ulcer/Bleed/Perforation							
Pregnancy Occurrence (female only)							NA
All-cause Mortality							NA
Hepatitis B Reactivation							NA
Serious Infusion/Immunologic Reaction							NA
Serious Hypersensitivity Reaction							NA

Serious Lupus/Lupus-Like Illness							NA
Serious skin Reaction							NA

*Data cut at 7 years after start of therapy. *p < 0.05*

1 Following 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). Note: Number of first events and rates of first events may also change following this sensitivity analysis.

Table 7: Number of first events and rates of first safety endpoint events in patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, among patients ≥65.

Serious Adverse Events		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Total serious infection						
Pneumonia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Septicaemia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Bone/Joint infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Herpes Zoster						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Other serious infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
TB						
Serious Hepatic Dysfunction/Failure						
Fractures						
Total malignant events (overall, excluding NMSC)						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						

NHL						
Hodgkin						
Myeloma						
Leukaemia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
Melanoma						
Brain neoplasms						
Of which, Glioblastoma						
Total cardiac disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						
Venous Thromboembolic Events						
DVT						
PE						
Total haematologic events						
Aplastic anaemia						
Pancytopenia						
Agranulocytosis						
Other dyscrasia						
Serious Neutropenia						
Serious haemorrhage						
CNS Disorders						
Cerebrovascular accident						
Central Demyelination						

Peripheral neuropathy						
Other CNS						
Optic Neuritis						
Progressive Multifocal Leukoencephalopathy (PML)						
GI perforation						
Serious Lower Gastrointestinal Ulcer/Bleed/Perforation						
Pregnancy Occurrence (female only)						
All-cause Mortality						
Hepatitis B Reactivation						
Serious Infusion/Immunologic Reaction						
Serious Hypersensitivity Reaction						
Serious Lupus/Lupus-Like Illness						
Serious Skin Reaction						

Table 8: Number of first events and rates of first safety endpoints in patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, among patients <65.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Total serious infection						
Pneumonia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Septicaemia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Bone/Joint infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Herpes Zoster						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Other serious infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
TB						
Serious Hepatic Dysfunction/Failure						
Fractures						
Total malignant events (overall, excluding NMSC)						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						

NHL						
Hodgkin						
Myeloma						
Leukaemia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
Melanoma						
Brain neoplasms						
Of which, Glioblastoma						
Total cardiac disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						
Venous Thromboembolic Events						
DVT						
PE						
Total haematologic events						
Aplastic anaemia						
Pancytopenia						
Agranulocytosis						
Other dyscrasia						
Serious Neutropenia						
Serious haemorrhage						
CNS Disorders						
Cerebrovascular accident						

Central Demyelination						
Peripheral neuropathy						
Other CNS						
Optic Neuritis						
Progressive Multifocal Leukoencephalopathy (PML)						
GI perforation						
Serious Lower Gastrointestinal Ulcer/Bleed/Perforation						
Pregnancy Occurrence (female only)						
All-cause Mortality						
Hepatitis B Reactivation						
Serious Infusion/Immunologic Reaction						
Serious Hypersensitivity Reaction						
Serious Lupus/Lupus- Like Illness						
Serious Skin Reaction						

Table 9: Number of first events and rates of first safety endpoint events in patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, among patients with no prior non-tofacitinib JAK inhibitors.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Total serious infection						
Pneumonia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Septicaemia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Bone/Joint infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Herpes Zoster						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Other serious infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
TB						
Serious Hepatic Dysfunction/Failure						
Fractures						
Total malignant events (overall, excluding NMSC)						
Lymphoproliferative malignancy						

Lymphoma (NHL, Hodgkins)						
<i>NHL</i>						
<i>Hodgkin</i>						
Myeloma						
Leukaemia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
<i>Melanoma</i>						
<i>Brain neoplasms</i>						
<i>Of which, Glioblastoma</i>						
Total cardiac disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						
Venous Thromboembolic Events						
DVT						
PE						
Total haematologic events						
Aplastic anaemia						
Pancytopenia						
Agranulocytosis						
Other dyscrasia						
Serious Neutropenia						
Serious haemorrhage						
CNS Disorders						
Cerebrovascular accident						

Central Demyelination						
Peripheral neuropathy						
Other CNS						
Optic Neuritis						
Progressive Multifocal Leukoencephalopathy (PML)						
GI perforation						
Serious Lower Gastrointestinal Ulcer/Bleed/Perforation						
Pregnancy Occurrence (female only)						
All-cause Mortality						
Hepatitis B Reactivation						
Serious Infusion/Immunologic Reaction						
Serious Hypersensitivity Reaction						
Serious Lupus/Lupus-Like Illness						
Serious Skin Reaction						

