NON-INTERVENTIONAL FINAL STUDY REPORT ABSTRACT

Title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

Date: 24-JULY-2026

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

Rationale and background: Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome. Tofacitinib was approved in the European Union (EU) in March 2017 at a dose of 5 mg administered twice daily (BID) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have responded inadequately to, or who are intolerant to, one or more disease modifying antirheumatic drugs (DMARDs). To enable assessment of adverse 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 prospective data embedded within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika Therapie (RABBIT).

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

Research question and objectives:
This study aims to examine the rates of safety events of interest in RA patients treated with tofacitinib in relation to those treated with biologic DMARDs (bDMARDs) and non-biologic DMARDs (nbDMARDs). The objective of this study is to evaluate the rates of serious infections, malignancy, cardiovascular (CV) events, and other specified outcomes among patients with RA in a Germany based register in the three cohorts specified above.

This final study report summarizes patient characteristics and (1) evaluates and compares incidence rates (IR) of pre-defined outcomes in patients with RA exposed to tofacitinib (main cohort), bDMARDs (bDMARD cohort), or b/tsDMARD-naive conventional synthetic DMARDs (nbDMARD cohort) and (2) estimates hazard ratios (HR) of pre-defined outcomes in patients with RA who have been treated with tofacitinib vs. bDMARDs or nbDMARDs. Pre-defined outcomes include serious infections, malignancy (overall, excluding non-melanoma skin cancer (NMSC)), subtypes of lymphoma, lung cancer, CV events, Major Adverse

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Cardiovascular Events (MACE), myocardial infarction (MI), venous thromboembolisms and other safety events of interest, including fractures.

Study design: This is an active surveillance study using data within the existing German register Rheumatoide Arthritis: Beobachtung der Biologika Therapie (RABBIT), an ongoing disease registry started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post marketed clinical use. RABBIT is a long-term observational cohort, and patients can have up to 10 years of observation.

Setting: The German Biologics Register RABBIT has been active since May 2001 under the auspices of the "Kompetenznetz entzündlich rheumatische Systemerkrankungen" ("Competence Network Rheumatology"). Participating patients provide informed consent, have a diagnosis of RA according to American College of Rheumatology (ACR) criteria, have onset of RA at age 16 or older, and have initiated an approved therapy for the treatment of RA. For this final report, only treatments initiated after 01-MAY-2017 were included, since this is the first date that patients initiating tofacitinib treatment could be enrolled in RABBIT. This report contains data through 30-JUNE-2025, to allow for the possibility of at least one follow-up visit.

Subjects and study size, including dropouts: Treatment episodes initiated in one of the three cohorts between 01-MAY-2017 and 31-DEC-2024 were analyzed. For the tofacitinib and the bDMARD cohorts, episodes were only included if there was no exposure to the specific active substance 365 days prior to prescription of this drug.

Variables and data sources: The study variables include baseline patient characteristics (i.e., clinical and demographic characteristics, baseline disease activity, comorbidities and current and past therapies) and the following safety events of interest: serious infections excluding tuberculosis (TB) (overall and by subtype), TB, herpes zoster (HZ), fractures, cardiac disorders (overall and by subtype), hematologic disorders (overall and by subtype), disorders of the nervous system (overall and by subtype), progressive multifocal leukoencephalopathy (PML), allergic conditions and hypersensitivity, hepatic failure, gastrointestinal (GI) perforations (overall and by subtype), pregnancy, embolic and thrombotic events, venous or vessel type unspecified (overall and by subtype), operations and hospitalizations (overall and by type), other serious diagnoses, symptoms, and syndromes, NMSC, malignancies (overall, excluding NMSC), lung cancer, all-cause mortality, leukemia (excl. B-cell chronic lymphocytic leukemia), other haematopoietic neoplasms (malignant and benign), solid malignancies (overall), glioblastoma, benign neoplasms, unspecified neoplasms and precanceroses, metastases, cancer related and morbidities and associated syndromes, interstitial lung disease. RABBIT is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardized form. All safety events occurring during the observation are regularly reported from the rheumatologist and captured in the register.

Results: A total of 13,905 episodes from 12,083 patients with RA were included in the analyses, there were 1,235 episodes based on 1,227 patients for tofacitinib, 9,087 episodes based on 7,747 patients for the bDMARD cohort, and 3,583 episodes based on 3,109 patients for the nbDMARD cohort. At index date (i.e., time of initiation of cohort defining drug), the median age was 59.9 years in the tofacitinib cohort, 60.4 years in the bDMARD cohort and 60.3 years in the nbDMARD cohort. Proportions of episodes of females were

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77.1% in the tofacitinib cohort, 73.5% in the bDMARD cohort and 71.3% in the nbDMARD cohort. Several differences between the cohorts were noted at index date, including the lower proportions of b/tsDMARD naive treatment and combination therapy with nbDMARD use among the tofacitinib cohort relative to the bDMARD cohort (26% and 41% in the tofacitinib cohort compared to 45% and 52% in the bDMARD cohort, respectively). Patients presented with longer RA disease duration, higher RA disease activity and lower percentage of full physical function in the tofacitinib cohort relative to the patients in the comparator cohorts (bDMARDs and nbDMARDs). The following observations were made:

- Whereas in the tofacitinib cohort, the vast majority (96%) of treatment initiations occurred prior to 30-JUNE-2021, in the bDMARD cohort, only 63% of treatment initiations occurred before 30-JUNE-2021, while 37 % of treatment initiations occurred after that date. This indicates that after the June 2021 signal procedure, channeling of patients from tofacitinib to other treatment options took place.

- For all of the investigated outcomes with at least 5 events in the tofacitinib cohort, crude and age/sex-standardized IRs were overall highest in the tofacitinib cohort, except for coronary artery disease, disorders of the peripheral nervous system, psychiatric disorders, GI perforations, and bone and joint surgery and other joint therapeutic procedures.

- For the fully adjusted main Cox regression models, statistically significantly increased hazards for the tofacitinib cohort compared to the bDMARD cohort were observed for HZ (HR 2.38; 95% CI: 1.65 – 3.43) and MACE (HR 1.78; 95% CI: 1.04 – 3.06). There was a hazard increase not reaching statistical significance when comparing tofacitinib vs. bDMARDs for cardiac disorders (HR 1.45; 95% CI: 0.99 – 2.12), MI (HR 1.97; 95% CI: 0.98 – 3.96) and stroke (HR 1.93; 95% CI: 0.98 – 3.81). When comparing the tofacitinib cohort to the nbDMARD cohort, statistically significant differences were seen for HZ (HR 5.79; 95% CI: 2.75 – 12.18), fractures (HR 2.19; 95% CI: 1.27 – 3.77), cardiac disorders (HR 2.53; 95% CI: 1.29 – 4.96) and other serious diagnoses, symptoms and syndromes (HR 1.91; 95% CI: 1.36 – 2.69). No statistically significant, increased hazard was observed for any of the malignancy outcomes or all-cause mortality when comparing tofacitinib to bDMARDs using the ever-exposed approach. However, the hazard of NMSC was statistically significantly increased using the on-drug approach (HR 2.40; 95% CI: 1.21 – 4.80), while the hazard of lung cancer was statistically significantly increased in the on-drug sensitivity analysis without censoring at switch (HR 2.50, 95% CI: 1.07 – 5.84).

Discussion: In summary, this final study report describes the occurrence of a series of pre-defined safety outcomes in German patients with RA treated with tofacitinib and in bDMARD and nbDMARD cohorts. Any crude or minimally adjusted comparisons of IRs for the tofacitinib and the comparison cohorts should be interpreted with caution, as comparisons may be confounded by baseline differences between cohorts, such as disease duration and comorbidities, and due to potential channeling of patients following recommendations and warnings from EMA.

After adjusting for measured potential confounders, a statistically significant, increased hazard of HZ, MACE, and NMSC was observed among tofacitinib initiators vs. bDMARD

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initiators under the on-drug approach. Using the ever-exposed approach, the hazard of NMSC was increased for tofacitinib vs. bDMARD treatment, without reaching statistical significance.

After adjusting for measured potential confounders, a statistically significant increased hazard of HZ, fractures, cardiac disorders (overall), and other serious diagnoses, symptoms and syndromes was observed among tofacitinib initiators vs. nbDMARD under the on-drug approach.

Whilst the increased hazard of HZ is well-known, the statistically significant result for MACE has not been reported in previous studies (including the ORAL Surveillance study, independent RABBIT publications, and other studies based on claims data or register data). However, the result is plausible, particularly given previous results from the ORAL Surveillance study (demonstrating a slightly increased, but non-statistically significant hazard for tofacitinib vs. TNFis) and an independent RABBIT publication (indicating both a considerably higher IR for tofacitinib than for other JAKis and a more beneficial risk profile for other bDMARDs compared to TNFis, implying that the hazard of MACE for tofacitinib vs. bDMARDs overall is higher than for tofacitinib vs. TNFis). For the outcome malignancies (excluding NMSC), a statistically significant increased hazard was found only in the subgroup of patients aged 65 years or older, consistent with previous results from the ORAL Surveillance study and an independent RABBIT publication. For several of the study outcomes, the number of events was too small to conduct comparative analyses.

These results are consistent with the known safety profile of tofacitinib, as HZ, NMSC, and MI, are important identified risks in the EU RMP, while CV risk (excl. MI) and fractures are important potential risks.

Marketing Authorization Holder(s): Pfizer Limited

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NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)
Protocol number	A3921317
Version identifier of the study report	1.0
Date	24-JULY-2026
EU Post Authorization Study (PAS) register number	EUPAS31164
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001--0014
Procedure number	Procedure number for protocol update assessment to be provided upon submission (Product Code: EMEA/H/C/0004214)
Marketing Authorization Holder (MAH)	Pfizer Europe
Joint Post-Authorization Safety Study (PASS)	No
Research question and objectives	**Research Question:** What are the rates of adverse outcomes of interest in RA patients treated with tofacitinib in relation to those treated with biologic disease modifying anti-rheumatics and non-biologic disease modifying anti-rheumatics?

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	Objectives: To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, MACE, MI, VTE (DVT and PE) and other specified outcomes, including fractures, among patients with RA who initiate tofacitinib in a German register. Rates will also be estimated among existing cohorts of biologic disease modifying antirheumatic drugs (bDMARDs) and non-biologic DMARDs (nbDMARDs) patients to provide context for rates observed on tofacitinib. Further, incidence rates will be estimated in elderly patients aged 65 years and older. Pending feasibility, hazard rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE and other events, including fractures, will be compared between tofacitinib treated RA patients and other comparator cohorts using methods to adjust for sex, age, year of therapy start, treatment history, disease severity, comorbidities and other potential confounders.
Country(-ies) of study	Germany
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TABLE OF CONTENTS

LIST OF TABLES 5
LIST OF FIGURES 6
1. ABSTRACT (STAND-ALONE DOCUMENT) 8
2. LIST OF ABBREVIATIONS 9
3. INVESTIGATORS 13
4. OTHER RESPONSIBLE PARTIES 14
5. MILESTONES 15
6. RATIONALE AND BACKGROUND 16
7. RESEARCH QUESTION AND OBJECTIVES 18
8. AMENDMENTS AND UPDATES 19
9. RESEARCH METHODS 28
9.1. Study Design 28
9.2. Setting 28
9.3. Subjects 30
9.4. Variables 31
9.4.1 Outcomes 31
9.4.2 Therapy Exposure 33
9.4.3 Confounders 36
9.5. Data Sources And Measurement 38
9.5.1. Assessments 38
9.5.2. Ascertainment Of Adverse Events 38
9.5.3. Quality Control 39
9.6. Bias 39
9.7. Study Size 40
9.8. Data Transformation 40
9.9. Statistical Methods 40
9.9.1. Main Summary Measures 40
9.9.2. Main Statistical Methods 42
9.9.3. Missing Values 45
9.9.4. Sensitivity And Additional Analyses 45
9.9.5. Amendments To The Statistical Analysis Plan 46
9.10. Quality Control 47

9.11. Protection Of Human Subjects 48
10. RESULTS....49
10.1. Participants 49
10.2. Descriptive Data....50
10.3. Outcome Data....95
10.4. Main Results 217
10.5. Other Analyses....231
10.6. Adverse Events/Adverse Reactions 232
11. DISCUSSION....232
11.1. Key results 232
11.2. Limitations....246
11.3. Interpretation....248
11.4. Generalizability....251
12. OTHER INFORMATION....252
13. CONCLUSIONS....252
14. REFERENCES....253
15. APPENDIX....259

LIST OF TABLES

Table 1. Enrolment therapies of the RABBIT register cohort 2 30
Table 2. Classification of medications (ATC codes) for the therapy of RA....33
Table 3. Assessment and definition of potential confounders....36
Table 4. Confounders for the Cox regression analysis for selected outcomes 44
Table 5. Baseline Characteristics for time of enrolment (I), overall....51
Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs 57
Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy 62
Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs 67
Table 9. Baseline Characteristics for therapy starts at index date (II), overall....75

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs 79
Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy 85
Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs 90
Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) 116
Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups 126
Table 15. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) 198
Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups 201
Table 17. Cox regression models for the on-drug approach 222
Table 18. Cox regression models for Tofacitinib vs. bDMARDs in the on-drug approach, sensitivity analysis (Model C) 226
Table 19. Cox regression models for Tofacitinib vs. bDMARDs in the ever-exposed / ever-exposed with latency period approach 229
Table 20. Counts of Pregnancies, pregnancy-related outcomes, and pregnancy-related events 231
Table 21. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort 259
Table 22. Histograms of the propensity score distributions of the primary regression analyses 260
Table 23. SMDs of the primary regression analyses 275

LIST OF FIGURES

Figure 1. Flowchart with therapy episodes started at (I) enrolment or (II) enrolment and during follow-up 50

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

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 for tofacitinib RA PASS

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1. ABSTRACT (STAND-ALONE DOCUMENT)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
AE	adverse event
B-CLL	B-cell chronic lymphocytic leukemia
bDMARD	biologic disease-modifying anti-rheumatic drug
BMI	body mass index
CAD	coronary artery disease
CeVD	cerebrovascular disease
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
CKD	chronic kidney disease
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DAS28	disease activity score 28

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Abbreviation	Definition
DAS28-ESR	disease activity score 28 based on erythrocyte sedimentation rate
DHPC	direct healthcare professional communications
DMARD	disease-modifying anti-rheumatic drug
DRFZ	Deutsches Rheuma-Forschungszentrum, German Rheumatology Research Center
DVT	deep vein thrombosis
EC	European Commission
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EPITT	European Pharmacovigilance Issues Tracking Tool
EULAR	European Alliance of Associations for Rheumatology
FFbH	% of full function by Hannover Functional Status Questionnaire
GC	glucocorticoids
GI	gastrointestinal
HAQ	health assessment questionnaire
HMA	Heads of Medicines Agencies
HR	hazard ratio
i.v.	intravenous
ICH	International Council for Harmonisation
IEC	independent ethics committee
IPCW	inverse probability of censoring weighting
IPTW	inverse probability of treatment weighting
IPW	inverse probability weighting

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Abbreviation	Definition
IR	incidence rate
IRB	institutional review board
JAK	Janus kinase
JAKi	Janus kinase inhibitor
MACE	major cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mm	millimeter
mm/1h	millimeter / 1 hour
MTX	Methotrexate
N	number
NA	not applicable
nbDMARD	non-biologic disease-modifying anti-rheumatic drug
NMSC	non-melanoma skin cancer
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
ORAL	Oral Rheumatoid Arthritis Trial
PASS	post-authorization safety study
PE	pulmonary embolism
PML	progressive multifocal leukoencephalopathy
PRIND	prolonged reversible ischemic neurological deficit
PS	propensity score

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Abbreviation	Definition
PY	patient year
Q1	first quartile
Q3	third quartile
RA	rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RCT	randomised controlled trial
RF	rheumatoid factor
RWD	real-world data
s.c.	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMD	standardized mean difference
SmPC	summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	tuberculosis
TIA	transient ischemic attack
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic disease-modifying anti-rheumatic drug
VTE	venous thromboembolism

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3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Martin Schaefer, PhD	Senior Statistician, Epidemiologist	German Rheumatology Research Center, Programme Area Epidemiology and Health Services Research, Berlin, Germany

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4. OTHER RESPONSIBLE PARTIES

Not Applicable.

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol	The original study protocol was approved on 01-MAR-2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001).	A revised and updated study protocol received approval on 05-JULY-2021 (Protocol number EA4/123/21).	
Start of data collection	15-SEPT-2019	15-SEPT-2019	
End of data collection	14-SEPT-2025	14-SEPT-2025	
Registration in the HMA-EMA Catalogues of RWD Studies	01-SEPT-2019	05-SEPT-2019	
Interim report 1	14-MAR-2021	04-MAR-2021	
Interim report 2	14-MAR-2023	22-FEB-2023	
Interim report 3	14-MAR-2025	14-MAR-2025	
Final report of study results	14-AUG-2026		

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6. RATIONALE AND BACKGROUND

Rheumatoid Arthritis (RA) is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations [1]. RA is characterized by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of comorbidities.

Compared with the general population, RA patients are at a higher risk of infections, cardio-vascular 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 (JAKi) 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 signal-ing of multiple cytokines important in the pathogenesis of RA [4]. Unlike biological therapies, such as tumour necrosis factor (TNF) inhibitor (TNFi) and anti-interleukin (IL)-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity relative to other kinases in the human genome.

In March 2017, XELJANZ® (tofacitinib citrate) was approved in the European Union (EU) at a dose of 5 mg administered BID (twice a day) for the therapy 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 therapy. 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 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, therapy 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 therapies.

There is an increased risk of premature mortality, serious infection and lymphoma in patients with RA and other connective tissue diseases, independent of the therapy 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 event rates of major adverse CV events (MACE) and malignancies

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excluding non-melanoma skin cancer (NMSC) in patients treated with tofacitinib for RA, lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma (overall) were already included as study endpoints prior to the signal evaluation). It is therefore fundamentally important to describe the occurrence of these events among patients treated with newly approved therapies and among patients who remained on “conventional” therapy or received a different targeted agent.

To enable assessment of safety events of interest including rare events and endpoints with long latency periods, Pfizer implemented a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data embedded within the German
Registry Rheumatoide Arthritis: Beobachtung der Biologika Therapie (RABBIT). This is one of the four registry-based post authorization safety studies (PASS), which are being conducted in the United Kingdom, Sweden, Spain, and Germany. This non- interventional study was designated as a PASS and was 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 therapy for RA. Persons with RA 65 years of age or older were found to be at increased risk of serious infections relative to those <65 years of age in both clinical trial and observational data [5,6]. The mechanism by which infection risk is increased in RA patients is likely to be multifactorial. In addition to the underlying disease (RA), therapies used to treat the disease have suppressive effects on the immune system. For example, TNFis may affect host defense against infection since TNF mediates inflammation and modulates cellular immune response. Tofacitinib, a JAKi, 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 treated with nbDMARDs[6-9], however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time [10,11]. The decline may reflect a change in the risk profile of the population as a result of at-risk patients switching therapies, reduced co-administration of corticosteroids, in addition to any impact of TNFi therapy on overall health [11].

Tuberculosis (TB) is the most common opportunistic infection 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 (HZ) in patients with RA and general population cohorts have been inconsistent, with some showing no increased risk and some showing modestly elevated risk [13-16].

Serious infections, including TB and HZ, 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 therapy modality, including Hodgkin’s and non-Hodgkin’s lymphoma, leukemia, myeloma, and

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lung cancer [14,17]. In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

Due to the immunosuppressive properties of approved RA therapies, researchers have investigated the risk of lymphopoietic and hematopoietic cancers in patients with RA. It is not clear whether the risk of lymphoma in RA patients is increased further by use of 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 therapy of RA. As part of the June 2021 signal procedure (EPITT No. 19832), lung cancer and lymphoma were categorized as important identified risks for tofacitinib.

Cardiovascular Disease
Patients with RA have higher rates of CVD than does the general population [19]. The body of published evidence for increased risk of serious 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 therapy of RA. 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
RABBIT 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 potential safety concerns (see 9.4.1).

7. RESEARCH QUESTION AND OBJECTIVES

This study aims to examine the rates of safety events of interest in RA patients treated with tofacitinib in relation to those treated with biologic DMARDs (bDMARDs) and non-biologic DMARDs (nbDMARDs) other than tofacitinib.

Objectives:

To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, MACE, MI, VTE (DVT and PE) and other specified outcomes, including fractures, among patients with RA who initiate tofacitinib in a German register. Rates were also estimated among existing cohorts of biologic disease modifying antirheumatic drugs (bDMARDs) and non-biologic DMARDs (nbDMARDs) patients to provide context for rates observed on tofacitinib. Further, incidence rates (IRs) were estimated in elderly patients aged 65 years and older.

To compare (pending feasibility) the hazard rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE and other

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events, including fractures between tofacitinib treated RA patients and other comparator cohorts using methods to adjust for sex, age, year of therapy start, therapy history, disease severity, comorbidities and other potential confounders.

8. AMENDMENTS AND UPDATES

Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	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 contact information for three protocol authors. Updated contact information for the MAH Contact Person	Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor
			Section 2	Updated to include new abbreviations	Editorial change
			Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principal investigator.
			Section 4	Revised version and date. Updated Objective 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.	PRAC request and clarification.

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Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			Section 7	Updated to include information on changes to protocol resulting from 2021 signal evaluation procedures Updated to include fractures as an additional safety event of interest	Editorial changes Based on available data, Pfizer has identified fractures as a potential risk
			Section 8	Updated objectives to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated objective to include estimation of event rates in the elderly aged 65 years and older.	PRAC request and clarifications
			Section 9.5.1	Updated to include CV risk factors	PRAC request and clarifications
			Section 9.5.3	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.
			Section 9.9	Updated analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes.	PRAC request and clarifications

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Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Updated to specify 'elderly' as aged 65 years and older.	Editorial change.
			Section 9.11	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.
1.0	August 2021	Substantial	Annex 2	Author name change. Signature and signature date updated. Instructions for form completion removed.	Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Editorial change
			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
			Section 4	Revised version and date. Updated Objective and Variables to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added	Editorial change PRAC request and clarification

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Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				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. Removed 6-monthly reports from the Milestones.	PRAC request and clarification
			Section 7	Updated the Cardiovascular Disease section to remove MACE as an "important identified risk".	PRAC request and clarification
			Section 8	Updated Objective to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added VTE (DVT and PE) as an outcome of interest for consistency with other sections of the protocol (VTE was an outcome of interest in the previous version of the protocol).	PRAC request and clarification
			Section 9.5.1	Updated CV risk factors to include chronic kidney disease and hypercholesterolemia	PRAC request and clarification
			Section 9.5.3	Updated the Endpoints to replace the	PRAC request and clarification

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				term 'lymphoproliferative malignancy' with 'lymphoma'.	
			Section 9.9	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
			Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
			All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
			Annex 2	Signature date updated	Editorial change.
3.0	February 2023	Substantial	Section 6	Added footnote to milestone table to indicate anticipated data availability	To accommodate data lag
			Section 9.5.1	Removed Charlson Index	Data required to estimate the Charlson Index is not captured in the registry
			Section 9.5.1	Removed ACR rating scale from baseline covariates	Data required to estimate the ACR rating scale is not captured in the registry
			All sections where applicable	Updated language to 'safety events of interest' to be consistent with the study title	Editorial change
4.0	October 2023	Substantial	Title page, Author address, MAH Contact Person	Updated author address and name and address of MAH contact person	Editorial change

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Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			Section 3.0	Updated Pfizer contact address; updated job title for other investigators	Editorial change
			Section 9.5.2	Deletion of text related to rheumatologist assessment of severity of reported adverse events	Updating to remove language regarding severity assessment as this is not well captured within registry
5.0	February 2025	Substantial	PASS Information, Abstract, Sections 8, 9.2.1, 9.5.3, 9.9	Distinguished between analyses conducted in the interim reports and final reports.	The protocol addresses both the interim reports and the final report. As the methods differ between the reports, a better differentiation of which analyses will be provided in which reports was necessary. When describing overall study objectives, the wording was aligned to correspond with the final report analyses which estimate incidence rates.
			List of abbreviations, Abstract, Section 8	Definition of nbDMARD	The group of non-biologic disease modifying antirheumatic drug (nbDMARD) usually comprises conventional synthetic disease modifying antirheumatic drugs (csDMARD) and targeted synthetic disease modifying antirheumatic drugs (tsDMARD). In this protocol, the term solely refers to csDMARDs, but not to tsDMARDs.
			Section 3	Corrected job title of one of the principal investigators	Job title needed correction
			Abstract	Deleted “including link data”	No data linkage possible in Germany

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			Abstract, Section 9.2	Added start of observation time for final report	Start of observation for all cohorts will be from 01 May 2017 onwards
			Sections 8, 9.9	Stated that incidence rates will be estimated in the final report	Clarified which report will present incidence rates
			Section 9.2	Updated the number of patients in the registry	Updated number better reflects current enrollment in the registry
			Section 9.2	For final reports, no exposure to the active substance 365 days prior to index date	To reduce prevalent user bias
			Section 9.2.1	Prior tsDMARD exposure is no longer an exclusion criteria.	Applied similar inclusion criteria across cohorts with respect to prior therapy for the final report to reduce potential bias.
			Section 9.4	In the analyses where follow-up is censored after a switch to a different therapy class, the censoring event in the tofacitinib-treated cohort was changed from censoring from switch to non-JAK-inhibitor advanced systemic therapy to non-tofacitinib advanced systemic therapy.	Updated censoring event to account for non-tofacitinib JAK inhibitors, as there are drug-specific safety risks
			Section 9.4	Adaption of risk window definition	Improved clarity of the analysis.
			Section 9.5.1	Removed several VTE risk and CV risk factors	Data required to include these risk factors is not captured by the registry

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				Removed baseline variables that are not collected and provided additional detail on variables that are collected	Clarified which baseline data is collected by the registry
			Sections 9.5.2, 9.9	Removed listing of outcomes	Listing was redundant since all outcomes are listed in section 9.5.3
			Section 9.5.3	Several outcomes were added.	Reflected the additional outcomes provided in the interim reports.
			Sections 9.8, 9.10	Added additional detail	Additional detail helps clarify the RABBIT processes
			Section 9.9	Added clause of exclusion of patients with documented prior history of the safety endpoint of interest from analysis of that specific safety endpoint	To limit potential bias as patients with prior history of the safety endpoints are often at increased risk of future occurrences of the same endpoint
			Section 9.9	Added sensitivity analysis with stratification by prior use of non-tofacitinib JAK inhibitor therapies	Results from patients with prior non-tofacitinib JAK inhibitors may be confounded. The stratified analysis will examine potential risk of endpoints from only tofacitinib versus other JAK inhibitor therapies
			Section 9.9	Updated semi-annual report section	Clarification that semi-annual reports present event rates
			Section 9.11	Limitations section was revised to provide additional detail and clarity.	More limitations were identified and redundant sentences were deleted.

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			Section 9.11	Deletion of "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"	RABBIT is an ongoing cohort study recruiting new patients receiving TNF and DMARD therapy regimes after January 2020
			Section 11	Section was revised	Updated to reflect the processes applied in RABBIT
			Annex 2	Updated Section number references where appropriate	Corrected Section number references
6.0	06 July 2025	Substantial	Section 6	In the footnote, updated the start date for data availability for the final report based on data availability	Editorial update
			Section 8	Added clarification on estimation of event and incidence rates	Improved clarity of the analytic methods
			PASS information, Section 4, Section 8, Section 9.9, Section 9.11	Added clarification that comparative analyses will report hazard ratios since the adjusted regression models used are Cox proportional hazards models. Crude incidence rates will also be reported.	Improved clarity of the analytic methods
			Section 9.5.1	Updated 'hypercholesteremia' to 'hyperlipoproteinaemia'	This is the information collected in the questionnaire

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			Section 9.9	Removed clause of exclusion of patients with documented prior history of the safety endpoint of interest from analysis of that specific safety endpoint. Specified that baseline comorbidities include history of the outcomes of interest (when data is available).	Per PRAC request. Prior history will be accounted for using model adjustment for baseline comorbidities.
			Section 9.9	Added clarification language on the data collection of the registry	Improved clarity
			Abstract	Added 'excluding NMSC'	For consistency with PASS Information and Objectives sections

9. RESEARCH METHODS

9.1. Study Design

This is an active surveillance study using existing data from the German RABBIT register, an ongoing prospective observational cohort study that started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use (non-interventional post-authorization safety study). RABBIT is being conducted by Deutsches Rheuma-Forschungszentrum (German Rheumatology Research Center, DRFZ), equally supported by several industry partners. Patients may switch and/or discontinue therapies during observation time, which can be up to 10 years. Data capture and follow-up methods are the same for all cohorts within RABBIT.

No time restrictions relating to the start of therapy initiation were applied. All patients enter the cohorts at therapy initiation, regardless of previous therapies. No pre-specified hypotheses were tested. Results in this final study report refer to data reported since 01-MAY-2017, as of 30-JUNE-2025.

9.2. Setting

The German Biologics Register RABBIT has been active since May 2001 under the auspices of the "Kompetenznetz entzündlich-rheumatische Systemerkrankungen" ("Competence Network Rheumatology"). The content of the original study protocol (i.e., not the PASS protocol) as well as later amendments were agreed with the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology). Physicians interested in participating in RABBIT must sign a contract with the DRFZ. Participating patients have provided informed consent, have

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been diagnosed with RA, had the onset of RA at age 16 or older, were 18 year of age or older at the time of enrollment, and have initiated an approved therapy for the therapy of RA (either a bDMARD (biologic disease modifying anti-rheumatic drug), tsDMARD (targeted synthetic disease modifying anti-rheumatic drug), or an nbDMARD (non-biologic disease modifying anti-rheumatic drug) after at least 1 prior DMARD, see Table 1 for an overview of the therapies and therapy classes. Please note that until 2016 at least 4 out of the 7 American College of Rheumatology (ACR) criteria for RA had to be fulfilled. Since 2017, a rheumatologist-confirmed diagnosis of RA is required including the indication of the number of ACR criteria fulfilled.

Due to the inclusion criteria, patients can be enrolled at different stages of the RA disease, and they are not assigned to specific therapies using randomised methods. Data is reported by
physicians and patients at predefined time points of follow-up (enrolment, at three and six months, thereafter every six months). Once enrolled, patients are followed up regardless of therapy changes, therapy cessation or initiation of a new therapy. The type of therapy administered and the conduct of individual therapy, including dosages, is solely determined by the treating physician in agreement with the patient. Consequently, there is no influence on any therapy decision by the principal investigators, the scientific advisory board or the pharmaceutical companies sponsoring the study. After five years of observation, observation time can be extended for another five years if the patient consents.

Patients provide written informed consent before study entry into the RABBIT registry. The original study protocol was approved on 01-MAR-2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001). A revised and updated study protocol received approval on 05-JULY-2021 (Protocol number EA4/123/21).

RABBIT encompasses two cohorts reflecting different enrolment periods: From 01-MAY-2001 until 31-DEC-2006 patients starting therapy with adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), or infliximab (Remicade), or with a nbDMARD, were recruited into RABBIT cohort 1. The originally planned recruitment period of five years for the TNFis and anakinra was reached by the end of 2006. Enrolment in RABBIT cohort 1 was stopped, and follow-up ended after an additional five years on 31-DEC-2011. For the newly licensed bDMARDs rituximab (MabThera) and abatacept (Orencia), a new cohort (cohort 2) was established starting on 1 January 2007, in which only patients initiating therapy with MabThera or Orencia were eligible to be enrolled. During this second enrolment period, control patients starting on an nbDMARD were not included. To overcome the disadvantage of comparing patients on a newly licensed drug with historical controls, in 2009, the RABBIT cohort 2 was opened for the enrolment of patients starting a therapy with nbDMARDs as well as for patients starting any of the available bDMARDs licensed for the therapy of RA. As of 2017, enrolments under tsDMARDs were possible.

This final study report only includes therapy and safety data from patients with RA initiating tofacitinib or a drug from the comparator groups from 01-MAY-2017 to 30-JUNE-2025 as the therapy landscape has evolved in the last decades with the introduction of new therapies, therapy recommendations and approaches to manage adverse events. This approach allows fair comparison. All enrolment therapies of the RABBIT cohort 2 are depicted in Table 1.

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Table 1. Enrolment therapies of the RABBIT register cohort 2

Trade name	Active substance	Start of enrolment#	Trade name	Active substance	Start of enrolment#
bDMARDs			**tsDMARDs**		
Humira	Adalimumab	01-JAN-2009	Olumiant	Baricitinib	01-MAY-2017
Hyrimoz	Adalimumab	01-JAN-2019	Xeljanz	Tofacitinib	01-MAY-2017
Amgevita	Adalimumab	01-JAN-2019	Rinvoq	Upadacitinib	01-JAN-2020
Imraldi	Adalimumab	01-APR-2019	Jyseleca	Filgotinib	01-JAN-2021
Hulio	Adalimumab	01-JULY-2019			
Idacio	Adalimumab	01-JULY-2019			
Yuflyma	Adalimumab	01-JULY-2021	**nbDMARDs (= csDMARDs)**		
Hukyndra	Adalimumab	01-FEB-2023	Several names	Azathioprine	01-JAN-2009
Enbrel	Etanercept	01-JAN-2009	Several names	Cyclophosphamide	01-JAN-2009
Benepali	Etanercept	01-APR-2016	Several names	Cyclosporine A	01-JAN-2009
Erelzi	Etanercept	01-AUG-2017	Several names	D-penicillamine	01-JAN-2009
Nepexto	Etanercept	01-JULY-2020	Several names	Gold	01-JAN-2009
Remicade	Infliximab	01-JAN-2009	Several names	Hydroxychloroquine/	01-JAN-2009
Remsima i.v./s.c.*	Infliximab	01-APR-2015		Chloroquine	
Inflectra	Infliximab	02-APR-2015	Several names	Leflunomide	01-JAN-2009
Flixabi	Infliximab	01-MAR-2017	Several names	Methotrexate	01-JAN-2009
Zessly	Infliximab	01-JAN-2019	Several names	Sulfasalazine	01-JAN-2009
Cimzia	Certolizumab	01-SEP-2009			
Simponi	Golimumab	01-JAN-2009			
Orencia	Abatacept	01-JULY-2007			
Kevzara	Sarilumab	01-JAN-2018			
MabThera	Rituximab	01-JAN-2007			
Rixathon	Rituximab	01-AUG-2017			
Ruxience	Rituximab	01-JULY-2020			
RoActemra	Tocilizimab	01-JAN-2009			

start of enrolment in RABBIT, differing from start of enrolment for this report (i.e., 01-MAY-2017);
* Enrolment with Remsima s.c. started from 01-JULY-2020 onwards.
Abbreviations: *bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; i.v., intravenous; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; RABBIT, Rheumatoide Arthritis: Beobachtung der Biologika-Therapie; s.c., subcutaneous; tsDMARD, targeted-synthetic disease-modifying anti-rheumatic drug.*

9.3. Subjects

As initiation of tofacitinib in RABBIT was from 01-MAY-2017 (i.e., once product fully available in Germany) onwards, only therapies initiated after this date were included in this final study report. End of data collection for this report was 30-JUNE-2025. To allow the possibility of at least one follow-up visit, the initiation of tofacitinib, bDMARDs and nbDMARDs had to be before 31-DEC-2024.

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For the tofacitinib and the bDMARD exposed cohorts, episodes were only included if there was no exposure of the specific active substance (e.g., adalimumab, etanercept, infliximab, rituximab, certolizumab, golimumab, tocilizumab, sarilumab, abatacept for the bDMARD cohort, tofacitinib for the tofacitinib cohort) 365 days prior to prescription of the drug.

Inclusion criteria

Tofacitinib Exposed Cohort Inclusion Criteria

- Included in RABBIT.
- Initiation of tofacitinib.

nbDMARD Cohort Inclusion Criteria

- Included in RABBIT.
- Initiation of csDMARD therapy after 01-MAY-2017.
- Failure of at least one DMARD and initiation of a new csDMARD.
- No previous exposure to bDMARD or targeted synthetic DMARD (tsDMARD).
- Patients with no exposure to any DMARD were excluded.

bDMARD Exposed Cohort Inclusion Criteria

- Included in RABBIT.

Initiation of bDMARD therapy after 01-MAY-2017.

Exclusion criteria
Any patient with RA enrolled within RABBIT who did not meet the inclusion criteria for at least one of the considered cohorts was excluded.

9.4. Variables

The study variables included baseline patient characteristics (i.e., clinical and demographic characteristics, comorbidities and current and past therapies) and safety events of interest including, but were not restricted to, the following: serious infections, malignancies (including lymphoma subtypes and lung cancer), and heart disease (including MACE), and VTE (DVT and PE)

9.4.1 Outcomes

The following outcomes were defined a priori and investigated in the final report:

1. Serious infections (excluding TB) (overall) and by subtype:
   - Pneumonia
   - Other infections of the respiratory system
   - Infections of the central nervous system (CNS)
   - Sepsis
   - Bone or joint infections
   - Opportunistic infections
   - Other infections
2. TB
3. HZ
4. Fractures

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5. Cardiac disorders (overall) and by subtype:
   - Heart failure
   - Coronary artery disease
   - Myocardial infarction (MI)
   - MACE
   - Other cardiac disorders.
6. Hematologic disorders (overall) and by type:
   - Bone marrow depression and hypoplastic anaemia
   - Decreased white blood cells
   - Platelet disorders
   - Other blood dyscrasia.
7. Disorders of the nervous system (excluding infections) (overall) and by type:
   - Stroke
   - Central demyelination
   - Other disorders of the CNS
   - Disorders of the peripheral nervous system
   - Psychiatric disorders.
8. Progressive multifocal leukoencephalopathy (PML).
9. Allergic conditions and hypersensitivity.
10. Hepatic failure
11. Gastrointestinal (GI) perforations (overall) and
    - Lower intestinal perforations
    - Other GI perforations.
12. Pregnancy
13. Embolic and thrombotic events, venous or vessel type unspecified (overall) and:
    - Thromboembolic events (VTE) and its components separately:
      - Deep vein thrombosis (DVT)
      - Pulmonary embolism (PE).
14. Operations and hospitalizations (overall) and by type:
    - Bone and joint surgery and other joint therapeutic procedures
    - Other operations and (major) therapeutic procedures that lead to hospitalization.
15. Other serious diagnoses, symptoms, and syndromes.
16. NMSC
17. Malignancies (overall, excluding NMSC)
18. Lymphoma (overall) and by subtype:
    - Non-Hodgkin lymphoma
    - Hodgkin lymphoma
    - Chronic lymphatic leukemia
19. Lung cancer
20. All-cause mortality
21. Leukemia (excl. B-CLL)
22. Other haematopoietic neoplasms (malignant and benign)
23. Solid malignancies (overall)
24. Glioblastoma
25. Benign neoplasms
26. Unspecified neoplasms and precanceroses
27. Metastases, cancer related and morbidities and associated syndromes
28. Interstitial lung disease, pending feasibility

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9.4.2 Therapy Exposure

As described in section 9.3, this study included three cohorts defined by their therapy for RA: (1) the tofacitinib cohort, (2) the bDMARD cohort (initiating a bDMARD) and (3) the nbDMARD cohort (initiating a csDMARD).

Patients were assigned to a therapy exposure cohort when initiating therapy with one of the drugs from the respective therapy exposure cohort.

If patients in the tofacitinib cohort or in the bDMARD cohort augmented their initial therapy by initiating concomitant use of a csDMARD after cohort entry, they maintained their initial cohort assignment (rather than being re-assigned to the nbDMARD cohort).

Table 2. Classification of medications (ATC codes) for the therapy of RA

bDMARD		tsDMARD (JAKi)	nbDMARD
Abatacept (L04AA24)	Anakinra (L04AC03)	Tofacitinib (Xeljanz, L04AA29)	Methotrexate (L01BA01, L04AX03, L04AX03)
Adalimumab (L04AB04)	Certolizumab pegol (L04AB05)	Baricitinib (L04AA37)	Sulfasalazine (A07EC01)
Etanercept (L04AB01)	Golimumab (L04AB06)	Upadacitinib (L04AA44)	Hydroxychloroquine (P01BA02)
Infliximab (L04AB02)	Rituximab (L01XC02)	Filgotinib (L04AA45)	Leflunomide (L04AA13)
Sarilumab (L04AC14)	Tocilizumab (L04AC07)		

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; JAK, Janus kinase; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; tsDMARD, targeted-synthetic disease-modifying anti-rheumatic drug.

As described in Appendix 4, the following definitions for the time at risk were applied:

Tofacitinib cohort:
For patients initiating a therapy with tofacitinib, the following definitions for the time at risk were applied:

- On-drug approach ("censoring at switch approach"; "censor follow up time after a switch to a different therapy"): Time at risk was calculated from drug initiation until the first occurrence of the outcome of interest, the discontinuation of tofacitinib or switch to another therapy, death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first.
- Ever-exposed approach ("once exposed always at risk"): Time at risk was calculated from tofacitinib initiation until the first occurrence of the outcome of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first. A

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patient was considered as once exposed, always at risk, despite stopping tofacitinib therapy or switching to another drug.
- Ever-exposed approach plus latency period ("once exposed, always at risk"): Time at risk was calculated from the day six months after drug initiation until the first occurrence of the outcome of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first. A patient was considered as once exposed, always at risk, despite stop of the tofacitinib therapy or switching to another drug. The latency period of 6 months after therapy initiation was respected to take into account the delayed onset of malignancy outcomes and to prevent reverse causation.
- Exposure during pregnancy: Time at risk was calculated if the patient was exposed during pregnancy (no additional risk window was added after the end of pregnancy), specifically beginning one month before conception for women, and for men two months before conception.

bDMARD cohort:
For patients initiating a therapy with bDMARD, the following definitions for the time at risk were applied:

- On-drug approach ("censoring at switch approach"; "censor follow up time after a switch to a different therapy"): Time at risk was calculated from bDMARD initiation until the first occurrence of the outcome of interest, the stop of the respective drug therapy or switch to another therapy, death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first.
- Ever-exposed approach ("once exposed always at risk"): Time at risk was calculated from bDMARD initiation until the first occurrence of the outcome of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first. A patient was considered as once exposed, always at risk, despite stopping bDMARD therapy or switching to another drug.
- Ever-exposed approach plus latency period ("once exposed, always at risk"): Time at risk was calculated from the day six months after drug initiation until the first occurrence of the event of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurred first. A patient was considered as once exposed, always at risk, despite stop of the respective drug therapy or switching to another drug. The latency period of 6 months after therapy initiation was respected to take into account the delayed onset of malignancy outcomes and to prevent reverse causation.
- Exposure during pregnancy: Time at risk was calculated if the patient was exposed during pregnancy (no additional risk window was added after the end of pregnancy), specifically beginning one month before conception for women, and for men two months before conception.

nbDMARD cohort:

- For the nbDMARD cohort, only the on-drug approach was used. For patients on a nbDMARD therapy as mono- or combination therapy (i.e., a therapy involving more than one csDMARD) but not in combination with a bDMARD or a tsDMARD, the time at risk was calculated as current exposure starting from drug initiation until the first occurrence of the outcome of interest, the initiation of a bDMARD or tsDMARD, death, loss to follow-up,

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end of study, or 7 years of follow-up, whichever occurred first. Time at risk continued if patients stopped nbDMARDs and remained without any DMARD therapy.

- The nbDMARD cohort was designed hierarchically as the complement to b/tsDMARD therapy (i.e., patients contributed to the nDMARD cohort only when they were not exposed to b/tsDMARD therapy at the same time). Since with an ever-exposed approach the prolonged nbDMARD exposure overlapped with the following bDMARD or tofacitinib therapy, the ever-exposed approach was not implemented for this cohort.
- Exposure during pregnancy: Time at risk was calculated if the patient was exposed during pregnancy (no additional risk window was added after the end of pregnancy), specifically beginning one month before conception for women, and for men two months before conception.

Risk window definitions

Tofacitinib cohort:

A 90-day risk window was applied to the on-drug approach. Starting from the first month after discontinuation, an additional three months of exposure (90-day risk window) was added when using the on-drug approach. For the ever-exposed and ever-exposed plus latency period approaches, an additional risk window after exposure was not applicable since exposure extends until end of follow-up. For the exposed during pregnancy approach, no risk window was added after the end of pregnancy.

bDMARD cohort:

A 90-day risk window was applied to the on-drug approach. Starting with the first month after discontinuation, an additional three months of exposure (risk window) was added. For medications containing rituximab, a risk window of nine months was added due to its pharmacologic properties (depletion of B-cells) when using the on-drug approach. For the ever-exposed and ever-exposed plus latency period approaches, an additional risk window after exposure was not applicable since exposure extends until end of follow-up. For the exposed during pregnancy approach, no risk window was added after the end of pregnancy.

nbDMARD cohort:

The duration of follow up within the nbDMARD cohort did not rely on any risk window or the once-exposed at-risk paradigm.

Tofacitinib and bDMARD cohorts: The on-drug approach was implemented applying the “censor at switch” principle: if a new medication was started during the 90-day window after discontinuation of a previous medication, initiation of the new medication stopped the 90-day risk window, and only events prior to the new medication start were assigned to the discontinued medication. For regression models, as a sensitivity analysis, initiation of the new medication did not stop the 90-day risk window, and follow-up time and events occurring after the switch were attributed to prior therapy and not current therapy.