Table 10: Number of first events and rates of first safety endpoint in patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, among patients with at least one non-tofacitinib JAK inhibitors.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Total serious infection						
Pneumonia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Septicaemia						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Bone/Joint infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Herpes Zoster						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
Other serious infection						
<i>Non-opportunistic</i>						
<i>Opportunistic</i>						
TB						
Serious Hepatic Dysfunction/Failure						
Fractures						
Total malignant events						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						

NHL						
Hodgkin						
Myeloma						
Leukaemia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
Melanoma						
Brain neoplasms						
Of which, Glioblastoma						
Total cardiac disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						
Venous Thromboembolic Events						
DVT						
PE						
Total haematologic events						
Aplastic anaemia						
Pancytopenia						
Agranulocytosis						
Other dyscrasia						
Serious Neutropenia						
Serious haemorrhage						
CNS Disorders						
Cerebrovascular accident						
Central Demyelination						

Peripheral neuropathy						
Other CNS						
Optic Neuritis						
Progressive Multifocal Leukoencephalopathy (PML)						
GI perforation						
Serious Lower Gastrointestinal Ulcer/Bleed/Perforation						
Pregnancy Occurrence (female only)						
All-cause Mortality						
Hepatitis B Reactivation						
Serious Infusion/Immunologic Reaction						
Serious Hypersensitivity Reaction						
Serious Lupus/Lupus-Like Illness						
Serious Skin Reaction						

Table 11: Incidence rates of VTE events among patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by type of VTE event risk factors and by indicator (≥1 VTE risk factor versus no VTE risk factor).

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
No VTE Risk Factor						
VTE						
DVT						
PE						
At Least 1 VTE Risk Factor						
VTE						
DVT						
PE						

Table 12: Incidence rates of VTE events among patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Prior 31 January 2020						
VTE						
DVT						
PE						
After 31 January 2020						
VTE						
DVT						
PE						

Table 13: Incidence rates of CV events among patients initiating Tofacitinib to patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by type of CV event.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic-experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Total Cardiac Disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						

Table 14: Incidence rates of CV events among patients initiating Tofacitinib to patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by indicator of CV risk factors (≥1 CV risk factor versus no CV risk factor).

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic-experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
No CV Risk Factor						
Total Cardiac Disorders						
Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						
At Least 1 CV Risk Factor						
Total Cardiac Disorders						

Serious CHF (new or worsening)						
Myocardial infarction/Acute Coronary Syndrome						
MACE (including MI)						
Other cardiac events						

Table 15: Incidence rates of lymphoma among patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by lymphoma subtypes.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic-experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Prior 31 January 2020						
Lymphoma subtypes						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						
NHL						
Hodgkin						
CLL						

Table 16: Number of first and incidence rates of first malignancy event in patients initiating Tofacitinib and patients registered in the bDMARD cohort: (a) biologic-naïve patients and (b) biologic experienced patients, stratified by time periods defined by the changes in the SmPC for tofacitinib use.

Safety Endpoints		Tofacitinib Cohort Patients [N =]		bDMARD Biologic-naïve* [N =]		bDMARD Biologic- experienced* [N =]
	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)	Events	Rate/1000 pyrs (95% CI)
Prior 31 January 2020						
All malignant endpoints						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						
NHL						
Hodgkin						
CLL						
Myeloma						
Leukamia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
Melanoma						
Brain neoplasms						
Of which, Glioblastoma						
After 31 January 2020						
All malignant endpoints						
Lymphoproliferative malignancy						
Lymphoma (NHL, Hodgkins)						
NHL						
Hodgkin						
CLL						

Myeloma						
Leukamia						
Non-melanoma skin cancer						
Lung Cancer						
Solid tumors						
<i>Brain neoplasms</i>						
<i>Of which, Glioblastoma</i>						

6.2. Appendix B: Additional information

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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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Annex 1. List of stand-alone documents

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

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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

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

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 BSRBRR 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)

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 (BSRBRA)
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 Rheumatoid 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,

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.

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

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4.6.2. Main Statistical Methods

A meta-analysis was planned to be conducted using an inverse-variance method² 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.

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.



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.

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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.

- 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

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,

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.



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 Estimates⁶									
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 Estimates⁶									
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 Estimates⁶									
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).



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 Estimates⁶									
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 Estimates⁶									
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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