Under the “once exposed always at risk” approach, events were double-counted for IRs if a patient who was indexed to a bDMARD switched to tofacitinib and subsequently developed a malignancy after exposure to tofacitinib. In other words, the event was assigned to both the bDMARD and the tofacitinib exposure cohorts, as were the corresponding PYs since index date to the respective cohorts. For regression analyses, under the “once exposed always at

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risk" approach events were only be assigned to the first considered therapy episode of a patient.

Unless noted otherwise, assignment of exposure time and events to therapies were handled as described for both estimating IRs and implementing Cox regression models.

9.4.3 Confounders

The potential confounders were age, sex, RA disease duration, rheumatoid factor (RF) / anti-citrullinated protein antibodies (ACPA), year of therapy start, Disease activity score based on 28 tender and swollen joints and erythrocyte sedimentation rate (ESR) and patient's global health assessment (DAS28-ESR) , functional capacity measured by Hannover Functional Status Questionnaire (FFbH), previous use of b/tsDMARDs, dosage of concomitant use of glucocorticoids, smoking, chronic obstructive pulmonary disease (COPD), chronic renal disease, obesity, CV risk factors, diabetes, prior heart failure, prior malignancy, prior hypertension and chronic heart disease. DAS28 and its components are considered indicators of disease severity. Further details of assessment and definition are given in Table 3.

Table 3. Assessment and definition of potential confounders

Potential confounder	Data source(s)	Operational definition
Age at index date	Calculation	Year of birth is recorded at enrolment. Every initiation of a DMARD therapy is registered with the date of therapy start. Age at index date was calculated by subtracting the year of birth from the year of therapy initiation.
Sex	Questionnaire	Recorded at enrolment, coded as male and female.
RA disease duration	Calculation	Calculated by using year of symptom onset and year of therapy initiation.
Rheumatoid factor and/or ACPA positive	Questionnaire	Recorded at enrolment, either positive for rheumatoid factor and or anti-citrullinated protein antibodies.
Year of therapy start	Questionnaire	Every initiation of a DMARD therapy is registered with the date of therapy start.
Disease Activity Score (DAS)28-ESR	Questionnaire	Calculated by using the following information, which is recorded at every visit (at enrolment and during observation): 28 counts of swollen and tender joints, ESR in mm/h, patient global health numerical rating scale (0-10).
FFbH (% of full function by Hannover Functional Status Questionnaire)	Questionnaire	Recorded at every visit (at enrolment and during observation), patient-reported information.
Number of Previously used b/tsDMARDs	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
Glucocorticoid dosage	Questionnaire	Recorded at every visit (at enrolment and during observation).

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Table 3. Assessment and definition of potential confounders

Smoking	Questionnaire	Recorded at enrolment, patient-reported information.
COPD	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Chronic renal disease	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Obesity	Calculation	Obesity is defined as BMI ≥30 kg/m2. BMI is calculated by weight and height. Both are recorded at enrolment.
CV risk factors	Calculation	CV risk factors were defined as age ≥65 years, history of or current diabetes, history of hyperlipidemia, history of or current hypertension, history of or current coronary heart disease, history of chronic renal disease.
Diabetes mellitus	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Prior heart failure	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Prior malignancy	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Prior hypertension	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.
Chronic heart disease	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a predefied list.

Abbreviations: ACPA, anti-citrullinated protein antibodies; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DAS28-ESR, disease activity score 28 based on erythrocyte sedimentation rate; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire; RA, rheumatoid arthritis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

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9.5. Data Sources And Measurement

9.5.1. Assessments

The RABBIT register served as the only data source for this final report, including core baseline and follow up data such as patient demographics, disease characteristics and therapy for all cohorts included.

In RABBIT, outcome parameters and covariates are assessed by physicians and/or patients as applicable, on pre-defined case report forms (CRFs) at study enrolment and follow-up visits. Apart from socio-demographic characteristics including education, occupation and smoking habits, data on disease duration, comorbid conditions and anti-rheumatic comedications are assessed. The main outcome measures are the occurrence of AEs, the course of disease activity assessed by physician- and patient-reported measures, the disability in daily life activities reported by patients, the medical therapy adherence detected by physician-reported therapy duration and medical indications for initiation of therapy, therapy change, or therapy discontinuation. Therapy starts, stops and switches are recorded as the dates on which they occurred.

Patients have predefined study visits at enrolment directly prior to the onset of a new medical therapy (t0), after three (t1) and six months (t2), and then every six months up to month 120 (t3 to t21). Assessments performed at each of the respective study visits during the 120-month observation period are presented in Table 21 in the Appendix.

9.5.2. Ascertainment Of Adverse Events

All AEs and serious AEs (SAEs) are recorded in the RABBIT register following the International Conference of Harmonization guidelines on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95/E2A) [20]. Accordingly, any untoward medical occurrence observed in a patient is reported as an AE, independently of a relationship between event and current medication. Physicians document the onset of symptoms, duration, intensity, the assumed causal relationship with DMARDs and the outcome of each reported AE. All serious and non-serious events occurring during the observation are regularly reported from the rheumatologist and captured in the register, with judgement from the rheumatologist on severity (mild, moderate, severe; and causality to given medication). All reported AEs are registered continuously in a separate database.

For events of special interest or in case of an SAE, which had been judged to be possibly related to a DMARD, detailed queries are sent out to the treating physician, to get more information on the events (and additional discharge letters from hospitals, or results from biopsies etc). For all events of interest, as well as for pregnancies and pregnancy-related outcomes, additional event-specific queries are used. For SAEs with a possible relation to DMARD use, a general additional query is used without event-specific questions. All additional queries comprise details for greater specification of the event, related diagnostic and therapeutic procedures, as well as the course of DMARD therapy. In addition, all other medications the patient had been treated with at the time when the event occurred, are reported.

Any AE resulting in death or persistent or significant disability, being life-threatening, requiring hospitalization or prolongation of hospitalization, or being a congenital anomaly or birth defect is reported as an SAE. Physicians can indicate whether they assume a causal relationship

(clearly, probably, possible, unlikely, no connection, unknown). SAEs with missing assignment of the causal relationship are considered as possibly related. These definitions of AEs and SAEs are also provided in CRFs. For non-serious AEs, severity grading is performed according to the recommendations of the Outcome Measures in Rheumatology (OMERACT) Toxicity Working Group. For the coding of AE and SAE the Medical Dictionary for Regulatory Activities (MedDRA) dictionary is used on the preferred term (pt) level [21]. It is intended to update the AE/SAE database with every update of MedDRA.

RABBIT data cannot be linked with any other data due to strict data protection rules and due to the fact that there is no national cancer register or death register with the possibility of linkage. However, all events are carefully monitored and several national offices are sometimes contacted to get more information.

Further details are given in the original RABBIT study protocol EA4/123/21 (i.e., not the PASS protocol). This document is not publicly available and cannot be included here.

9.5.3. Quality Control

For details on the quality control procedures in RABBIT, please see section 9.10.

9.6. Bias

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing RABBIT, a well-established Germany-based rheumatology register. Despite the strengths of the register, the data must be evaluated in light of their limitations. A common problem of observational studies is the lack of randomisation of patients to therapy arms resulting in effect measures being possibly confounded by indication to a therapy [22]. Therapy decision and therefore, exposure to a DMARD are usually based on the availability of drugs, the physician's experience, and on patients' characteristics such as age, severity of symptoms, the individual disease course and specific comorbidities. On the other hand, patients are
individually susceptible to developing a particular AE depending on characteristics such as age, inflammatory activity of the RA, smoking habits, comorbid conditions or co-medication.

Event misclassification may be a concern within the observational setting due to less stringent monitoring relative to clinical trials. While RABBIT 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 followed patients for a period of 7 years after therapy initiation. Conclusions may not be generalizable outside of the 7-year period since initiation of therapy. Additionally, generalizability to other European countries may be limited given only German data is included. Therefore, additional PASS are being conducted in three additional European countries.

There is no possibility to link RABBIT data with any other data due to strict data protection rules and since there is no national cancer register or death register with the possibility of

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linkage. However, all events are carefully monitored, and several national offices are sometimes contacted to get more information.

9.7. Study Size

All patients enrolled in the RABBIT cohort between 01-MAY-2017 until 30-JUNE-2025 were included in the analyses, except for patients not eligible due to non-fulfilment of inclusion criteria (see section 9.3). This active surveillance study was not intended to test a single pre-specified statistical hypothesis. The targeted sample size for tofacitinib-treated patients was 500. Enrolment was not capped at 500; the size of the population depended largely on the use of tofacitinib in Germany. Power calculations are provided in Appendix 4.

9.8. Data Transformation

All data management activities occurred within the overarching RABBIT study.

The Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Obesity was defined according to the definition of the World Health Organization as BMI ≥30 kg/m^2. The DAS28-ESR was calculated [23]. Disability was assessed using the FFbH, which is highly correlated to the Health Assessment Questionnaire [24].

Detailed methodology for data transformations, particularly complex transformations (e.g. the many raw variables used to derive an analytic variable), are documented in Section 4.3.3 of the statistical analysis plan (SAP) (Appendix 4), which is dated, filed and maintained by the sponsor.

9.9. Statistical Methods

9.9.1. Main Summary Measures

All statistical analyses were performed by the RABBIT register.

Patient descriptive characteristics – Baseline characteristics

The following summary measures were calculated for baseline patient descriptive characteristics in all three therapy exposure cohorts (see Table 5):

- median with interquartile range or mean with standard deviation (for continuous variables)
- counts and their respective proportion (for categorical variables)
- missing (n, (%)) (for both continuous and categorical variables).

All therapy exposure cohorts are described:
(I) at the time of enrolment into the study (every patient counts only once) and
(II) at the time of the start of a new therapy either at enrolment or during follow-up observation. In the latter case, every new therapy start was considered as baseline. This implies that patients can contribute to several exposure cohorts during the time of observation, and also several times to one exposure cohort.

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For tofacitinib cohort and the bDMARD cohort, baseline characteristics are presented furthermore stratified by:
a. The number of previous b/tsDMARD (0, 1, ≥2; see Table 6)
b. Prior use of non-tofacitinib JAKi therapy (0, >0; see Table 7
c. Mono vs. combination therapy with nbDMARDs, specifically MTX (see Table 8).

IRs

IRs were restricted to the first event per patient per exposure group (i.e., patients who experience the event of interest within one exposure cohort were censored at the first event, however, further events after switch to another exposure cohort were counted and attributed to newly initiated exposure groups). Crude IRs per 1000 PYs and corresponding 95% confidence intervals (CIs) were estimated. The cumulative number of incident events were also tabulated for each cohort and safety outcome of interest. Results for all safety outcomes except for pregnancies and adverse pregnancy outcomes are presented as:

- cumulative number of incident events during the time of observation,
- total PYs,
- female PYs,
- male PYs,
- total mean follow-up time (in years),
- crude IR per 1,000 PYs and corresponding 95% CI,
- Age-sex standardized IR per 1,000 PYs and corresponding 95% CI

The calculation of PYs was based on the sum of the months at risk per patient and exposure cohort divided by twelve. To estimate corresponding CIs, a Poisson distribution was assumed [25].

IRs are shown overall and stratified by:

1) the number of previous b/tsDMARDs (0, 1, ≥2) for the tofacitinib cohort and the bDMARD cohort
2) prior use of non-tofacitinib JAKi therapy (0; >0) for the tofacitinib cohort and the bDMARD cohort
3) monotherapy vs. combination therapy with concomitant nbDMARDs, specifically MTX, for the tofacitinib cohort and the bDMARD cohort
4) age (<65 years and ≥65 years) for all cohorts
5) patients with ≥1 VTE risk factors vs. no VTE risk factors for the outcome of VTE and for all cohorts
6) patients with ≥1 CV risk factors vs. no CV risk factors for the outcomes of MACE and MI and for all cohorts
7) patients without prior history of malignancy vs. with prior history of malignancy for the outcomes of malignancy and for all cohorts

Additionally, provided there were events in the considered strata:

8) IR for VTE stratified by time periods prior to 31-JAN-2020 vs. after 31-JAN-2020 (since this was the date of SmPC revision that included the addition of VTE as an important identified risk associated with the use of tofacitinib);

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9) IR for VTE among patients with VTE risk factors stratified by time periods prior to 31-JAN-2020 vs. after 31-JAN-2020;
10) IR for malignancy/CV risk stratified by time periods prior to 30-JUNE-2021 vs. after 30-JUNE-2021 (since the signal procedure (EPITT No. 19382) in which MI was categorized as an important identified risk for tofacitinib occurred in June 2021);
11) IR for malignancy/CV risk among patients with malignancy and CV risk factors, respectively, stratified by time periods prior to 30-JUNE-2021 vs. after 30-JUNE-2021.

Pregnancies
Additionally, the number of tofacitinib-exposed pregnancies are given both for pregnant patients and for patients with a pregnant partner (see Table 20). Pregnancy and events associated with pregnancies were investigated descriptively and are reported as frequencies. Outcomes occurring during pregnancies are described only for pregnant patients with RA.

9.9.2. Main Statistical Methods

Hazard ratios (HR)
Pending sufficient numbers of events in the tofacitinib cohort and sufficient numbers of events per covariate in the respective outcome models, adjusted HRs were estimated using Cox proportional hazards regression models with a robust variance estimator (see Table 17, Table 18 and Table 19). No Cox analyses were conducted for outcomes of interest with fewer than five events in the tofacitinib cohort.

For estimating HRs, patients who experienced the event of interest were censored at the first event. For all safety endpoints of interest, when prior medical history for a particular safety endpoint was collected by the registry, the prior documented history of that particular safety endpoint was included as binary variable (Y/N) in the adjusted analysis for that specific endpoint, but not for other endpoints. At enrolment and then every 2.5 years, RABBIT collects medical history on the following conditions as comorbidity: hypertension, coronary heart disease, heart failure, cerebrovascular diseases (Apoplex/TIA/PRIND), hyperlipoproteinaemia, diabetes, malignant neoplasia, lymphoma/leucosis, chronic kidney diseases, psychological diseases/depression, and latent (inactive) TB.

For all outcomes, propensity scores (PSs) were estimated, and inverse probability of treatment weighting (IPTW) as well as inverse probability of censoring weighting (IPCW) were used to control for potential confounding (see section 9.4.3).

The following comparisons were performed:
- Tofacitinib cohort vs. bDMARD cohort;
- Tofacitinib cohort vs. nbDMARD cohort; for this comparison patients with prior exposure to b/tsDMARDs were excluded.

Two PSs for each patient were estimated using two multivariable logistic regression models, in which the outcomes were set as a) the therapy received and b) the presence of censoring/dropout judged as informative (e.g., a patient does not return to his/her institution for visits and/or cannot be reached, or a patient does not wish to continue in the study), respectively. PSs were estimated for each pair of therapy cohorts (i.e., tofacitinib vs. bDMARDs and tofacitinib vs. nbDMARDs) and for each safety outcome of interest separately. Variables included in the two PS models are presented in section 9.4.3**.** For time-varying covariates, the measurements closest in time before the switch to the drug under investigation were used (defined

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as baseline for this drug). This allowed control for factors that were proximally related to the therapy initiation (index date) but not impacted by the new therapy. Stabilized weights were used to reduce variability induced by patients with large weights. The stabilized therapy (censoring) weights were estimated by multiplying the original weights by the proportion of patients in the respective cohort depending on the therapy (censoring) status of the patient. Final weights were obtained by multiplying the therapy and censoring weights. Additionally, weights below the 1% percentile and above the 99% percentile were winsorized (i.e., set to the corresponding quantile to limit the influence of potential outliers). Histograms were produced to visually depict the overlap in PSs in the two therapies being compared. Standardized mean differences (SMDs) were used to compare the balance in baseline covariates between therapy exposure cohorts before and after weighting. The cut-off SMD value indicating substantial imbalance was chosen as ±0.1 (10%) [26]. In case of substantial imbalance, the variable(s) in question were added as covariates to the Cox proportional hazards regression model. Cox models were only run if the amount of overfitting was acceptable. The amount of overfitting was deemed as acceptable if the number of covariates in the model was less than m/5, where m is the number of events for the considered outcome [27]. However, this rule did not lead to the exclusion of any models that had at least 5 events in the tofacitinib cohort.

Generally, the PSs were estimated at the time of a therapy initiation to model therapy decisions. For therapies started at enrolment, data for covariates of the PSs were taken from the enrolment visit. For therapies started during follow-up, data for covariates of the PSs were taken from the visit date occurring most recently prior to the therapy start date. In other words, for time-varying covariates only covariates measured before or at the time of the new therapy start were included when calculating PSs. This allowed control for factors that were proximally-related to the therapy switch but not impacted by the new therapy. Covariates affected by the therapy and assumed to be in the causal path from therapy to the safety outcome of interest (i.e., intermediate variables) were not included in the logistic PS models as adjustment for post-exposure variables could induce bias in the total causal effect estimate. A limitation of this approach is that due to censoring triggered by a therapy switch, effects of the discontinued therapy that may need longer time to develop may not be captured.

As described in section 9.4.2 four analytical approaches were considered:

- On-drug approach: as primary analysis for non-malignancy and non-mortality outcomes except pregnancy outcomes, and secondary analysis for malignancy outcomes and all-cause mortality
- Ever-exposed approach: as primary analysis for all-cause mortality
- Ever-exposed approach plus latency period: as primary analysis for all malignancy outcomes
- Exposed during pregnancy approach: for pregnancy outcomes

On-drug approach: The PSs were estimated at the time of each therapy initiation in one of the cohorts to model therapy decisions. Therapy episodes were included in the regression analysis by applying an extended Cox model based on adjustment at start of therapy episodes (i.e. a start–stop ('counting-process') data structure (Andersen-Gill)) [28,29].

Ever-exposed approaches: The PSs were estimated using data for the covariates measured at the time of the first therapy initiation during the inclusion period. Using the ever-exposed approach, the duration of therapy and how proximate the therapy was in relation to the safety

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outcome of interest were not accounted for (i.e., short-term therapies and therapies that occurred several months prior to an event were included). It is important to note that differences in follow-up time between therapy cohorts could introduce bias. In the ever-exposed approach, PSs were estimated per patient (and not per therapy episode as in the on-drug approach, below), and weighted Cox proportional hazard regression analyses were used.

Unadjusted and adjusted HRs and corresponding 95% CIs were estimated. The potential confounders included in each of the Cox regression models are specified in section 9.4.3 and presented in Table 4. These confounders were selected a priori, in agreement with recommendations from the RABBIT scientific advisory board (and aligned with previous publications from RABBIT). For each outcome, three models were calculated run with three different sets of covariables (Table 4).

Table 4. Confounders for the Cox regression analysis for selected outcomes

	Outcome (outcomes as listed in section 9.4.1					
	Infections (outcome 1, 2 and 3)	**CV disease** (outcome 5)	**VTE** (outcome 13)	**Malignancy** (outcomes 16 – 19 and 21 – 27)	**All-cause mortality** (outcome 20)	**All other outcomes except pregnancy** (outcomes 4, 6 – 11, 14, 15, 28)
Model A	None (crude/ unadjusted)					
Model B	Age (< 50 vs. ≥ 50 and < 60 / ≥ 60 and < 70 / ≥ 70 years) Sex (male vs. female)					
Model C	*General covariates*					
	Age (< 50 vs. ≥ 50 and < 60 / ≥ 60 and < 70 / ≥ 70 years) Sex (male vs. female) RA disease duration[#] RF/ ACPA (no vs. yes)[$] Year of therapy start (before 30-JUNE-2021, 30-JUNE-2021 and afterwards) DAS28-ESR[#] FFbH[#] Previous b/tsDMARDs* (0 vs. 1 / ≥ 2) Glucocorticoid dosage (0 vs. > 0 and ≤ 5 / > 5 and ≤ 10 / > 10 mg/d) Smoking (never vs. ever)					
	Outcome-specific covariates					
	COPD (no vs. yes) Chronic renal disease (no vs. yes)	Obesity (no vs. yes) CV risk factors (0 vs. ≥1) [§]	Obesity (no vs. yes)	Diabetes (no vs. yes) Chronic renal disease (no vs. yes) Prior heart failure (no vs. yes)	None	

#Added as continuous variable.
$Positive for rheumatoid factor and/or anti-citrullinated protein antibodies.
*Only for the comparison tofacitinib vs. bDMARDs. For the comparison tofacitinib vs. nbDMARDs, only b/tsDMARD-naive patients were considered, therefore the variable was excluded from the PS model.

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Table 4. Confounders for the Cox regression analysis for selected outcomes

§CV risk factors are defined as age ≥65 years, history of (or current) diabetes, history of hyperlipidemia, history of (or current) hypertension, history of (or current) coronary heart disease, history of chronic renal disease.
Abbreviations: ACPA, anti-citrullinated protein antibodies; CV, cardiovascula, DAS28, disease activity score 28 based on erythrocyte sedimentation rate; b/tsDMARD, biologic / targeted synthetic disease modifying antirheumatic drugs; COPD, chronic obstructive pulmonary disease; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; RF, Rheumatoid factor

9.9.3. Missing Values

Proportion of missing data was provided for the main baseline variables and no imputation of missing values was performed in the baseline tables.

For all potential confounders, missing information was assumed to be missing at random and was addressed by tenfold imputation. The multiple imputation was performed by regression with fully conditional specification, including the covariates from Table 9-4 and the outcome. Statistical analyses then proceeded as normal for the multiple imputation strata and results for the individual strata were combined employing Rubin's rules [30,31]. The robust sandwich variance estimator was used for all Cox models to reduce the impact of the additional variance of the imputation method as well as of dependencies between therapy episodes of the same patient on the estimates.

When the date of an occurrence of an event was missing, the start date was assigned as the midpoint between the last two follow-up visits if the event did not lead to the death of the patient. If the event did lead to the death of the patient, the start date was assigned as the day of death. When the start or end date of a therapy was missing, the missing start or end date was estimated as the midpoint between the last two follow-up visits, or if another therapy was given, the date was estimated as just before or after the additional therapy, so that a parallel therapy of several b/tsDMARDs was avoided. When a therapy ended due to the patient's death, a missing end date was set to the date of death.

9.9.4. Sensitivity And Additional Analyses

For regression models, a sensitivity analysis was conducted in which initiation of the new therapy did not stop (i.e., lead to censoring in) the 90-day risk window, and follow-up time and events occurring after the switch were attributed to prior therapy (rather than the new therapy).

As additional analysis, age/sex-standardized IRs were estimated for each outcome, using the tofacitinib cohort as standard; a direct standardization approach was implemented, using the age-sex-distribution of person-time in the tofacitinib cohort. The following groups were defined: women <65 years, women ≥65 years, men <65 years, men ≥65 years. Direct standardization is known to become unstable in case of categories with small numbers that may occur for some outcomes. Therefore, if there were fewer than five events in any of the groups, an indirect standardization approach using the combined cohorts as standard was used instead.

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9.9.5. Amendments To The Statistical Analysis Plan

The following amendments were made:

- In baseline tables, additionally the following variables were added: seropositivity regarding either rheumatoid factor or ACPA; remission and “other reason” as reason for therapy stop; and the information on missing values for joint replacement.

- Without making additions to the baseline tables, in the text additional information was given on the following variables in some occasions: type of enrolling institution of patients (rheumatology clinic or rheumatology practice), presence of osteoporosis as comorbidity, and mode of action of started therapy.

- In baseline tables, additionally osteoporosis was considered due to a potential relevance for the outcome fractures.

- For Cox regression models, the variable age was considered not as a continuous variable but in a categorical way to account for the nonlinear influence of age, with the following categories: < 50, ≥ 50 and < 60, ≥ 60 and < 70, ≥ 70 years.

- For Cox regression models, glucocorticoid use was considered with the following categories: 0 vs. > 0 and ≤ 5, > 5 and ≤ 10, > 10 mg/d instead of <5 vs. 5-<10 / ≥ 10 mg/d, in order to differentiate patients who have not received any glucocorticoids from those who received ≤ 5 mg/d. The frequent value of 5 mg/d was included in the category > 0 - ≤ 5 mg/d instead of in a category ≥ 5 - < 10 mg/d to account for the situation in Germany, where the current guidelines recommend to reduce the dosis of a concomitant glucocorticoid therapy to 5 mg/d or less within 8 weeks of therapy start [32]. For consistency, the value of 10 mg/d was likewise assigned to the lower category instead of to the higher one.

- For Cox regression models, the variable previous b/tsDMARDs was considered not as a binary variable (with categories 0,1 vs. ≥ 2) but with the following categories: 0, 1, ≥ 2. The rationale was that b/tsDMARD naive patients should be differentiated from patients who have already received one prior b/tsDMARD due to differing patient characteristics (see Table 10). The balance between cohorts achieved by inverse probability weighting (IPW) was not affected by this change.

- Indirect standardization of IRs (instead of direct standardization) was used when in any of the four standardization categories there were fewer than five (instead of fewer than four) events, for greater consistency with the criterion for fitting regression models (see 9.8.2).

- In case of outcomes for which there were discrepancies between the respective definitions in the PASS protocol and the statistical analysis plan, the PASS protocol was given priority over the SAP. Specifically, for the outcomes explicitly defined in Appendix 1 of the PASS protocol via MedDRA pt terms, SOC terms or SMQ terms and, potentially, additional specifications (i.e., serious infections, HZ, CV risk, GI perforation, PML, NMSC, malignancies excl. NMSC (overall), lung cancer, lymphoma, fractures),

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those definitions were employed even if this implied differences compared to the outcomes list in the SAP.
As a result, in particular

- serious infections (outcome 1 in section 9.4.1) and the corresponding subtypes included only hospitalized cases, according to Appendix 1 of the PASS protocol, while no restriction to hospitalized cases was made in the SAP;

- HZ (outcome 3 in section 9.4.1) was not restricted to hospitalized (or generally serious) cases, according to Appendix 1 of the PASS protocol, while the corresponding outcome listed in the SAP was HZ (hospitalized);

- malignancies (overall, excluding NMSC) (outcome 17 in section 9.4.1) were defined using the SMQ term malignant or unspecified tumours, in line with Appendix 1 of the PASS protocol, although the corresponding outcome listed in the SAP was neoplasms excl. NMSC, which would also have included e.g. benign neoplasms.

- For patient characteristics and IRs, the results for tofacitinib and bDMARD cohorts are documented in the overall tables (Table 5 for patient characteristics at time of enrolment, Table 9 for patient characteristics at time of enrolment or during follow-up, Table 13 for IRs), whereas the results for the b/tsDMARD naive nbDMARD cohort are documented in the stratified tables (Table 6 for patient characteristics at time of enrolment, Table 10 for patient characteristics at time of enrolment or during follow-up, Table 14 for IRs). The rationale was to always have those therapy groups in the same table that are being compared with each other.

- For the outcome of malignancy (overall, excluding NMSC), additionally Cox regression models were calculated for the subgroup of patients aged ≥ 65 years, due to older age having been found as a major risk factor for this outcome in both the ORAL Surveillance study [33] and analyses in RABBIT [34].

- For the outcome of fractures, additionally Cox regression models were calculated for female and male patients, due to differing therapy-specific percentages of patients with osteoporosis among females (21.2 % in the tofacitinib group, 18.1 % in the bDMARDs group), but not male patients (10.2 % in the tofacitinib group, 10.5 % in the bDMARDs group).

9.10. Quality Control

All CRFs are sent to the RABBIT registry holder by fax. After having received them, the initial plausibility checks are performed by medical documentalists. Missing or implausible variables are stratified into different groups: for some variables, missing values or implausible values are always queried, for other variables, missing or implausible values are only queried when values of other variables are also queried, and for some variables, missing or implausible values are not queried at all. Disease related information (joint count, inflammation markers, physician reported disease activity, etc.) and information related to DMARD therapy (start and stop dates, reasons for discontinuation of DMARDs, etc.) are always queried. There are no inquiries if physician- reported weight or any patient- reported variables (e.g., general health

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state, functional state, fatigue, pain, smoking habits, etc.) are missing. After the first monitoring steps, data are entered into the database. At regular intervals (every eight weeks) a new dataset is created by adding the new data. After this process, the next monitoring steps are performed, mainly regarding longitudinal data plausibility.

If more than two follow-up time points are missing in one patient, an intensive dropout inquiry is initiated. First, the physician is queried to determine if anything is known about the patient's whereabouts. Secondly, the patient (or his/her relatives living in the same household) is contacted to determine why there have been no visits to the rheumatologist and whether the patient is still in rheumatologic care. If insufficient information is received after these first steps, authorities (e.g., registration office) are asked about new addresses, or whether the patient has died. In the latter case, health authorities are subsequently contacted to obtain causes of death.

Standardised procedures to obtain and report AE information are described in section 9.5.2.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed.

9.11. Protection Of Human Subjects

Subject information and consent

Not applicable

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

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

The original RABBIT study protocol was approved on 01-MAR-2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001). A revised and updated study protocol, including any amendments and informed consent documentation, received approval on 5-JULY-2021 (Protocol number EA4/123/21).

The final protocol, any amendments, and informed consent documentation were reviewed and approved by the DRFZ data protection officer.

The study management team is supported by a scientific advisory board comprising e.g. four experienced community and hospital rheumatologists as well as a patient representative. The scientific advisory board was appointed by the governing board of the German Society for Rheumatology in agreement with the Professional Association of German Rheumatologists. The advisory board’s duties are: regular review of the reports, consultation in case of serious events, discussion of the research agenda and the SAPs. The advisory board members meet personally at least once annually with the principal investigators and the study physicians and otherwise communicate by telephone conferences and email.

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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 the 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, and the STROBE guidelines.

10. RESULTS

10.1. Participants

From 01-MAY-2017 until 31-DEC-2024, at enrolment, 400 patients initiated therapy with tofacitinib and 4,433 started a bDMARD (Figure 1). After excluding patients with prior use of the cohort-defining therapy in the last 365 days, there were 398 new users in the tofacitinib cohort and 4,427 new users in the bDMARD cohort (Table 5). The number of patients with prior b/tsDMARD use was 166 among tofacitinib initiators, resulting in 232 b/tsDMARD naive patients enrolled with tofacitinib. These patients were compared with 3,442 b/tsDMARD naive bDMARD treated patients, and 1,364 b/tsDMARD naive patients in the nbDMARD cohort (Table 6).

Considering therapy initiation only during follow-up between 01-MAY-2017 and 31-DEC-2024, 847 patients initiated 868 episodes with tofacitinib and 4,450 patients started 5,940 episodes with a drug from the bDMARD cohort. There were 31 episodes with prior use of the same substance within the tofacitinib cohort and 1280 episodes with the same substance the last 365 days within the bDMARD cohort, resulting in 837 new user episodes in the tofacitinib cohort and 4,660 new user episodes in the bDMARD cohort.

Considering therapy initiations at enrolment and during follow-up between 01-MAY-2017 and 31-DEC-2024, 1,230 patients initiated 1,268 therapy episodes with tofacitinib and 8,269 patients started 10,373 episodes with a bDMARD (Figure 1). After excluding therapy episodes of patients who at the time of initiation had prior use of the same substance, there were 1,235 therapy episodes contributed by 1,227 patients for the tofacitinib cohort and 9,087 therapy episodes contributed by 7,747 patients for the bDMARD cohort (Table 9). The number of episodes with prior b/tsDMARD use was 914 in tofacitinib initiators, resulting in 321 b/tsDMARD naive episodes in the tofacitinib cohort from 321 patients. The nbDMARD cohort included 3,583 therapy episodes contributed by 3,109 b/tsDMARD naive patients (Table 10).

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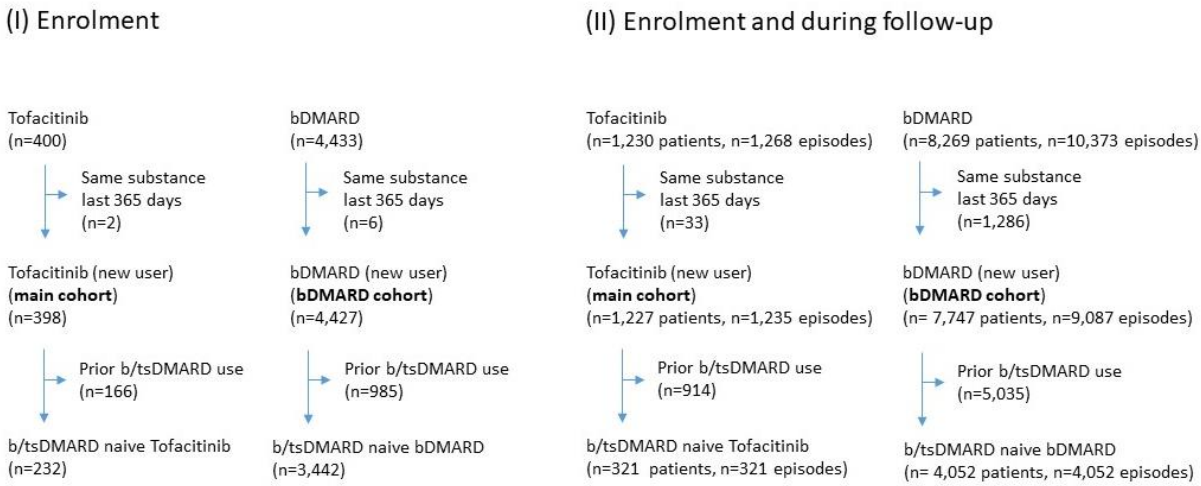
Figure 1. Flowchart with therapy episodes started at (I) enrolment or (II) enrolment and during follow-up



Cohorts used for the main analyses are marked in bold. For (I) enrolment, the number of episodes corresponds to the number of patients, while it does not for (II) enrolment and during follow-up.
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

10.2. Descriptive Data

(I) At Time of Enrolment

Characteristics of patients (at the time of enrolment in RABBIT) in the tofacitinib cohort and the bDMARD comparator cohort are presented in Table 5 Characteristics for the b/tsDMARD naive tofacitinib, bDMARD and nbDMARD patients at time of enrolment in RABBIT are presented in Table 6 (which is stratified by the number of previous b/tsDMARDs) for better comparison.

As can be seen in Table 5, median age at enrolment was 60.3 years in the tofacitinib cohort and 59.8 years in the bDMARD cohort. Proportions of female patients were similar in the tofacitinib and bDMARD cohorts (72.4% versus 71.9%). Proportions of patients with seropositivity measured as RF and/or ACPA were 70.3% in the tofacitinib cohort and 75.2% in the bDMARD cohort. The median RA disease duration was longer in the tofacitinib cohort with 8.2 years compared to 5.7 years in the bDMARD cohort. Likewise, median disease activity measured by DAS28-ESR was higher for patients starting tofacitinib (4.8), compared to patients starting bDMARD (4.5). There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 5). The proportion of bionaive patients was only 58.3% in the tofacitinib cohort compared to 77.8% in the bDMARD cohort. Likewise, only 38.9% in the tofacitinib cohort compared to 55.4% in the bDMARD cohort were on combination therapy with nbDMARDs. In the bDMARD cohort, 41.6% initiated etanercept, 28.2% adalimumab, 0.8% infliximab, 7.2% certolizumab pegol, 1.5% golimumab, 1.1% rituximab, 5.1% sarilumab, 6.2% tocilizumab, and 8.2% abatacept. The number of patients with glucocorticoid therapy and the used average

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doses were comparable between the cohorts (Table 5). The median percentage of full physical function measured by FFbH was lower in the tofacitinib cohort (66.7%), compared with the bDMARD cohort (72.2%). Likewise, the mean number of comorbidities was higher in the tofacitinib cohort (2.8) compared to the bDMARD cohort (2.5). This difference was driven by higher percentage of patients diagnosed with diabetes, hypertension, coronary heart disease, and chronic kidney disease in the tofacitinib cohort; however, there was a higher percentage of patients with history of malignancy in the bDMARD cohort. Patients in the tofacitinib cohort were more likely to report being never smokers relative to those in the bDMARD cohort (45.5% versus 38.9%, respectively) and also less likely to report being current smokers (26.5% versus 29.1%, respectively).

Only 3.8% of the patients in the tofacitinib cohort compared to 41.0% in the bDMARD cohort were enrolled on 30-JUNE-2021 or afterwards. 10.8% of patients in the tofacitinib and 14.4% in the bDMARD cohort were enrolled by a rheumatology clinic.

Table 5. Baseline Characteristics for time of enrolment (I), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=398)	bDMARD (n=4,427)
Demographics		
Age (median [Q1, Q3])	60.3 [52.8, 68.1]	59.8 [51.5, 67.9]
Female sex (N (%))	288 (72.4%)	3184 (71.9%)
Disease-related characteristics		
Year of therapy start before 30-JUNE-2021 (N (%))	383 (96.2%)	2611 (59.0%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	15 (3.8%)	1816 (41.0%)
Rheumatoid factor positive (N (%))	255 (65.1%)	2895 (66.9%)
Rheumatoid factor positive missing (N (%))	6 (1.5%)	99 (2.2%)
Rheumatoid factor /ACPA positive (N (%))	275 (70.3%)	3262 (75.2%)
Rheumatoid factor /ACPA positive missing (N (%))	7 (1.8%)	88 (2.0%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	7 (1.8%)	45 (1.0%)
Calendar year of recalled RA symptom onset (N (%))		
< 1990	21 (5.3%)	120 (2.7%)
≥ 1990 and < 2000	45 (11.3%)	322 (7.3%)
≥ 2000 and < 2007	68 (17.1%)	530 (12.0%)
≥ 2007 and < 2017	192 (48.2%)	1799 (40.7%)
≥ 2017	72 (18.1%)	1650 (37.3%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	6 (0.1%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	8.2 [3.8, 15.6]	5.7 [2.1, 12.3]
Disease duration missing (N (%))	0 (0.0%)	9 (0.2%)

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Table 5. Baseline Characteristics for time of enrolment (I), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=398)	bDMARD (n=4,427)
Disease duration <5 years (N (%))	139 (34.9%)	2043 (46.2%)
DAS28-ESR (median [Q1, Q3])	4.8 [3.8, 5.8]	4.5 [3.6, 5.4]
DAS28-ESR missing (N (%))	22 (5.5%)	484 (10.9%)
HAQ (median [Q1, Q3])	1.3 [0.8, 2.0]	1.1 [0.7, 1.7]
HAQ missing (N (%))	3 (0.8%)	58 (1.3%)
Patients with previous nb/b/tsDMARDs (N (%))	396 (99.5%)	4332 (97.9%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	226 (56.8%)	1768 (39.9%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	109 (27.4%)	1057 (23.9%)
Therapy stop of last previous DMARD therapy due to re-mission	1 (0.3%)	32 (0.7%)
Therapy stop of last previous DMARD therapy due to other reasons	10 (2.5%)	192 (4.3%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	102 (25.6%)	1819 (41.1%)
Patients with previous bDMARDs (N (%))	166 (41.7%)	956 (21.6%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	0.9 (1.3)	0.4 (0.8)
Patients with previous tsDMARDs (N (%))	0 (0.0%)	93 (2.1%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))		
0	232 (58.3%)	3.442 (77.8%)
1	78 (19.6%)	540 (12.2%)
≥2	88 (22.1%)	445 (10.1%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	1.9 (0.9)	1.7 (0.9)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	155 (38.9%)	2454 (55.4%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	140 (35.2%)	2298 (51.9%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	215 (54.0%)	2322 (53.5%)
Concomitant oral steroids missing (N (%))	0 (0.0%)	90 (2.0%)
Dose of concomitant Glucocorticoids (N (%))		
<5 mg/d	221 (55.5%)	2497 (57.6%)
5-<10 mg/d	139 (34.9%)	1346 (31.0%)
≥ 10 mg/d	38 (9.5%)	494 (11.4%)

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Table 5. Baseline Characteristics for time of enrolment (I), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=398)	bDMARD (n=4,427)
Dose of concomitant Glucocorticoids missing (N (%))	0 (0.0%)	90 (2.0%)
Concomitant NSAIDs (N (%))	87 (22.0%)	1203 (27.2%)
Concomitant NSAIDs missing (N (%))	2 (0.5%)	12 (0.3%)
Global Health (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.5 (2.1)
Global Health missing (N (%))	2 (0.5%)	44 (1.0%)
Pain (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.5 (2.3)
Pain missing (N (%))	1 (0.3%)	25 (0.6%)
FFbH (median [Q1, Q3])	66.7 [41.7, 83.3]	72.2 [52.8, 88.2]
FFbH missing (N (%))	3 (0.8%)	58 (1.3%)
28 Tender Joint Count (median [Q1, Q3])	7.0 [3.0, 12.0]	6.0 [2.0, 10.0]
28 Tender Joint Count missing (N (%))	0 (0.0%)	18 (0.4%)
28 Swollen Joint Count (median [Q1, Q3])	4.0 [2.0, 8.0]	3.0 [1.0, 6.0]
28 Swollen Joint Count missing (N (%))	0 (0.0%)	16 (0.4%)
CRP (mg/liter) (median [Q1, Q3])	6.3 [3.0, 15.0]	5.6 [2.3, 13.9]
CRP missing (N (%))	19 (4.8%)	163 (3.7%)
ESR (mm/1h) (median [Q1, Q3])	20.0 [9.0, 34.0]	18.0 [8.0, 32.0]
ESR missing (N (%))	20 (5.0%)	425 (9.6%)
Smoking		
Current (N (%))	99 (26.5%)	1.223 (29.1%)
Previous (N (%))	105 (28.1%)	1.345 (32.0%)
Never (N (%))	170 (45.5%)	1.633 (38.9%)
Missing (N (%))	24 (6.0%)	226 (5.1%)
Disease history		
Malignancies (N (%))	14 (3.5%)	213 (4.8%)
Lymphoma (N (%))	3 (0.8%)	22 (0.5%)
Tuberculosis (N (%))	8 (2.0%)	95 (2.1%)
Joint replacement surgery (N (%))	57 (14.4%)	464 (10.6%)
Joint replacement surgery missing (N (%))	3 (0.8%)	30 (0.7%)
COPD (N (%))	18 (4.5%)	229 (5.2%)
Diabetes mellitus (N (%))	64 (16.1%)	551 (12.4%)
Hypertension (N (%))	191 (48.0%)	1904 (43.0%)
CHD/CAD (N (%))	39 (9.8%)	300 (6.8%)
CKD (N (%))	34 (8.5%)	277 (6.3%)
Heart failure (incl. CHF) (N (%))	11 (2.8%)	93 (2.1%)
Comorbidities		
Number of comorbidities (mean (SD))	2.8 (2.3)	2.5 (2.3)
No comorbidity (N (%))	80 (20.1%)	1093 (24.7%)

Table 5. Baseline Characteristics for time of enrolment (I), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=398)	bDMARD (n=4,427)
One comorbidity (N (%))	44 (11.1%)	696 (15.7%)
Two comorbidities (N (%))	67 (16.8%)	747 (16.9%)
Three or more comorbidities (N (%))	207 (52.0%)	1891 (42.7%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

Stratified analyses

When restricting the population to bionaive patients (Table 6), there were 232 patients enrolled with tofacitinib, 3,392 patients enrolled with bDMARDs and 1,364 enrolled with nbDMARDs. The median age at enrolment was comparable in all three cohorts (61.0 years in the tofacitinib cohort, 59.6 years in the bDMARD cohort and 61.0 years in the nbDMARD cohort). Proportions of female patients were comparable (71.6% in the tofacitinib cohort, 71.3% in the bDMARD cohort, and 73.3% in the nbDMARD cohort). Proportions of patients with seropositivity measured as RF and/or ACPA varied by cohort; 67.5% of patients were seropositive in the tofacitinib cohort, 74.1% in the bDMARD cohort and 66.5% in the nbDMARD cohort.

Even for bionaive patients, the median RA disease duration was longer in the tofacitinib cohort with 5.3 years (compared to 4.4 years in the bDMARD cohort and 3.3 years in the nbDMARD cohort). Likewise, median disease activity, measured by DAS28-ESR, was higher for patients starting tofacitinib (4.8), compared to patients starting bDMARD (4.6) and nbDMARD (4.2). There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD and nbDMARD cohort (Table 6). Only 40.5% of patients in the tofacitinib cohort compared to 58.1% of patients in the bDMARD cohort were on combination therapy with nbDMARDs. In the bDMARD cohort, the distribution of therapies initiated was as follows: 47.8% initiated etanercept, 30.0% adalimumab, 0.5% infliximab, 7.3% certolizumab pegol, 1.4% golimumab, 0.4% rituximab, 3.0% sarilumab, 4.1% tocilizumab, and 5.6% abatacept. The number of patients with glucocorticoid therapy was comparable between the cohorts. The median percentage of full physical function, measured by FFbH, was 69.4% in the tofacitinib cohort, compared to 75.0% in the bDMARD cohort and 77.8% in the nbDMARD cohort. The mean number of comorbidities was higher in the tofacitinib cohort (2.6) compared to the bDMARD cohort (2.4) and the nbDMARD cohort (2.0). Patients in the tofacitinib cohort were more likely to report being never smokers (47.0%) relative to patients in the bDMARD cohort (38.0%) and in the nbDMARD cohort (39.6%); patients in the tofacitinib cohort were also less likely to report being current smokers (27.4% relative to 29.9% and 31.7%), respectively.

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When restricting the population to patients with exactly one previous b/tsDMARD (Table 6), there were 78 patients in the tofacitinib cohort and 540 patients in the bDMARD cohort. When restricting the population to patients with at least two previous b/tsDMARDs (Table 6), there were 88 patients in the tofacitinib cohort and 445 patients in the bDMARD cohort. Due to the small numbers in the tofacitinib cohort, comparisons of these subgroups should be interpreted cautiously.

None of the patients in the tofacitinib cohort had prior use of non-tofacitinib JAKi therapy (Table 7) and similarly there were very few patients with prior use of non-tofacitinib JAKi therapy in the bDMARD cohort (2.1%) (Table 7).

When restricting the population to patients on monotherapy (Table 8), there were 243 patients in the tofacitinib cohort and 1,973 patients in the bDMARD cohort. The median age at enrolment was similar in both cohorts (61.3 years in the tofacitinib cohort and 60.6 years in the bDMARD cohort). Proportions of female patients were comparable (both 76.1%). Proportions of patients with seropositivity measured as RF and/or ACPA were 66.7% in the tofacitinib cohort and 71.9% in the bDMARD cohort. The median RA disease duration was longer in the tofacitinib cohort with 8.4 years compared to 6.2 years in the bDMARD cohort. Likewise, median disease activity measured by DAS28-ESR was higher for patients starting tofacitinib (4.9), compared to patients starting bDMARD (4.6). There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 8). In the bDMARD cohort, the distribution of therapies initiated was as follows: 42.2% initiated etanercept, 25.3% adalimumab, 0.7 infliximab, 9.1% certolizumab pegol, 1.1% golimumab, 0.8% rituximab, 7.3% sarilumab, 9.8% tocilizumab, and 3.8% abatacept. The number of patients with glucocorticoid therapy was 55.1% in the tofacitinib and 51.6% in the bDMARD cohort. The median percentage of full physical function measured by FFbH was only 61.1% in the tofacitinib cohort, compared to 72.2% in the bDMARD cohort. The mean number of comorbidities was higher in the tofacitinib cohort (2.9) compared to the bDMARD cohort (2.6). Patients in the tofacitinib cohort were more likely to report never smoking relative to patients in the bDMARD cohort (46.2% versus 42.0%, respectively), and less likely to report being current smokers (22.7% versus 25.6%, respectively).

When restricting the population to patients with a concomitant nbDMARD therapy (Table 8), there were 155 patients in the tofacitinib cohort and 2,454 patients in the bDMARD cohort. The median age at enrolment was comparable (59.1 years in the tofacitinib cohort, and 59.2 years in the bDMARD cohort). Likewise, the proportions of female patients were comparable (66.5% in the tofacitinib cohort, and 68.5% in the bDMARD cohort). Proportions of patients with seropositivity measured as RF and/or ACPA were comparable (76.0% in the tofacitinib cohort and 77.8% in the bDMARD cohort). The median RA disease duration was longer in the tofacitinib cohort with 7.6 years compared to 5.3 years in the bDMARD cohort. The median disease activity measured by DAS28-ESR was 4.7 for patients starting tofacitinib, compared to 4.5 for patients starting bDMARD. In the bDMARD cohort, the distribution of therapies initiated was as follows: 41.2% initiated etanercept, 30.6% adalimumab, 1.0% infliximab, 5.6% certolizumab pegol, 1.9% golimumab, 1.4% rituximab, 3.3% sarilumab, 3.3% tocilizumab, and 11.7% abatacept. The percentages of patients with glucocorticoid therapy were comparable between the cohorts (52.3% in the tofacitinib and 55.1% in the bDMARD cohort). The median percentage of full physical function measured by FFbH was 70.8% in the tofacitinib cohort, compared to 75.0% in the bDMARD cohort. The mean number of comorbidities was higher in the tofacitinib cohort (2.7) compared to the bDMARD cohort (2.4). Patients in the tofacitinib

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cohort were more likely to report never smoking relative to patients in the bDMARD cohort (44.3% versus 36.4%, respectively), and slightly less likely to report being current smokers (32.2% versus 31.9%, respectively).

The most commonly used nbDMARD was MTX (90.3% in the tofacitinib and 93.6% in the bDMARD cohort).

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Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=232)	bDMARD (n=3442)	nbDMARD (n=1364)	Tofacitinib (n=78)	bDMARD (n=540)	Tofacitinib (n=88)	bDMARD (n=445)
Demographics							
Age (median [Q1, Q3])	61.0 [53.4, 70.2]	59.6 [51.4, 67.6]	61.0 [53.2, 69.5]	58.5 [51.2, 67.4]	60.7 [52.7, 69.5]	60.2 [53.4, 65.8]	59.8 [51.8, 67.9]
Female sex (N (%))	166 (71.6%)	2453 (71.3%)	1000 (73.3%)	56 (71.8%)	378 (70.0%)	66 (75.0%)	353 (79.3%)
Disease-related characteristics							
Year of therapy start before 30-JUNE-2021 (N (%))	223 (96.1%)	1976 (57.4%)	1052 (77.1%)	74 (94.9%)	340 (63.0%)	86 (97.7%)	295 (66.3%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	9 (3.9%)	1466 (42.6%)	312 (22.9%)	4 (5.1%)	200 (37.0%)	2 (2.3%)	150 (33.7%)
Rheumatoid factor positive (N (%))	144 (62.6%)	2209 (65.6%)	771 (59.4%)	53 (69.7%)	378 (72.1%)	58 (67.4%)	308 (70.6%)
Rheumatoid factor positive missing (N (%))	2 (0.9%)	74 (2.1%)	65 (4.8%)	2 (2.6%)	16 (3.0%)	2 (2.3%)	9 (2.0%)
Rheumatoid factor /ACPA positive (N (%))	154 (67.5%)	2503 (74.1%)	868 (66.5%)	58 (76.3%)	416 (79.1%)	63 (72.4%)	343 (78.7%)
Rheumatoid factor /ACPA positive missing (N (%))	4 (1.7%)	65 (1.9%)	59 (4.3%)	2 (2.6%)	14 (2.6%)	1 (1.1%)	9 (2.0%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	5.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	4 (1.7%)	37 (1.1%)	12 (0.9%)	2 (2.6%)	6 (1.1%)	1 (1.1%)	2 (0.4%)
Calendar year of recalled RA symptom onset (N (%))							
< 1990	7 (3.0%)	56 (1.6%)	21 (1.5%)	4 (5.1%)	35 (6.5%)	10 (11.4%)	29 (6.5%)
≥ 1990 and < 2000	15 (6.5%)	177 (5.1%)	38 (2.8%)	14 (17.9%)	63 (11.7%)	16 (18.2%)	82 (18.5%)
≥ 2000 and < 2007	27 (11.6%)	329 (9.6%)	110 (8.1%)	16 (20.5%)	103 (19.1%)	25 (28.4%)	98 (22.1%)
≥ 2007 and < 2017	121 (52.2%)	1378 (40.1%)	583 (42.8%)	36 (46.2%)	231 (42.9%)	35 (39.8%)	190 (42.8%)
≥ 2017	62 (26.7%)	1498 (43.6%)	609 (44.7%)	8 (10.3%)	107 (19.9%)	2 (2.3%)	45 (10.1%)

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Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs

Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	4 (0.1%)	3 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	5.3 [2.6, 11.0]	4.4 [1.7, 10.1]	3.3 [1.3, 8.0]	10.7 [6.5, 20.0]	10.0 [5.0, 17.9]	14.3 [8.5, 21.5]	12.7 [7.3, 20.6]
Disease duration missing (N (%))	0 (0.0%)	7 (0.2%)	3 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Disease duration <5 years (N (%))	112 (48.3%)	1841 (53.6%)	834 (61.3%)	17 (21.8%)	135 (25.0%)	10 (11.4%)	67 (15.1%)
DAS28-ESR (median [Q1, Q3])	4.8 [3.7, 5.8]	4.6 [3.7, 5.4]	4.2 [3.3, 5.1]	4.8 [3.5, 5.8]	4.3 [3.4, 5.2]	5.0 [4.0, 5.9]	4.5 [3.6, 5.5]
DAS28-ESR missing (N (%))	8 (3.4%)	332 (9.6%)	217 (15.9%)	8 (10.3%)	81 (15.0%)	6 (6.8%)	71 (16.0%)
HAQ (median [Q1, Q3])	1.2 [0.7, 1.8]	1.1 [0.7, 1.6]	1.0 [0.6, 1.6]	1.3 [0.8, 1.9]	1.2 [0.8, 1.8]	1.7 [1.0, 2.1]	1.3 [0.9, 1.8]
HAQ missing (N (%))	2 (0.9%)	45 (1.3%)	20 (1.5%)	1 (1.3%)	6 (1.1%)	0 (0.0%)	7 (1.6%)
Patients with previous nb/b/tsDMARDs (N (%))	230 (99.1%)	3347 (97.2%)	1364 (100.0%)	78 (100.0%)	540 (100.0%)	88 (100.0%)	445 (100.0%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	108 (46.6%)	1174 (34.1%)	371 (27.2%)	52 (66.7%)	315 (58.3%)	66 (75.0%)	279 (62.7%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	65 (28.0%)	861 (25.0%)	433 (31.7%)	25 (32.1%)	93 (17.2%)	19 (21.6%)	103 (23.1%)
Therapy stop of last previous DMARD therapy due to remission	0 (0.0%)	11 (0.3%)	6 (0.4%)	1 (1.3%)	15 (2.8%)	0 (0.0%)	6 (1.3%)
Therapy stop of last previous DMARD therapy due to other reasons	3 (1.3%)	99 (2.9%)	14 (1.0%)	2 (2.6%)	51 (9.4%)	5 (5.7%)	42 (9.4%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	79 (34.1%)	1608 (46.7%)	618 (45.3%)	9 (11.5%)	130 (24.1%)	14 (15.9%)	81 (18.2%)
Patients with previous bDMARDs (N (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	78 (100.0%)	540 (100.0%)	88 (100.0%)	416 (93.5%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0.0 (0.0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.0 (0.0)	1.0 (0.0)	3.0 (1.2)	2.3 (1.1)
Patients with previous tsDMARDs (N (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	93 (20.9%)

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Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs

Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))							
0	232 (100.0%)	3442 (100.0%)	1364 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	78 (100.0%)	540 (100.0%)	0 (0.0%)	0 (0.0%)
≥2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	88 (100.0%)	445 (100.0%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	1.8 (0.9)	1.6 (0.8)	1.2 (0.5)	2.3 (1.1)	2.3 (1.2)	2.3 (1.0)	2.1 (1.0)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2.0 (1.0)	1.9 (1.0)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	94 (40.5%)	2000 (58.1%)	NA	29 (37.2%)	260 (48.1%)	32 (36.4%)	194 (43.6%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	84 (36.2%)	1873 (54.4%)	NA	26 (33.3%)	245 (45.4%)	30 (34.1%)	180 (40.4%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	125 (53.9%)	1851 (55.0%)	718 (53.2%)	44 (56.4%)	259 (48.8%)	46 (52.3%)	212 (47.9%)
Concomitant oral steroids missing (N (%))	0 (0.0%)	79 (2.3%)	15 (1.1%)	0 (0.0%)	9 (1.7%)	0 (0.0%)	2 (0.4%)
Dose of concomitant Glucocorticoids (N (%))							
<5 mg/d	134 (57.8%)	1902 (56.6%)	766 (56.8%)	41 (52.6%)	327 (61.6%)	46 (52.3%)	268 (60.5%)
5-<10 mg/d	76 (32.8%)	1075 (32.0%)	480 (35.6%)	32 (41.0%)	152 (28.6%)	31 (35.2%)	119 (26.9%)
≥ 10 mg/d	22 (9.5%)	386 (11.5%)	103 (7.6%)	5 (6.4%)	52 (9.8%)	11 (12.5%)	56 (12.6%)
Dose of concomitant Glucocorti-coids missing (N (%))	0 (0.0%)	79 (2.3%)	15 (1.1%)	0 (0.0%)	9 (1.7%)	0 (0.0%)	2 (0.4%)
Concomitant NSAIDs (N (%))	46 (20.0%)	903 (26.3%)	330 (24.3%)	17 (21.8%)	156 (28.9%)	24 (27.3%)	144 (32.4%)

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Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs

Concomitant NSAIDs missing (N (%))	2 (0.9%)	10 (0.3%)	8 (0.6%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Global Health (NRS 0 to 10) (mean (SD))	5.5 (2.3)	5.4 (2.1)	5.2 (2.1)	5.3 (2.2)	5.5 (2.1)	6.3 (1.8)	5.8 (2.2)
Global Health missing (N (%))	1 (0.4%)	34 (1.0%)	8 (0.6%)	1 (1.3%)	5 (0.9%)	0 (0.0%)	5 (1.1%)
Pain (NRS 0 to 10) (mean (SD))	5.5 (2.3)	5.5 (2.3)	5.3 (2.4)	5.5 (2.3)	5.5 (2.3)	6.4 (1.8)	6.0 (2.3)
Pain missing (N (%))	1 (0.4%)	18 (0.5%)	8 (0.6%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	0.0, 10.0
FFbH (median [Q1, Q3])	69.4 [50.0, 88.9]	75.0 [55.6, 88.9]	77.8 [55.9, 89.8]	67.6 [44.4, 83.3]	69.4 [50.0, 83.3]	52.8 [37.5, 75.7]	66.7 [46.9, 80.6]
FFbH missing (N (%))	2 (0.9%)	45 (1.3%)	20 (1.5%)	1 (1.3%)	6 (1.1%)	0 (0.0%)	7 (1.6%)
28 Tender Joint Count (median [Q1, Q3])	7.0 [3.0, 11.0]	6.0 [2.0, 10.0]	4.0 [2.0, 8.0]	6.0 [2.0, 11.0]	5.0 [2.0, 10.0]	8.0 [4.0, 12.5]	6.0 [2.0, 11.0]
28 Tender Joint Count missing (N (%))	0 (0.0%)	9 (0.3%)	1 (0.1%)	0 (0.0%)	4 (0.7%)	0 (0.0%)	5 (1.1%)
28 Swollen Joint Count (median [Q1, Q3])	4.0 [2.0, 8.0]	3.0 [1.0, 6.0]	2.0 [0.0, 5.0]	4.0 [1.0, 7.0]	3.0 [1.0, 6.0]	5.0 [1.0, 9.5]	3.0 [1.0, 7.0]
28 Swollen Joint Count missing (N (%))	0 (0.0%)	12 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.4%)
CRP (mg/liter) (median [Q1, Q3])	7.4 [3.1, 15.0]	6.0 [2.5, 14.4]	5.4 [2.2, 12.0]	6.1 [2.8, 19.5]	4.3 [1.7, 12.0]	5.0 [2.0, 11.0]	5.2 [2.1, 13.0]
CRP missing (N (%))	13 (5.6%)	114 (3.3%)	342 (25.1%)	3 (3.8%)	27 (5.0%)	3 (3.4%)	22 (4.9%)
ESR (mm/1h) (median [Q1, Q3])	20.0 [9.0, 31.0]	18.0 [9.0, 33.0]	18.0 [8.0, 32.0]	26.0 [10.0, 48.0]	15.0 [8.0, 29.0]	19.0 [9.0, 32.0]	18.0 [8.0, 32.5]
ESR missing (N (%))	7 (3.0%)	290 (8.4%)	209 (15.3%)	7 (9.0%)	74 (13.7%)	6 (6.8%)	61 (13.7%)
Smoking							
Current (N (%))	60 (27.4%)	982 (29.9%)	406 (31.7%)	24 (31.6%)	133 (26.4%)	15 (19.0%)	108 (26.2%)
Previous (N (%))	56 (25.6%)	1,055 (32.1%)	366 (28.6%)	23 (30.3%)	165 (32.7%)	26 (32.9%)	125 (30.3%)
Never (N (%))	103 (47.0%)	1,247 (38.0%)	507 (39.6%)	29 (38.2%)	206 (40.9%)	38 (48.1%)	180 (43.6%)
Missing (N (%))	13 (5.6%)	158 (4.6%)	85 (6.2%)	2 (2.6%)	36 (6.7%)	9 (10.2%)	32 (7.2%)
Disease history							
Malignancies (N (%))	8 (3.4%)	159 (4.6%)	51 (3.7%)	3 (3.8%)	31 (5.7%)	3 (3.4%)	23 (5.2%)
Lymphoma (N (%))	1 (0.4%)	15 (0.4%)	5 (0.4%)	2 (2.6%)	4 (0.7%)	0 (0.0%)	3 (0.7%)
Tuberculosis (N (%))	5 (2.2%)	78 (2.3%)	9 (0.7%)	2 (2.6%)	10 (1.9%)	1 (1.1%)	7 (1.6%)

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Table 6. Baseline Characteristics for time of enrolment (I), stratified by the number of previous b/tsDMARDs

Joint replacement surgery (N (%))	27 (11.8%)	314 (9.2%)	97 (7.2%)	11 (14.1%)	76 (14.2%)	19 (21.6%)	74 (16.9%)
Joint replacement surgery missing (N (%))	3 (1.3%)	20 (0.6%)	9 (0.7%)	0 (0.0%)	4 (0.7%)	0 (0.0%)	6 (1.3%)
COPD (N (%))	11 (4.7%)	169 (4.9%)	67 (4.9%)	2 (2.6%)	37 (6.9%)	5 (5.7%)	23 (5.2%)
Diabetes mellitus (N (%))	37 (15.9%)	415 (12.1%)	141 (10.3%)	14 (17.9%)	69 (12.8%)	13 (14.8%)	67 (15.1%)
Hypertension (N (%))	104 (44.8%)	1,477 (42.9%)	592 (43.4%)	36 (46.2%)	238 (44.1%)	51 (58.0%)	189 (42.5%)
CHD/CAD (N (%))	17 (7.3%)	206 (6.0%)	90 (6.6%)	10 (12.8%)	56 (10.4%)	12 (13.6%)	38 (8.5%)
CKD (N (%))	24 (10.3%)	199 (5.8%)	78 (5.7%)	5 (6.4%)	41 (7.6%)	5 (5.7%)	37 (8.3%)
Heart failure (incl. CHF) (N (%))	7 (3.0%)	75 (2.2%)	34 (2.5%)	2 (2.6%)	10 (1.9%)	2 (2.3%)	8 (1.8%)
Comorbidities							
Number of comorbidities (mean (SD))	2.6 (2.1)	2.4 (2.2)	2.0 (2.0)	2.7 (2.6)	2.7 (2.4)	3.5 (2.4)	2.9 (2.6)
No comorbidity (N (%))	46 (19.8%)	872 (25.3%)	428 (31.4%)	22 (28.2%)	128 (23.7%)	12 (13.6%)	93 (20.9%)
One comorbidity (N (%))	29 (12.5%)	540 (15.7%)	180 (13.2%)	8 (10.3%)	75 (13.9%)	7 (8.0%)	81 (18.2%)
Two comorbidities (N (%))	44 (19.0%)	598 (17.4%)	274 (20.1%)	11 (14.1%)	91 (16.9%)	12 (13.6%)	58 (13.0%)
Three or more comorbidities (N (%))	113 (48.7%)	1,432 (41.6%)	482 (35.3%)	37 (47.4%)	246 (45.6%)	57 (64.8%)	213 (47.9%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milli-gram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=398)	bDMARD (n=4334)	Tofacitinib (n=0)	bDMARD (n=93)
Demographics				
Age (median [Q1, Q3])	60.3 [52.8, 68.1]	59.8 [51.5, 67.9]	NA	58.6 [48.7, 65.2]
Female sex (N (%))	288 (72.4%)	3112 (71.8%)	NA	72 (77.4%)
Disease-related characteristics				
Year of therapy start before 30-JUNE-2021 (N (%))	383 (96.2%)	2548 (58.8%)	NA	63 (67.7%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	15 (3.8%)	1786 (41.2%)	NA	30 (32.3%)
Rheumatoid factor positive (N (%))	255 (65.1%)	2831 (66.8%)	NA	64 (70.3%)
Rheumatoid factor positive missing (N (%))	6 (1.5%)	97 (2.2%)	NA	2 (2.2%)
Rheumatoid factor /ACPA positive (N (%))	275 (70.3%)	3192 (75.1%)	NA	70 (77.8%)
Rheumatoid factor /ACPA positive missing (N (%))	7 (1.8%)	85 (2.0%)	NA	3 (3.2%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	NA	5.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	7 (1.8%)	45 (1.0%)	NA	0 (0.0%)
Calendar year of recalled RA symptom onset (N (%))				
< 1990	21 (5.3%)	118 (2.7%)	NA	2 (2.2%)
≥ 1990 and < 2000	45 (11.3%)	311 (7.2%)	NA	11 (11.8%)
≥ 2000 and < 2007	68 (17.1%)	515 (11.9%)	NA	15 (16.1%)
≥ 2007 and < 2017	192 (48.2%)	1753 (40.5%)	NA	46 (49.5%)
≥ 2017	72 (18.1%)	1631 (37.7%)	NA	19 (20.4%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	6 (0.1%)	NA	0 (0.0%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	8.2 [3.8, 15.6]	5.7 [2.1, 12.3]	NA	9.1 [4.7, 17.0]
Disease duration missing (N (%))	0 (0.0%)	9 (0.2%)	NA	0 (0.0%)
Disease duration <5 years (N (%))	139 (34.9%)	2016 (46.6%)	NA	27 (29.0%)
DAS28-ESR (median [Q1, Q3])	4.8 [3.8, 5.8]	4.5 [3.6, 5.4]	NA	4.4 [3.5, 5.7]

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Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=398)	bDMARD (n=4334)	Tofacitinib (n=0)	bDMARD (n=93)
DAS28-ESR missing (N (%))	22 (5.5%)	476 (11.0%)	NA	8 (8.6%)
HAQ (median [Q1, Q3])	1.3 [0.8, 2.0]	1.1 [0.7, 1.7]	NA	1.3 [0.7, 1.8]
HAQ missing (N (%))	3 (0.8%)	56 (1.3%)	NA	2 (2.2%)
Patients with previous nb/b/tsDMARDs (N (%))	396 (99.5%)	4239 (97.8%)	NA	93 (100.0%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	226 (56.8%)	1719 (39.7%)	NA	49 (52.7%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	109 (27.4%)	1034 (23.9%)	NA	23 (24.7%)
Therapy stop of last previous DMARD therapy due to remission	1 (0.3%)	32 (0.7%)	NA	0 (0.0%)
Therapy stop of last previous DMARD therapy due to other reasons	10 (2.5%)	178 (4.1%)	NA	14 (15.1%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	102 (25.6%)	1796 (41.4%)	NA	23 (24.7%)
Patients with previous bDMARDs (N (%))	166 (41.7%)	892 (20.6%)	NA	64 (68.8%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	0.9 (1.3)	0.3 (0.8)	NA	1.5 (1.5)
Patients with previous tsDMARDs (N (%))	0 (0.0%)	0 (0.0%)	NA	93 (100.0%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))				
0	232 (58.3%)	3442 (79.4%)	NA	0 (0.0%)
1	78 (19.6%)	540 (12.5%)	NA	0 (0.0%)
≥2	88 (22.1%)	352 (8.1%)	NA	93 (100.0%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	1.9 (0.9)	1.7 (0.9)	NA	2.0 (0.8)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Concomitant nbDMARDs (N (%))	155 (38.9%)	2413 (55.7%)	NA	41 (44.1%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)

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Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=398)	bDMARD (n=4334)	Tofacitinib (n=0)	bDMARD (n=93)
Concomitant MTX (N (%))	140 (35.2%)	2259 (52.1%)	NA	39 (41.9%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)
Concomitant oral steroids (N (%))	215 (54.0%)	2269 (53.5%)	NA	53 (57.0%)
Concomitant oral steroids missing (N (%))	0 (0.0%)	90 (2.1%)	NA	0 (0.0%)
Dose of concomitant Glucocorticoids (N (%))				
<5 mg/d	221 (55.5%)	2449 (57.7%)	NA	48 (51.6%)
5-<10 mg/d	139 (34.9%)	1317 (31.0%)	NA	29 (31.2%)
≥ 10 mg/d	38 (9.5%)	478 (11.3%)	NA	16 (17.2%)
Dose of concomitant Glucocorticoids missing (N (%))	0 (0.0%)	90 (2.1%)	NA	0 (0.0%)
Concomitant NSAIDs (N (%))	87 (22.0%)	1180 (27.3%)	NA	23 (24.7%)
Concomitant NSAIDs missing (N (%))	2 (0.5%)	12 (0.3%)	NA	0 (0.0%)
Global Health (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.5 (2.1)	NA	5.8 (2.3)
Global Health missing (N (%))	2 (0.5%)	43 (1.0%)	NA	1 (1.1%)
Pain (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.5 (2.3)	NA	5.9 (2.4)
Pain missing (N (%))	1 (0.3%)	0.0 10.0	NA	1 (1.1%)
FFbH (median [Q1, Q3])	66.7 [41.7, 83.3]	72.2 [52.8, 88.9]	NA	66.7 [47.1, 86.1]
FFbH missing (N (%))	3 (0.8%)	56 (1.3%)	NA	2 (2.2%)
28 Tender Joint Count (median [Q1, Q3])	7.0 [3.0, 12.0]	6.0 [2.0, 10.0]	NA	6.0 [2.0, 9.5]
28 Tender Joint Count missing (N (%))	0 (0.0%)	17 (0.4%)	NA	1 (1.1%)
28 Swollen Joint Count (median [Q1, Q3])	4.0 [2.0, 8.0]	3.0 [1.0, 6.0]	NA	3.0 [1.0, 6.0]
28 Swollen Joint Count missing (N (%))	0 (0.0%)	16 (0.4%)	NA	0 (0.0%)
CRP (mg/liter) (median [Q1, Q3])	6.3 [3.0, 15.0]	5.6 [2.3, 13.9]	NA	5.8 [2.5, 13.5]
CRP missing (N (%))	19 (4.8%)	155 (3.6%)	NA	8 (8.6%)
ESR (mm/1h) (median [Q1, Q3])	20.0 [9.0, 34.0]	18.0 [8.0, 32.0]	NA	20.0 [7.0, 33.0]

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Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=398)	bDMARD (n=4334)	Tofacitinib (n=0)	bDMARD (n=93)
ESR missing (N (%))	20 (5.0%)	419 (9.7%)	NA	6 (6.5%)
Smoking				
Current (N (%))	99 (26.5%)	1205 (29.3%)	NA	18 (21.7%)
Previous (N (%))	105 (28.1%)	1318 (32.0%)	NA	27 (32.5%)
Never (N (%))	170 (45.5%)	1595 (38.7%)	NA	38 (45.8%)
Missing (N (%))	24 (6.0%)	216 (5.0%)	NA	10 (10.8%)
Disease history				
Malignancies (N (%))	14 (3.5%)	200 (4.7%)	NA	5 (5.4%)
Lymphoma (N (%))	3 (0.8%)	22 (0.5%)	NA	0 (0.0%)
Tuberculosis (N (%))	8 (2.0%)	89 (2.1%)	NA	3 (3.2%)
Joint replacement surgery (N (%))	57 (14.4%)	434 (10.3%)	NA	14 (15.1%)
Joint replacement surgery missing (N (%))	3 (0.8%)	30 (0.7%)	NA	0 (0.0%)
COPD (N (%))	18 (4.5%)	223 (5.3%)	NA	4 (4.3%)
Diabetes mellitus (N (%))	64 (16.1%)	524 (12.4%)	NA	11 (11.8%)
Hypertension (N (%))	191 (48.0%)	1824 (43.0%)	NA	34 (36.6%)
CHD/CAD (N (%))	39 (9.8%)	283 (6.7%)	NA	10 (10.8%)
CKD (N (%))	34 (8.5%)	261 (6.2%)	NA	7 (7.5%)
Heart failure (incl. CHF) (N (%))	11 (2.8%)	91 (2.1%)	NA	2 (2.2%)
Comorbidities				
Number of comorbidities (mean (SD))	2.8 (2.3)	2.5 (2.3)	NA	2.5 (2.5)
No comorbidity (N (%))	80 (20.1%)	1058 (25.0%)	NA	22 (23.7%)
One comorbidity (N (%))	44 (11.1%)	663 (15.6%)	NA	20 (21.5%)
Two comorbidities (N (%))	67 (16.8%)	713 (16.8%)	NA	12 (12.9%)
Three or more comorbidities (N (%))	207 (52.0%)	1805 (42.6%)	NA	39 (41.9%)

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Table 7. Baseline Characteristics for time of enrolment (I), stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=398)	bDMARD (n=4334)	Tofacitinib (n=0)	bDMARD (n=93)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, JAK, Janus kinase; MTX, methotrexate; N, Number; NA, not applicable; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=243)	bDMARD (n=1973)	Tofacitinib (n=155)	bDMARD (n=2454)
Demographics				
Age (median [Q1, Q3])	61.3 [53.3, 69.7]	60.6 [51.1, 69.4]	59.1 [52.2, 66.2]	59.2 [51.8, 67.0]
Female sex (N (%))	185 (76.1%)	1502 (76.1%)	103 (66.5%)	1682 (68.5%)
Disease-related characteristics				
Year of therapy start before 30-JUNE-2021 (N (%))	232 (95.5%)	1131 (57.3%)	151 (97.4%)	1480 (60.3%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	11 (4.5%)	842 (42.7%)	4 (2.6%)	974 (39.7%)
Rheumatoid factor positive (N (%))	145 (61.2%)	1244 (64.5%)	110 (71.0%)	1651 (68.8%)
Rheumatoid factor positive missing (N (%))	6 (2.5%)	45 (2.3%)	0 (0.0%)	54 (2.2%)
Rheumatoid factor /ACPA positive (N (%))	158 (66.7%)	1391 (71.9%)	117 (76.0%)	1871 (77.8%)
Rheumatoid factor /ACPA positive missing (N (%))	6 (2.5%)	39 (2.0%)	1 (0.6%)	49 (2.0%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	4.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	5 (2.1%)	18 (0.9%)	2 (1.3%)	27 (1.1%)
Calendar year of recalled RA symptom onset (N (%))				
< 1990	10 (4.1%)	61 (3.1%)	11 (7.1%)	59 (2.4%)
≥ 1990 and < 2000	29 (11.9%)	147 (7.5%)	16 (10.3%)	175 (7.1%)
≥ 2000 and < 2007	43 (17.7%)	246 (12.5%)	25 (16.1%)	284 (11.6%)
≥ 2007 and < 2017	117 (48.1%)	819 (41.6%)	75 (48.4%)	980 (40.0%)
≥ 2017	44 (18.1%)	697 (35.4%)	28 (18.1%)	953 (38.9%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	3 (0.2%)	0 (0.0%)	3 (0.1%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	8.4 [4.0, 15.4]	6.2 [2.5, 13.0]	7.6 [3.7, 15.7]	5.3 [1.9, 11.7]
Disease duration missing (N (%))	0 (0.0%)	3 (0.2%)	0 (0.0%)	6 (0.2%)
Disease duration <5 years (N (%))	82 (33.7%)	858 (43.6%)	57 (36.8%)	1185 (48.4%)
DAS28-ESR (median [Q1, Q3])	4.9 [3.9 5.9]	4.6 [3.6 5.5]	4.7 [3.7 5.5]	4.5 [3.7 5.3]
DAS28-ESR missing (N (%))	17 (7.0%)	252 (12.8%)	5 (3.2%)	232 (9.5%)

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Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=243)	bDMARD (n=1973)	Tofacitinib (n=155)	bDMARD (n=2454)
HAQ (median [Q1, Q3])	1.4 [0.9, 2.1]	1.1 [0.7, 1.7]	1.2 [0.7, 1.8]	1.1 [0.7, 1.6]
HAQ missing (N (%))	2 (0.8%)	26 (1.3%)	1 (0.6%)	32 (1.3%)
Patients with previous nb/b/tsDMARDs (N (%))	242 (99.6%)	1914 (97.0%)	154 (99.4%)	2.419 (98.6%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	156 (64.2%)	1014 (51.4%)	70 (45.2%)	754 (30.7%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	88 (36.2%)	766 (38.8%)	21 (13.5%)	291 (11.9%)
Therapy stop of last previous DMARD therapy due to remission	1 (0.4%)	18 (0.9%)	0 (0.0%)	14 (0.6%)
Therapy stop of last previous DMARD therapy due to other reasons	6 (2.5%)	135 (6.8%)	4 (2.6%)	57 (2.3%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	33 (13.6%)	367 (18.6%)	69 (44.5%)	1452 (59.2%)
Patients with previous bDMARDs (N (%))	105 (43.2%)	517 (26.2%)	61 (39.4%)	439 (17.9%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	0.9 (1.4)	0.4 (0.9)	0.8 (1.2)	0.3 (0.7)
Patients with previous tsDMARDs (N (%))	0 (0.0%)	52 (2.6%)	0 (0.0%)	41 (1.7%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))				
0	138 (56.8%)	1442 (73.1%)	94 (60.6%)	2.000 (81.5%)
1	49 (20.2%)	280 (14.2%)	29 (18.7%)	260 (10.6%)
≥2	56 (23.0%)	251 (12.7%)	32 (20.6%)	194 (7.9%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	2.0 (0.9)	1.8 (0.9)	1.8 (0.9)	1.6 (0.9)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	0 (0.0%)	0 (0.0%)	155 (100.0%)	2454 (100.0%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=243)	bDMARD (n=1973)	Tofacitinib (n=155)	bDMARD (n=2454)
Concomitant MTX (N (%))	0 (0.0%)	0 (0.0%)	140 (90.3%)	2298 (93.6%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	134 (55.1%)	997 (51.6%)	81 (52.3%)	1325 (55.1%)
Concomitant oral steroids missing (N (%))	0 (0.0%)	40 (2.0%)	0 (0.0%)	50 (2.0%)
Dose of concomitant Glucocorticoids (N (%))				
<5 mg/d	130 (53.5%)	1117 (57.8%)	91 (58.7%)	1380 (57.4%)
5-<10 mg/d	87 (35.8%)	572 (29.6%)	52 (33.5%)	774 (32.2%)
≥ 10 mg/d	26 (10.7%)	244 (12.6%)	12 (7.7%)	250 (10.4%)
Dose of concomitant Glucocorticoids missing (N (%))	0 (0.0%)	40 (2.0%)	0 (0.0%)	50 (2.0%)
Concomitant NSAIDs (N (%))	52 (21.5%)	509 (25.9%)	35 (22.7%)	694 (28.4%)
Concomitant NSAIDs missing (N (%))	1 (0.4%)	4 (0.2%)	1 (0.6%)	8 (0.3%)
Global Health (NRS 0 to 10) (mean (SD))	5.9 (2.2)	5.5 (2.2)	5.3 (2.2)	5.4 (2.0)
Global Health missing (N (%))	2 (0.8%)	20 (1.0%)	0 (0.0%)	24 (1.0%)
Pain (NRS 0 to 10) (mean (SD))	5.9 (2.3)	5.6 (2.4)	5.4 (2.1)	5.5 (2.3)
Pain missing (N (%))	1 (0.4%)	13 (0.7%)	0 (0.0%)	12 (0.5%)
FFbH (median [Q1, Q3])	61.1 [38.9, 81.3]	72.2 [52.8, 86.1]	70.8 [50.0, 86.1]	75.0 [55.6, 88.9]
FFbH missing (N (%))	2 (0.8%)	26 (1.3%)	1 (0.6%)	32 (1.3%)
28 Tender Joint Count (median [Q1, Q3])	8.0 [3.0, 12.0]	6.0 [2.0, 10.0]	6.0 [3.0, 11.0]	6.0 [2.0, 10.0]
28 Tender Joint Count missing (N (%))	0 (0.0%)	8 (0.4%)	0 (0.0%)	10 (0.4%)
28 Swollen Joint Count (median [Q1, Q3])	4.0 [2.0, 8.0]	3.0 [1.0, 7.0]	4.0 [2.0, 7.0]	3.0 [1.0, 6.0]
28 Swollen Joint Count missing (N (%))	0 (0.0%)	7 (0.4%)	0 (0.0%)	9 (0.4%)
CRP (mg/liter) (median [Q1, Q3])	5.9 [2.5, 15.0]	5.1 [2.2, 13.0]	7.8 [3.6, 15.0]	6.0 [2.4, 14.3]
CRP missing (N (%))	13 (5.3%)	79 (4.0%)	6 (3.9%)	84 (3.4%)
ESR (mm/1h) (median [Q1, Q3])	20.5 [9.5, 36.0]	18.0 [9.0, 33.0]	20.0 [9.0, 32.0]	18.0 [8.0, 32.0]
ESR missing (N (%))	15 (6.2%)	226 (11.5%)	5 (3.2%)	199 (8.1%)

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Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=243)	bDMARD (n=1973)	Tofacitinib (n=155)	bDMARD (n=2454)
Smoking				
Current (N (%))	51 (22.7%)	477 (25.6%)	48 (32.2%)	746 (31.9%)
Previous (N (%))	70 (31.1%)	603 (32.4%)	35 (23.5%)	742 (31.7%)
Never (N (%))	104 (46.2%)	782 (42.0%)	66 (44.3%)	851 (36.4%)
Missing (N (%))	18 (7.4%)	111 (5.6%)	6 (3.9%)	115 (4.7%)
Disease history				
Malignancies (N (%))	8 (3.3%)	110 (5.6%)	6 (3.9%)	103 (4.2%)
Lymphoma (N (%))	2 (0.8%)	7 (0.4%)	1 (0.6%)	15 (0.6%)
Tuberculosis (N (%))	4 (1.6%)	43 (2.2%)	4 (2.6%)	52 (2.1%)
Joint replacement surgery (N (%))	34 (14.1%)	209 (10.7%)	23 (14.9%)	255 (10.5%)
Joint replacement surgery missing (N (%))	2 (0.8%)	15 (0.8%)	1 (0.6%)	15 (0.6%)
COPD (N (%))	10 (4.1%)	98 (5.0%)	8 (5.2%)	131 (5.3%)
Diabetes mellitus (N (%))	39 (16.0%)	259 (13.1%)	25 (16.1%)	292 (11.9%)
Hypertension (N (%))	117 (48.1%)	873 (44.2%)	74 (47.7%)	1031 (42.0%)
CHD/CAD (N (%))	28 (11.5%)	145 (7.3%)	11 (7.1%)	155 (6.3%)
CKD (N (%))	29 (11.9%)	196 (9.9%)	5 (3.2%)	81 (3.3%)
Heart failure (incl. CHF) (N (%))	11 (4.5%)	55 (2.8%)	0 (0.0%)	38 (1.5%)
Comorbidities				
Number of comorbidities (mean (SD))	2.9 (2.4)	2.6 (2.4)	2.7 (2.1)	2.4 (2.2)
No comorbidity (N (%))	47 (19.3%)	501 (25.4%)	33 (21.3%)	592 (24.1%)
One comorbidity (N (%))	29 (11.9%)	288 (14.6%)	15 (9.7%)	408 (16.6%)
Two comorbidities (N (%))	40 (16.5%)	301 (15.3%)	27 (17.4%)	446 (18.2%)
Three or more comorbidities (N (%))	127 (52.3%)	883 (44.8%)	80 (51.6%)	1008 (41.1%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional

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Table 8. Baseline Characteristics for time of enrolment (I), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=243)	bDMARD (n=1973)	Tofacitinib (n=155)	bDMARD (n=2454)

Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

(II) time of enrolment or during follow-up

Characteristics of patients at initiation of the episodes in the tofacitinib cohort and the bDMARD cohort at the time of enrolment or during follow-up in RABBIT are presented in Table 9. Characteristics for the b/tsDMARD naive tofacitinib, bDMARD and nbDMARD patient episodes are presented in Table 10 (which is stratified by the number of previous b/tsDMARDs) for better comparison.

As seen in Table 9, median age at initiation of the therapy was 59.9 years in the tofacitinib cohort and 60.4 years in the bDMARD cohort. Proportions of episodes of females were 77.1% in the tofacitinib cohort and 73.5% in the bDMARD cohort. Proportions of episodes of patients with seropositivity measured as rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) were 74.2% in the tofacitinib cohort and 76.1% in the bDMARD cohort. The median RA disease duration was longer in the tofacitinib cohort (9.6 years) compared to 8.7 years in the bDMARD cohort. The median disease activity measured by DAS28-ESR was higher for tofacitinib episodes (with 4.4 for the tofacitinib cohort and 4.2 for the bDMARD cohort). There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 9). The proportion of bionaive episodes was only 26.0% in the tofacitinib cohort compared to 44.6% in the bDMARD cohort, whereas more episodes in the tofacitinib cohort had at least 2 previously used b/tsDMARDs (47.8%) compared to the bDMARD cohort (33.6%). Therapy initiation as an episode of combination therapy with a nbDMARD was less common in the tofacitinib cohort compared to the bDMARD cohort (41.4% versus 51.9%, respectively). In the bDMARD cohort, the distribution of therapies initiated was as follows: 33.3% initiated etanercept, 24.9% adalimumab, 1.5% infliximab, 6.0% certolizumab pegol, 1.9% golimumab, 9.4% rituximab, 6.3% sarilumab, 8.2% tocilizumab, and 8.5% abatacept. The proportion of episodes with concomitant glucocorticoid therapy was 53.3% in the tofacitinib and 49.7% in the bDMARD cohort. The median percentage of full physical function measured by FFbH was lower in the tofacitinib cohort (66.7) compared to the bDMARD cohort (72.2). The mean number of comorbidities was 2.8 in the tofacitinib cohort compared to 2.7 in the bDMARD cohort. Episodes in the tofacitinib cohort were slightly more likely to be reported as belonging to never smokers relative to those in the bDMARD cohort (39.6% versus 37.1%, respectively) and also slightly less likely reported being current smokers (26.9% versus 28.3%, respectively).

The percentage of episodes with history of malignancies was higher in the bDMARD cohort (5.2%) compared to the tofacitinib cohort (3.8%). Episodes in the tofacitinib cohort were slightly more likely to be reported as belonging to obese patients (29.9%) compared with episodes in the bDMARD cohort (28.6%). The percentages of the presence of CV risk factors (62.4% in the tofacitinib, 61.1% in the bDMARD cohort), of VTE risk factors (60.3% in the tofacitinib, 59.8% in the bDMARD cohort) and of malignancy risk factors (71.1% in the tofacitinib, 71.6% in the bDMARD cohort) were comparable for the bDMARD and the tofacitinib cohorts. Only 4.3% of the episodes in the tofacitinib cohort compared to 36.8% in the bDMARD cohort were initiated on 30-JUNE-2021 or afterwards. Fewer episodes in the tofacitinib cohort (12.8%) were initiated by a rheumatology clinic relative to episodes in the bDMARD cohort (16.8%).

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Stratified analyses

When restricting the population to b/tsDMARD-naive episodes (Table 10), there were 321 episodes of tofacitinib initiation and 4,052 episodes of bDMARD initiation. and 3583 episodes of nbDMARDs initiation. The median age at initiation of a therapy episode was similar across cohorts (60.9 years in the tofacitinib cohort, 59.7 years in the bDMARD cohort and 60.3 years in the nbDMARD cohort). There was a higher percentage of episodes of female patients in the tofacitinib cohort (74.5%) relative to the bDMARD (71.9%) and nbDMARD (71.3%) cohorts. Percentages of episodes of patients with seropositivity measured as RF and/or ACPA were 70.7% in the tofacitinib cohort, 73.8% in the bDMARD cohort and 69.6% in the nbDMARD cohort. Even for b/tsDMARD naive episodes, the median RA disease duration was longer in the tofacitinib cohort with 6.0 years compared to 4.6 years in the bDMARD cohort and 3.6 years in the nbDMARD cohort. However, the median disease activity measured by DAS28-ESR was comparable for tofacitinib episodes (4.6) and bDMARD episodes (4.5) compared to 4.2 for nbDMARD episodes. Only 38.6% of episodes in the tofacitinib cohort (compared to 57.4% in the bDMARD cohort) belonged to patients on combination therapy with nbDMARDs. In the bDMARD cohort, the distribution of therapies initiated was: 47.7% initiated etanercept, 29.7% adalimumab, 0.6% infliximab, 7.0% certolizumab pegol, 1.5% golimumab, 0.5% rituximab, 3.1% sarilumab, 4.4% tocilizumab and 5.4% abatacept. The percentages of episodes with concomitant glucocorticoid therapy were comparable between the cohorts (56.7% in the tofacitinib, 55.0% in the bDMARD and 53.0% in the nbDMARD cohort). The median percentage of full physical function measured by FFbH was 69.4% in the tofacitinib cohort, compared to 75.0% in the bDMARD cohort and the nbDMARD cohort. The mean number of comorbidities was 2.5 in the tofacitinib cohort, compared to 2.4 in the bDMARD cohort and 2.2 in the nbDMARD cohort. Episodes in the tofacitinib cohort were more likely to be reported for never smokers (43.6%) relative to episodes in the bDMARD cohort (37.6%) and in the nbDMARD cohort (37.1%); episodes in the tofacitinib cohort were also less likely reported being current smokers (27.0% relative to 30.0% and 32.4%), respectively. Only 3.4% of the episodes in the tofacitinib cohort compared to 41.4% in the bDMARD cohort and 29.4% in the nbDMARD cohort were initiated on 30-JUNE-2021 or afterwards. Fewer episodes in the tofacitinib cohort (5.3%) were initiated by a rheumatology clinic relative to episodes in the bDMARD cohort (11.1%) and the nbDMARD cohort (11.0%).

When restricting the population to episodes with exactly one previous b/tsDMARD (Table 10), there were 324 tofacitinib episodes and 1979 bDMARD episodes. Previous use of tsDMARDs was 13.1% in the bDMARD episodes and 3.1% in the tofacitinib episodes. The median disease activity (DAS28-ESR) was higher in patients initiating tofacitinib (4.2) compared to episodes initiated with bDMARDs (3.6). The percentage of episodes with combination therapy with nbDMARDs was lower in the tofacitinib cohort (46.3%) relative to the bDMARD cohort (48.1%). The mean number of comorbidities was 2.5 for tofacitinib episodes compared to 2.8 for bDMARD episodes.

When restricting the population to episodes with at least two previous b/tsDMARDs Table 10), there were 590 tofacitinib episodes and 3,056 bDMARDs episodes. Percentages of episodes of patients with seropositivity measured as RF and/or ACPA were 73.5% in the tofacitinib cohort and 78.6% in the bDMARD cohort. Previous use of tsDMARDs was 44.8% in the bDMARD episodes and 16.8% in the tofacitinib episodes. Median RA disease duration was comparable; however, the median disease activity was higher in tofacitinib episodes (4.4) compared to bDMARD episodes (4.0). The percentage of episodes with combination therapy

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with nbDMARDs was 40.2% in the tofacitinib and 47.1% in the bDMARD cohort. The percentage of episodes with concomitant glucocorticoid therapy was higher in the tofacitinib cohort (55.5%) compared to the bDMARD cohort (46.7%). There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 10). The mean number of comorbidities was comparable between both cohorts (3.2). In the bDMARD cohort, the distribution of therapies was as follows: 15.0% initiated etanercept, 15.9% adalimumab, 2.6% infliximab, 5.0% certolizumab pegol, 2.3% golimumab, 22.8% rituximab, 10.4% sarilumab, 12.6% tocilizumab, and 13.4% abatacept.

When restricting the population to episodes without prior use of non-tofacitinib JAKi therapy (Table 11), there were 1,130 tofacitinib (91.5% of the cohort) and 7,856 bDMARD episodes (86.5% of the cohort). Therefore, the percentage of patients with prior non-tofacitinib JAKi therapy was <15% in both cohorts and the number of patients in the tofacitinib cohort was very small (n=105, Table 11).

When restricting the population to episodes with monotherapy (Table 12), there were 724 tofacitinib episodes and 4,371 bDMARD episodes. The median age at therapy initiation was comparable, with 60.2 years in the tofacitinib cohort, and 61.0 years in the bDMARD cohort. The percentages of episodes of female patients were 80.7% in the tofacitinib cohort and 78.1% in the bDMARD cohort. The percentages of episodes of patients with seropositivity measured as RF and/or ACPA were 71.6% in the tofacitinib cohort and 73.2% in the bDMARD cohort. The median RA disease duration was longer in the tofacitinib cohort with 9.6 years compared to 9.0 years in the bDMARD cohort. The median disease activity measured by DAS28-ESR was 4.4 for tofacitinib episodes, compared to 4.2 in bDMARD episodes. There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 12). In the bDMARD cohort, the distribution of therapy initiation was as follows: 34.2% initiated etanercept, 23.2% adalimumab, 1.1 infliximab, 7.3% certolizumab pegol, 1.5% golimumab, 7.3% rituximab, 8.8% sarilumab, 11.5% tocilizumab, and 5.1% abatacept. The percentage of episodes with concomitant glucocorticoid therapy was 53.5% for the tofacitinib cohort and 48.7% for bDMARD cohort. The median percentage of full physical function measured by FFbH was only 63.9% in the tofacitinib cohort, compared to 69.4% in the bDMARD cohort. The mean number of comorbidities was slightly higher in the tofacitinib cohort (3.0) compared to the bDMARD cohort (2.9). Episodes in the tofacitinib cohort were slightly more likely reported being never smokers (40.5%) relative to episodes in the bDMARD cohort (39.4%); episodes in the tofacitinib cohort were also less likely to have reported being current smokers (23.8% relative to 25.8%).

When restricting the population to episodes with nbDMARD combination therapy (Table 12), there were 511 tofacitinib episodes and 4716 bDMARD episodes. The median age at therapy initiation was comparable (59.5 years in the tofacitinib, and 59.8 years in the bDMARD cohort). The percentages of episodes of female patients were 72.0% in the tofacitinib cohort and 69.2% in the bDMARD cohort. Percentages of episodes of patients with seropositivity measured as RF and/or ACPA were comparable (77.8% in the tofacitinib cohort and 78.9% in the bDMARD cohort). The median RA disease duration was longer in the tofacitinib cohort with 9.5 years compared to 8.3 years in the bDMARD cohort. The median disease activity measured by DAS28-ESR was 4.4 for tofacitinib episodes, compared to 4.1 for bDMARD episodes. There was a higher median 28 tender joint count and 28 swollen joint count in the tofacitinib cohort compared to the bDMARD cohort (Table 4). In the bDMARD cohort, the distribution of therapies initiated was as follows: 32.6% initiated etanercept, 26.5%

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adalimumab, 1.8 infliximab, 4.7% certolizumab pegol, 2.2% golimumab, 11.3% rituximab, 4.1% sarilumab, 5.1% tocilizumab, and 11.6% abatacept. The percentage of episodes with concomitant glucocorticoid therapy was 53.1% in the tofacitinib and 50.6% in the bDMARD cohort. The median percentage of full physical function measured by FFbH was 66.7% in the tofacitinib cohort, compared to 72.2% in the bDMARD cohort. The mean number of comorbidities and the current smoking status was comparable.

The most common nbDMARD used as concomitant therapy was MTX in both cohorts (92.8% in the tofacitinib and 93.3% in the bDMARD cohort).

Table 9. Baseline Characteristics for therapy starts at index date (II), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=1235)	bDMARD (n=9087)
Demographics		
Age (median [Q1, Q3])	59.9 [53.2, 67.4]	60.4 [52.7, 68.6]
Female sex (N (%))	952 (77.1%)	6677 (73.5%)
Disease-related characteristics		
Year of therapy start before 30-JUNE-2021 (N (%))	1182 (95.7%)	5741 (63.2%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	53 (4.3%)	3346 (36.8%)
Rheumatoid factor positive (N (%))	797 (65.8%)	6049 (68.2%)
Rheumatoid factor positive missing (N (%))	24 (1.9%)	211 (2.3%)
Rheumatoid factor /ACPA positive (N (%))	884 (74.2%)	6760 (76.1%)
Rheumatoid factor /ACPA positive missing (N (%))	43 (3.5%)	209 (2.3%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	829 (67.1%)	4625 (50.9%)
Calendar year of recalled RA symptom onset (N (%))		
< 1990	79 (6.4%)	373 (4.1%)
≥ 1990 and < 2000	155 (12.6%)	913 (10.1%)
≥ 2000 and < 2007	250 (20.2%)	1529 (16.8%)
≥ 2007 and < 2017	615 (49.8%)	4085 (45.0%)
≥ 2017	136 (11.0%)	2178 (24.0%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	9 (0.1%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	9.6 [4.9, 16.2]	8.7 [3.8, 15.3]
Disease duration missing (N (%))	0 (0.0%)	13 (0.1%)
Disease duration <5 years (N (%))	324 (26.2%)	2909 (32.1%)
DAS28-ESR (median [Q1, Q3])	4.4 [3.4, 5.4]	4.2 [3.1, 5.1]

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Table 9. Baseline Characteristics for therapy starts at index date (II), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=1235)	bDMARD (n=9087)
DAS28-ESR missing (N (%))	131 (10.6%)	1347 (14.8%)
HAQ (median [Q1, Q3])	1.3 [0.8, 1.9]	1.1 [0.7, 1.8]
HAQ missing (N (%))	23 (1.9%)	252 (2.8%)
Patients with previous nb/b/tsDMARDs (N (%))	1233 (99.8%)	8994 (99.0%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	542 (43.9%)	2874 (31.6%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	242 (19.6%)	1782 (19.6%)
Therapy stop of last previous DMARD therapy due to remission	12 (1.0%)	95 (1.0%)
Therapy stop of last previous DMARD therapy due to other reasons	63 (5.1%)	796 (8.8%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	471 (38.1%)	4216 (46.4%)
Patients with previous bDMARDs (N (%))	903 (73.1%)	4701 (51.7%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	1.8 (1.7)	1.1 (1.4)
Patients with previous tsDMARDs (N (%))	109 (8.8%)	1628 (17.9%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))		
0	321 (26.0%)	4052 (44.6%)
1	324 (26.2%)	1979 (21.8%)
≥2	590 (47.8%)	3056 (33.6%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	2.3 (1.1)	2.0 (1.0)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	511 (41.4%)	4716 (51.9%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	474 (38.4%)	4399 (48.4%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)

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Table 9. Baseline Characteristics for therapy starts at index date (II), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=1235)	bDMARD (n=9087)
Concomitant oral steroids (N (%))	658 (53.4%)	4440 (49.7%)
Concomitant oral steroids missing (N (%))	2 (0.2%)	151 (1.7%)
Dose of concomitant Glucocorticoids (N (%))		
<5 mg/d	690 (56.0%)	5551 (62.1%)
5-<10 mg/d	436 (35.4%)	2614 (29.3%)
≥ 10 mg/d	107 (8.7%)	771 (8.6%)
Dose of concomitant Glucocorticoids missing (N (%))	2 (0.2%)	151 (1.7%)
Concomitant NSAIDs (N (%))	330 (26.8%)	2507 (27.7%)
Concomitant NSAIDs missing (N (%))	2 (0.2%)	21 (0.2%)
Global Health (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.3 (2.2)
Global Health missing (N (%))	20 (1.6%)	208 (2.3%)
Pain (NRS 0 to 10) (mean (SD))	5.8 (2.3)	5.3 (2.4)
Pain missing (N (%))	17 (1.4%)	175 (1.9%)
FFbH (median [Q1, Q3])	66.7 [44.1, 83.3]	72.2 [50.0, 86.1]
FFbH missing (N (%))	23 (1.9%)	252 (2.8%)
28 Tender Joint Count (median [Q1, Q3])	5.0 [1.0, 10.0]	4.0 [1.0, 9.0]
28 Tender Joint Count missing (N (%))	8 (0.6%)	55 (0.6%)
28 Swollen Joint Count (median [Q1, Q3])	3.0 [0.0, 6.0]	2.0 [0.0, 5.0]
28 Swollen Joint Count missing (N (%))	7 (0.6%)	52 (0.6%)
CRP (mg/liter) (median [Q1, Q3])	5.5 [2.0, 13.5]	4.6 [2.0, 12.0]
CRP missing (N (%))	105 (8.5%)	784 (8.6%)
ESR (mm/1h) (median [Q1, Q3])	18.0 [8.0, 34.0]	17.0 [8.0, 31.0]
ESR missing (N (%))	110 (8.9%)	1138 (12.5%)
Smoking		
Current (N (%))	324 (26.9%)	2495 (28.3%)
Previous (N (%))	405 (33.6%)	3042 (34.5%)
Never (N (%))	477 (39.6%)	3270 (37.1%)
Missing (N (%))	29 (2.3%)	280 (3.1%)
Disease history		
Malignancies (N (%))	47 (3.8%)	477 (5.2%)
Lymphoma (N (%))	5 (0.4%)	51 (0.6%)
Tuberculosis (N (%))	24 (1.9%)	220 (2.4%)
Joint replacement surgery (N (%))	160 (13.1%)	948 (10.5%)
Joint replacement surgery missing (N (%))	9 (0.7%)	88 (1.0%)
COPD (N (%))	72 (5.8%)	553 (6.1%)
Diabetes mellitus (N (%))	182 (14.7%)	1173 (12.9%)
Hypertension (N (%))	575 (46.6%)	4078 (44.9%)

Table 9. Baseline Characteristics for therapy starts at index date (II), overall

	Main cohort	Comparator cohort
Status at entry	Tofacitinib (n=1235)	bDMARD (n=9087)
CHD/CAD (N (%))	102 (8.3%)	710 (7.8%)
CKD (N (%))	94 (7.6%)	618 (6.8%)
Heart failure (incl. CHF) (N (%))	35 (2.8%)	241 (2.7%)
Comorbidities		
Number of comorbidities (mean (SD))	2.8 (2.4)	2.7 (2.4)
No comorbidity (N (%))	255 (20.6%)	2037 (22.4%)
One comorbidity (N (%))	172 (13.9%)	1327 (14.6%)
Two comorbidities (N (%))	199 (16.1%)	1486 (16.4%)
Three or more comorbidities (N (%))	609 (49.3%)	4237 (46.6%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)
Demographics							
Age (median [Q1, Q3])	60.9 [53.5, 70.2]	59.7 [51.5, 67.7]	60.3 [52.4, 68.5]	59.1 [52.2, 67.4]	61.5 [53.6, 70.0]	59.7 [53.6, 66.6]	60.8 [53.4, 68.4]
Female sex (N (%))	239 (74.5%)	2915 (71.9%)	2555 (71.3%)	243 (75.0%)	1428 (72.2%)	470 (79.7%)	2334 (76.4%)
Disease-related characteristics							
Year of therapy start before 30-JUNE-2021 (N (%))	310 (96.6%)	2374 (58.6%)	2528 (70.6%)	308 (95.1%)	1415 (71.5%)	564 (95.6%)	1952 (63.9%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	11 (3.4%)	1678 (41.4%)	1055 (29.4%)	16 (4.9%)	564 (28.5%)	26 (4.4%)	1104 (36.1%)
Rheumatoid factor positive (N (%))	204 (64.4%)	2589 (65.3%)	2133 (61.5%)	219 (69.3%)	1332 (69.4%)	374 (64.7%)	2128 (71.1%)
Rheumatoid factor positive missing (N (%))	4 (1.2%)	87 (2.1%)	117 (3.3%)	8 (2.5%)	60 (3.0%)	12 (2.0%)	64 (2.1%)
Rheumatoid factor /ACPA positive (N (%))	222 (70.7%)	2933 (73.8%)	2422 (69.6%)	248 (78.7%)	1482 (77.1%)	414 (73.5%)	2345 (78.6%)
Rheumatoid factor /ACPA positive missing (N (%))	7 (2.2%)	80 (2.0%)	105 (2.9%)	9 (2.8%)	57 (2.9%)	27 (4.6%)	72 (2.4%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	5.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	88 (27.4%)	623 (15.4%)	777 (21.7%)	241 (74.4%)	1423 (71.9%)	500 (84.7%)	2579 (84.4%)
Calendar year of recalled RA symptom onset (N (%))							
< 1990	8 (2.5%)	67 (1.7%)	42 (1.2%)	16 (4.9%)	99 (5.0%)	55 (9.3%)	207 (6.8%)
≥ 1990 and < 2000	20 (6.2%)	208 (5.1%)	117 (3.3%)	33 (10.2%)	228 (11.5%)	102 (17.3%)	477 (15.6%)
≥ 2000 and < 2007	38 (11.8%)	396 (9.8%)	281 (7.9%)	62 (19.1%)	421 (21.3%)	150 (25.4%)	712 (23.3%)
≥ 2007 and < 2017	183 (57.0%)	1704 (42.1%)	1334 (37.3%)	169 (52.2%)	975 (49.3%)	263 (44.6%)	1406 (46.0%)
≥ 2017	72 (22.4%)	1672 (41.3%)	1804 (50.4%)	44 (13.6%)	254 (12.8%)	20 (3.4%)	252 (8.3%)

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	5 (0.1%)	5 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	6.0 [2.9, 11.0]	4.6 [1.8, 10.1]	3.6 [1.5, 8.3]	8.4 [4.0, 15.3]	10.3 [5.6, 16.6]	12.3 [7.4, 19.5]	12.5 [7.8, 19.5]
Disease duration missing (N (%))	0 (0.0%)	8 (0.2%)	8 (0.2%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	3 (0.1%)
Disease duration <5 years (N (%))	143 (44.5%)	2117 (52.3%)	2140 (59.9%)	103 (31.8%)	421 (21.3%)	78 (13.2%)	371 (12.2%)
DAS28-ESR (median [Q1, Q3])	4.6 [3.4, 5.5]	4.5 [3.6, 5.4]	4.2 [3.3, 5.1]	4.2 [3.3, 5.3]	3.6 [2.7, 4.8]	4.4 [3.4, 5.4]	4.0 [2.9, 5.0]
DAS28-ESR missing (N (%))	19 (5.9%)	464 (11.5%)	533 (14.9%)	38 (11.7%)	296 (15.0%)	74 (12.5%)	587 (19.2%)
HAQ (median [Q1, Q3])	1.2 [0.7, 1.8]	1.1 [0.7, 1.6]	1.1 [0.7, 1.6]	1.2 [0.7, 1.8]	1.1 [0.7, 1.7]	1.4 [0.9, 2.1]	1.3 [0.8, 1.9]
HAQ missing (N (%))	4 (1.2%)	70 (1.7%)	77 (2.1%)	9 (2.8%)	66 (3.3%)	10 (1.7%)	116 (3.8%)
Patients with previous nb/b/tsDMARDs (N (%))	319 (99.4%)	3957 (97.7%)	3583 (100.0%)	324 (100.0%)	1979 (100.0%)	590 (100.0%)	3056 (100.0%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	134 (41.7%)	1328 (32.8%)	770 (21.5%)	149 (46.0%)	567 (28.7%)	259 (43.9%)	979 (32.0%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	86 (26.8%)	975 (24.1%)	806 (22.5%)	56 (17.3%)	260 (13.1%)	100 (16.9%)	547 (17.9%)
Therapy stop of last previous DMARD therapy due to remission	2 (0.6%)	17 (0.4%)	47 (1.3%)	4 (1.2%)	30 (1.5%)	6 (1.0%)	48 (1.6%)
Therapy stop of last previous DMARD therapy due to other reasons	6 (1.9%)	123 (3.0%)	108 (3.0%)	15 (4.6%)	301 (15.2%)	42 (7.1%)	372 (12.2%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	121 (37.7%)	1947 (48.1%)	2014 (56.2%)	119 (36.7%)	931 (47.0%)	231 (39.2%)	1338 (43.8%)
Patients with previous bDMARDs (N (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	314 (96.9%)	1719 (86.9%)	589 (99.8%)	2982 (97.6%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)
Number of previously used bDMARDs (mean (SD))	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	0.9 (0.3)	3.2 (1.4)	2.6 (1.4)
Patients with previous tsDMARDs (N (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (3.1%)	260 (13.1%)	99 (16.8%)	1368 (44.8%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))							
0	321 (100.0%)	4052 (100.0%)	3583 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	324 (100.0%)	1979 (100.0%)	0 (0.0%)	0 (0.0%)
≥2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	590 (100.0%)	3056 (100.0%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	2.0 (0.9)	1.8 (0.8)	1.5 (0.7)	2.1 (0.9)	2.1 (1.0)	2.5 (1.2)	2.4 (1.1)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	124 (38.6%)	2324 (57.4%)	NA	150 (46.3%)	952 (48.1%)	237 (40.2%)	1440 (47.1%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	113 (35.2%)	2168 (53.5%)	NA	138 (42.6%)	894 (45.2%)	223 (37.8%)	1337 (43.8%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	182 (56.7%)	2184 (55.0%)	1857 (53.0%)	149 (46.1%)	848 (43.4%)	327 (55.5%)	1408 (46.7%)
Concomitant oral steroids missing (N (%))	0 (0.0%)	83 (2.0%)	82 (2.3%)	1 (0.3%)	27 (1.4%)	1 (0.2%)	41 (1.3%)
Dose of concomitant Glucocorticoids (N (%))							

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)
<5 mg/d	175 (54.5%)	2268 (57.1%)	2046 (58.4%)	194 (60.1%)	1347 (69.0%)	321 (54.5%)	1936 (64.2%)
5-<10 mg/d	117 (36.4%)	1276 (32.1%)	1149 (32.8%)	100 (31.0%)	501 (25.7%)	219 (37.2%)	837 (27.8%)
≥ 10 mg/d	29 (9.0%)	425 (10.7%)	306 (8.7%)	29 (9.0%)	104 (5.3%)	49 (8.3%)	242 (8.0%)
Dose of concomitant Glucocorticoids missing (N (%))	0 (0.0%)	83 (2.0%)	82 (2.3%)	1 (0.3%)	27 (1.4%)	1 (0.2%)	41 (1.3%)
Concomitant NSAIDs (N (%))	69 (21.6%)	1051 (26.0%)	869 (24.3%)	94 (29.0%)	546 (27.6%)	167 (28.3%)	910 (29.8%)
Concomitant NSAIDs missing (N (%))	2 (0.6%)	11 (0.3%)	14 (0.4%)	0 (0.0%)	4 (0.2%)	0 (0.0%)	6 (0.2%)
Global Health (NRS 0 to 10) (mean (SD))	5.5 (2.2)	5.4 (2.1)	5.2 (2.1)	5.5 (2.2)	4.9 (2.3)	5.9 (2.1)	5.4 (2.3)
Global Health missing (N (%))	3 (0.9%)	58 (1.4%)	48 (1.3%)	6 (1.9%)	52 (2.6%)	11 (1.9%)	98 (3.2%)
Pain (NRS 0 to 10) (mean (SD))	5.5 (2.3)	5.5 (2.3)	5.3 (2.4)	5.6 (2.4)	4.8 (2.5)	6.0 (2.2)	5.4 (2.5)
Pain missing (N (%))	2 (0.6%)	39 (1.0%)	45 (1.3%)	5 (1.5%)	45 (2.3%)	10 (1.7%)	91 (3.0%)
FFbH (median [Q1, Q3])	69.4 [50.0, 86.1]	75.0 [55.6, 88.9]	75.0 [55.6, 88.9]	69.4 [47.2, 86.1]	72.2 [52.8, 88.9]	61.1 [38.9, 80.6]	64.7 [44.4, 83.3]
FFbH missing (N (%))	4 (1.2%)	70 (1.7%)	77 (2.1%)	9 (2.8%)	66 (3.3%)	10 (1.7%)	116 (3.8%)
28 Tender Joint Count (median [Q1, Q3])	6.0 [2.0, 10.0]	6.0 [2.0, 10.0]	4.0 [1.0, 8.0]	4.0 [1.0, 8.0]	2.0 [0.0, 7.0]	5.0 [1.0, 11.0]	3.0 [0.0, 8.0]
28 Tender Joint Count missing (N (%))	1 (0.3%)	14 (0.3%)	5 (0.1%)	5 (1.5%)	18 (0.9%)	2 (0.3%)	23 (0.8%)
28 Swollen Joint Count (median [Q1, Q3])	4.0 [1.0, 7.0]	3.0 [1.0, 6.0]	2.0 [0.0, 5.0]	2.0 [0.0, 5.0]	1.0 [0.0, 4.0]	3.0 [0.0, 6.0]	1.0 [0.0, 4.0]
28 Swollen Joint Count missing (N (%))	1 (0.3%)	17 (0.4%)	8 (0.2%)	4 (1.2%)	15 (0.8%)	2 (0.3%)	20 (0.7%)
CRP (mg/liter) (median [Q1, Q3])	6.9 [3.0, 14.9]	5.8 [2.4, 14.2]	5.3 [2.2, 12.6]	5.5 [2.3, 13.0]	3.5 [1.6, 9.5]	4.9 [1.7, 12.5]	4.0 [1.6, 10.5]
CRP missing (N (%))	23 (7.2%)	233 (5.8%)	592 (16.5%)	21 (6.5%)	204 (10.3%)	61 (10.3%)	347 (11.4%)
ESR (mm/1h) (median [Q1, Q3])	20.0 [9.0, 32.0]	18.0 [8.0, 32.0]	17.0 [8.0, 30.0]	20.0 [10.0, 39.0]	16.0 [8.0, 30.0]	18.0 [8.0, 33.0]	16.0 [8.0, 30.0]
ESR missing (N (%))	15 (4.7%)	403 (9.9%)	488 (13.6%)	30 (9.3%)	246 (12.4%)	65 (11.0%)	489 (16.0%)
Smoking							
Current (N (%))	83 (27.0%)	1163 (30.0%)	1112 (32.4%)	104 (32.6%)	529 (27.4%)	137 (23.6%)	803 (26.7%)

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)
Previous (N (%))	90 (29.3%)	1253 (32.4%)	1045 (30.5%)	97 (30.4%)	685 (35.5%)	218 (37.6%)	1104 (36.7%)
Never (N (%))	134 (43.6%)	1455 (37.6%)	1272 (37.1%)	118 (37.0%)	717 (37.1%)	225 (38.8%)	1098 (36.5%)
Missing (N (%))	14 (4.4%)	181 (4.5%)	154 (4.3%)	5 (1.5%)	48 (2.4%)	10 (1.7%)	51 (1.7%)
Disease history							
Malignancies (N (%))	13 (4.0%)	187 (4.6%)	165 (4.6%)	10 (3.1%)	130 (6.6%)	24 (4.1%)	160 (5.2%)
Lymphoma (N (%))	1 (0.3%)	17 (0.4%)	18 (0.5%)	2 (0.6%)	20 (1.0%)	2 (0.3%)	14 (0.5%)
Tuberculosis (N (%))	8 (2.5%)	84 (2.1%)	49 (1.4%)	5 (1.5%)	52 (2.6%)	11 (1.9%)	84 (2.7%)
Joint replacement surgery (N (%))	35 (11.0%)	352 (8.7%)	269 (7.6%)	33 (10.2%)	191 (9.8%)	92 (15.7%)	405 (13.4%)
Joint replacement surgery missing (N (%))	3 (0.9%)	25 (0.6%)	25 (0.7%)	1 (0.3%)	23 (1.2%)	5 (0.8%)	40 (1.3%)
COPD (N (%))	15 (4.7%)	204 (5.0%)	182 (5.1%)	16 (4.9%)	123 (6.2%)	41 (6.9%)	226 (7.4%)
Diabetes mellitus (N (%))	43 (13.4%)	478 (11.8%)	411 (11.5%)	36 (11.1%)	246 (12.4%)	103 (17.5%)	449 (14.7%)
Hypertension (N (%))	143 (44.5%)	1730 (42.7%)	1556 (43.4%)	140 (43.2%)	901 (45.5%)	292 (49.5%)	1447 (47.3%)
CHD/CAD (N (%))	23 (7.2%)	239 (5.9%)	212 (5.9%)	29 (9.0%)	180 (9.1%)	50 (8.5%)	291 (9.5%)
CKD (N (%))	32 (10.0%)	230 (5.7%)	151 (4.2%)	26 (8.0%)	152 (7.7%)	36 (6.1%)	236 (7.7%)
Heart failure (incl. CHF) (N (%))	7 (2.2%)	93 (2.3%)	59 (1.6%)	7 (2.2%)	61 (3.1%)	21 (3.6%)	87 (2.8%)
Comorbidities							
Number of comorbidities (mean (SD))	2.5 (2.1)	2.4 (2.2)	2.2 (2.1)	2.5 (2.4)	2.8 (2.4)	3.2 (2.6)	3.2 (2.7)
No comorbidity (N (%))	70 (21.8%)	1071 (26.4%)	1008 (28.1%)	87 (26.9%)	426 (21.5%)	98 (16.6%)	540 (17.7%)
One comorbidity (N (%))	43 (13.4%)	615 (15.2%)	498 (13.9%)	41 (12.7%)	284 (14.4%)	88 (14.9%)	428 (14.0%)
Two comorbidities (N (%))	59 (18.4%)	718 (17.7%)	673 (18.8%)	62 (19.1%)	310 (15.7%)	78 (13.2%)	458 (15.0%)
Three or more comorbidities (N (%))	149 (46.4%)	1648 (40.7%)	1404 (39.2%)	134 (41.4%)	959 (48.5%)	326 (55.3%)	1630 (53.3%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic

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Table 10. Baseline Characteristics for therapy starts at index date (II), stratified by the number of previous b/tsDMARDs

	No previous b/tsDMARDs			One previous b/tsDMARDs		≥2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=321)	bDMARD (n=4052)	nbDMARD (n=3583)	Tofacitinib (n=324)	bDMARD (n=1979)	Tofacitinib (n=590)	bDMARD (n=3056)

disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy

	No prior use of non-Tofacitinib JAKi therapy		Prior use of non-Tofacitinib JAKi therapy	
Status at entry	Tofacitinib (n=1130)	bDMARD (n=7856)	Tofacitinib (n=105)	bDMARD (n=1231)
Demographics				
Age (median [Q1, Q3])	60.0 [53.2, 67.5]	60.4 [52.6, 68.7]	58.7 [53.2, 66.1]	60.2 [53.2, 68.2]
Female sex (N (%))	864 (76.5%)	5725 (72.9%)	88 (83.8%)	952 (77.3%)
Disease-related characteristics				
Year of therapy start before 30-JUNE-2021 (N (%))	1,089 (96.4%)	5281 (67.2%)	93 (88.6%)	460 (37.4%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	41 (3.6%)	2575 (32.8%)	12 (11.4%)	771 (62.6%)
Rheumatoid factor positive (N (%))	726 (65.5%)	5208 (67.9%)	71 (68.9%)	841 (69.7%)
Rheumatoid factor positive missing (N (%))	22 (1.9%)	186 (2.4%)	2 (1.9%)	25 (2.0%)
Rheumatoid factor /ACPA positive (N (%))	807 (74.0%)	5838 (76.1%)	77 (75.5%)	922 (76.3%)
Rheumatoid factor /ACPA positive missing (N (%))	40 (3.5%)	186 (2.4%)	3 (2.9%)	23 (1.9%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	4.0 [4.0, 4.0]	4.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	725 (64.2%)	3517 (44.8%)	104 (99.0%)	1108 (90.0%)
Calendar year of recalled RA symptom onset (N (%))				
< 1990	73 (6.5%)	323 (4.1%)	6 (5.7%)	50 (4.1%)
≥ 1990 and < 2000	130 (11.5%)	766 (9.8%)	25 (23.8%)	147 (12.0%)
≥ 2000 and < 2007	223 (19.7%)	1324 (16.9%)	27 (25.7%)	205 (16.7%)
≥ 2007 and < 2017	576 (51.0%)	3475 (44.3%)	39 (37.1%)	610 (49.6%)
≥ 2017	128 (11.3%)	1961 (25.0%)	8 (7.6%)	217 (17.7%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	7 (0.1%)	0 (0.0%)	2 (0.2%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	9.2 [4.7, 15.9]	8.2 [3.4, 15.0]	13.0 [7.2, 21.1]	10.8 [6.0, 17.4]
Disease duration missing (N (%))	0 (0.0%)	10 (0.1%)	0 (0.0%)	3 (0.2%)
Disease duration <5 years (N (%))	306 (27.1%)	2674 (34.1%)	18 (17.1%)	235 (19.1%)
DAS28-ESR (median [Q1, Q3])	4.4 [3.4, 5.4]	4.2 [3.2, 5.1]	4.2 [3.3, 5.4]	4.1 [3.0, 5.1]

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Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy

	No prior use of non-Tofacitinib JAKi therapy		Prior use of non-Tofacitinib JAKi therapy	
Status at entry	Tofacitinib (n=1130)	bDMARD (n=7856)	Tofacitinib (n=105)	bDMARD (n=1231)
DAS28-ESR missing (N (%))	111 (9.8%)	1098 (14.0%)	20 (19.0%)	249 (20.2%)
HAQ (median [Q1, Q3])	1.3 [0.8, 1.9]	1.1 [0.7, 1.7]	1.4 [0.9, 2.1]	1.4 [0.9, 2.0]
HAQ missing (N (%))	21 (1.9%)	201 (2.6%)	2 (1.9%)	51 (4.1%)
Patients with previous nb/b/tsDMARDs (N (%))	1,128 (99.8%)	7761 (98.8%)	105 (100.0%)	1231 (100.0%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	499 (44.2%)	2392 (30.4%)	43 (41.0%)	482 (39.2%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	212 (18.8%)	1509 (19.2%)	30 (28.6%)	273 (22.2%)
Therapy stop of last previous DMARD therapy due to remission	12 (1.1%)	80 (1.0%)	0 (0.0%)	15 (1.2%)
Therapy stop of last previous DMARD therapy due to other reasons	55 (4.9%)	662 (8.4%)	8 (7.6%)	134 (10.9%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	437 (38.7%)	3762 (47.9%)	34 (32.4%)	454 (36.9%)
Patients with previous bDMARDs (N (%))	808 (71.5%)	3702 (47.1%)	95 (90.5%)	999 (81.2%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	1.7 (1.6)	0.9 (1.2)	3.2 (2.0)	2.1 (1.9)
Patients with previous tsDMARDs (N (%))	4 (0.4%)	397 (5.1%)	105 (100.0%)	1231 (100.0%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))				
0	321 (28.4%)	4052 (51.6%)	0 (0.0%)	0 (0.0%)
1	315 (27.9%)	1821 (23.2%)	9 (8.6%)	158 (12.8%)
≥2	494 (43.7%)	1983 (25.2%)	96 (91.4%)	1073 (87.2%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	2.3 (1.0)	2.0 (1.0)	2.6 (1.2)	2.2 (1.0)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	479 (42.4%)	4225 (53.8%)	32 (30.5%)	491 (39.9%)

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Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy

	No prior use of non-Tofacitinib JAKi therapy		Prior use of non-Tofacitinib JAKi therapy	
Status at entry	Tofacitinib (n=1130)	bDMARD (n=7856)	Tofacitinib (n=105)	bDMARD (n=1231)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	444 (39.3%)	3932 (50.1%)	30 (28.6%)	467 (37.9%)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	605 (53.6%)	3822 (49.5%)	53 (50.5%)	618 (51.2%)
Concomitant oral steroids missing (N (%))	2 (0.2%)	127 (1.6%)	0 (0.0%)	24 (1.9%)
Dose of concomitant Glucocorticoids (N (%))				
<5 mg/d	627 (55.6%)	4809 (62.2%)	63 (60.0%)	742 (61.5%)
5-<10 mg/d	403 (35.7%)	2264 (29.3%)	33 (31.4%)	350 (29.0%)
≥ 10 mg/d	98 (8.7%)	656 (8.5%)	9 (8.6%)	115 (9.5%)
Dose of concomitant Glucocorticoids missing (N (%))	2 (0.2%)	127 (1.6%)	0 (0.0%)	24 (1.9%)
Concomitant NSAIDs (N (%))	300 (26.6%)	2157 (27.5%)	30 (28.6%)	350 (28.5%)
Concomitant NSAIDs missing (N (%))	2 (0.2%)	19 (0.2%)	0 (0.0%)	2 (0.2%)
Global Health (NRS 0 to 10) (mean (SD))	5.7 (2.2)	5.2 (2.2)	5.8 (2.3)	5.7 (2.2)
Global Health missing (N (%))	15 (1.3%)	155 (2.0%)	5 (4.8%)	53 (4.3%)
Pain (NRS 0 to 10) (mean (SD))	5.8 (2.3)	5.2 (2.4)	5.8 (2.6)	5.7 (2.5)
Pain missing (N (%))	13 (1.2%)	129 (1.6%)	4 (3.8%)	46 (3.7%)
FFbH (median [Q1, Q3])	66.7 [44.4, 83.3]	72.2 [52.8, 88.2]	61.1 [38.9, 80.6]	61.8 [41.7, 82.4]
FFbH missing (N (%))	21 (1.9%)	201 (2.6%)	2 (1.9%)	51 (4.1%)
28 Tender Joint Count (median [Q1, Q3])	5.0 [2.0, 10.0]	4.0 [1.0, 9.0]	4.0 [1.0, 10.0]	3.0 [0.0, 8.0]
28 Tender Joint Count missing (N (%))	5 (0.4%)	43 (0.5%)	3 (2.9%)	12 (1.0%)
28 Swollen Joint Count (median [Q1, Q3])	3.0 [0.0, 6.0]	2.0 [0.0, 5.0]	2.0 [0.0, 6.0]	2.0 [0.0, 4.0]
28 Swollen Joint Count missing (N (%))	4 (0.4%)	41 (0.5%)	3 (2.9%)	11 (0.9%)
CRP (mg/liter) (median [Q1, Q3])	5.6 [2.0, 13.5]	4.8 [2.0, 12.0]	5.0 [1.8, 14.5]	3.7 [1.6, 11.8]
CRP missing (N (%))	87 (7.7%)	667 (8.5%)	18 (17.1%)	117 (9.5%)

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Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy

	No prior use of non-Tofacitinib JAKi therapy		Prior use of non-Tofacitinib JAKi therapy	
Status at entry	Tofacitinib (n=1130)	bDMARD (n=7856)	Tofacitinib (n=105)	bDMARD (n=1231)
ESR (mm/1h) (median [Q1, Q3])	19.0 [8.0, 34.0]	17.0 [8.0, 31.0]	16.0 [9.0, 33.0]	18.0 [8.0, 32.0]
ESR missing (N (%))	95 (8.4%)	943 (12.0%)	15 (14.3%)	195 (15.8%)
Smoking				
Current (N (%))	307 (27.8%)	2158 (28.4%)	17 (16.5%)	337 (27.9%)
Previous (N (%))	361 (32.7%)	2592 (34.1%)	44 (42.7%)	450 (37.3%)
Never (N (%))	435 (39.4%)	2850 (37.5%)	42 (40.8%)	420 (34.8%)
Missing (N (%))	27 (2.4%)	256 (3.3%)	2 (1.9%)	24 (1.9%)
Disease history				
Malignancies (N (%))	41 (3.6%)	424 (5.4%)	6 (5.7%)	53 (4.3%)
Lymphoma (N (%))	3 (0.3%)	48 (0.6%)	2 (1.9%)	3 (0.2%)
Tuberculosis (N (%))	21 (1.9%)	186 (2.4%)	3 (2.9%)	34 (2.8%)
Joint replacement surgery (N (%))	144 (12.8%)	790 (10.2%)	16 (15.2%)	158 (12.9%)
Joint replacement surgery missing (N (%))	9 (0.8%)	78 (1.0%)	0 (0.0%)	10 (0.8%)
COPD (N (%))	60 (5.3%)	449 (5.7%)	12 (11.4%)	104 (8.4%)
Diabetes mellitus (N (%))	162 (14.3%)	984 (12.5%)	20 (19.0%)	189 (15.4%)
Hypertension (N (%))	531 (47.0%)	3510 (44.7%)	44 (41.9%)	568 (46.1%)
CHD/CAD (N (%))	95 (8.4%)	587 (7.5%)	7 (6.7%)	123 (10.0%)
CKD (N (%))	88 (7.8%)	523 (6.7%)	6 (5.7%)	95 (7.7%)
Heart failure (incl. CHF) (N (%))	30 (2.7%)	201 (2.6%)	5 (4.8%)	40 (3.2%)
Comorbidities				
Number of comorbidities (mean (SD))	2.8 (2.4)	2.7 (2.4)	3.3 (2.8)	3.2 (2.7)
No comorbidity (N (%))	237 (21.0%)	1814 (23.1%)	18 (17.1%)	223 (18.1%)
One comorbidity (N (%))	154 (13.6%)	1164 (14.8%)	18 (17.1%)	163 (13.2%)
Two comorbidities (N (%))	188 (16.6%)	1295 (16.5%)	11 (10.5%)	191 (15.5%)
Three or more comorbidities (N (%))	551 (48.8%)	3583 (45.6%)	58 (55.2%)	654 (53.1%)

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Table 11. Table Baseline Characteristics for therapy starts at index date (II), stratified by prior use of non-Tofacitinib JAKi therapy

	No prior use of non-Tofacitinib JAKi therapy		Prior use of non-Tofacitinib JAKi therapy	
Status at entry	Tofacitinib (n=1130)	bDMARD (n=7856)	Tofacitinib (n=105)	bDMARD (n=1231)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28, disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, JAK, Janus kinase; MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs

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Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=724)	bDMARD (n=4371)	Tofacitinib (n=511)	bDMARD (n=4716)
Demographics				
Age (median [Q1, Q3])	60.2 [53.5, 68.4]	61.0 [52.6, 69.9]	59.5 [52.6, 66.3]	59.8 [52.7, 67.5]
Female sex (N (%))	584 (80.7%)	3413 (78.1%)	368 (72.0%)	3264 (69.2%)
Disease-related characteristics				
Year of therapy start before 30-JUNE-2021 (N (%))	693 (95.7%)	2638 (60.4%)	489 (95.7%)	3103 (65.8%)
Year of therapy start on 30-JUNE-2021 or afterwards (N (%))	31 (4.3%)	1733 (39.6%)	22 (4.3%)	1613 (34.2%)
Rheumatoid factor positive (N (%))	452 (63.8%)	2798 (65.6%)	345 (68.7%)	3251 (70.6%)
Rheumatoid factor positive missing (N (%))	15 (2.1%)	103 (2.4%)	9 (1.8%)	108 (2.3%)
Rheumatoid factor /ACPA positive (N (%))	502 (71.6%)	3123 (73.2%)	382 (77.8%)	3637 (78.9%)
Rheumatoid factor /ACPA positive missing (N (%))	23 (3.2%)	104 (2.4%)	20 (3.9%)	105 (2.2%)
Number of features listed in 1987 ACR criteria for RA (median [Q1, Q3])	4.0 [4.0, 5.0]	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	4.0 [4.0, 5.0]
Number of features listed in 1987 ACR criteria for RA missing (N (%))	480 (66.3%)	2375 (54.3%)	349 (68.3%)	2250 (47.7%)
Calendar year of recalled RA symptom onset (N (%))				
< 1990	46 (6.4%)	196 (4.5%)	33 (6.5%)	177 (3.8%)
≥ 1990 and < 2000	91 (12.6%)	419 (9.6%)	64 (12.5%)	494 (10.5%)
≥ 2000 and < 2007	153 (21.1%)	767 (17.6%)	97 (19.0%)	762 (16.2%)
≥ 2007 and < 2017	358 (49.4%)	1986 (45.5%)	257 (50.3%)	2099 (44.5%)
≥ 2017	76 (10.5%)	998 (22.9%)	60 (11.7%)	1180 (25.0%)
Calendar year of recalled RA symptom onset missing (N (%))	0 (0.0%)	5 (0.1%)	0 (0.0%)	4 (0.1%)
Years since symptom onset (i.e., disease duration) (median [Q1, Q3])	9.6 [4.9, 16.1]	9.0 [4.2, 15.5]	9.5 [4.7, 16.4]	8.3 [3.4, 15.1]
Disease duration missing (N (%))	0 (0.0%)	6 (0.1%)	0 (0.0%)	7 (0.1%)
Disease duration <5 years (N (%))	187 (25.8%)	1304 (29.9%)	137 (26.8%)	1605 (34.1%)
DAS28-ESR (median [Q1, Q3])	4.4 [3.3, 5.6]	4.2 [3.1 5.2]	4.4 [3.5 5.3]	4.1 [3.1 5.1]
DAS28-ESR missing (N (%))	88 (12.2%)	745 (17.0%)	43 (8.4%)	602 (12.8%)

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Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=724)	bDMARD (n=4371)	Tofacitinib (n=511)	bDMARD (n=4716)
HAQ (median [Q1, Q3])	1.4 [0.8, 2.0]	1.2 [0.7, 1.8]	1.3 [0.8, 1.8]	1.1 [0.7, 1.7]
HAQ missing (N (%))	13 (1.8%)	125 (2.9%)	10 (2.0%)	127 (2.7%)
Patients with previous nb/b/tsDMARDs (N (%))	723 (99.9%)	4312 (98.7%)	510 (99.8%)	4681 (99.3%)
Therapy stop of last previous DMARD therapy due to therapy failure (N (%))	329 (45.4%)	1612 (36.9%)	213 (41.7%)	1262 (26.8%)
Therapy stop of last previous DMARD therapy due to adverse event / intolerance N (%)	183 (25.3%)	1256 (28.7%)	59 (11.5%)	526 (11.2%)
Therapy stop of last previous DMARD therapy due to remission	12 (1.7%)	47 (1.1%)	0 (0.0%)	48 (1.0%)
Therapy stop of last previous DMARD therapy due to other reasons	44 (6.1%)	459 (10.5%)	19 (3.7%)	337 (7.1%)
No given reason for therapy stop of last previous DMARD therapy or no therapy stop	230 (31.8%)	1487 (34.0%)	241 (47.2%)	2729 (57.9%)
Patients with previous bDMARDs (N (%))	517 (71.4%)	2418 (55.3%)	386 (75.5%)	2283 (48.4%)
Patients with previous bDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used bDMARDs (mean (SD))	1.8 (1.7)	1.1 (1.4)	1.8 (1.7)	1.0 (1.4)
Patients with previous tsDMARDs (N (%))	76 (10.5%)	969 (22.2%)	33 (6.5%)	659 (14.0%)
Patients with previous tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used b/tsDMARDs (N (%))				
0	197 (27.2%)	1728 (39.5%)	124 (24.3%)	2324 (49.3%)
1	174 (24.0%)	1027 (23.5%)	150 (29.4%)	952 (20.2%)
≥2	353 (48.8%)	1616 (37.0%)	237 (46.4%)	1440 (30.5%)
Number of previously used b/tsDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of previously used nbDMARDs (mean (SD))	2.3 (1.0)	2.1 (1.0)	2.2 (1.1)	2.0 (1.0)
Number of previously used nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant nbDMARDs (N (%))	0 (0.0%)	0 (0.0%)	511 (100.0%)	4716 (100.0%)
Concomitant nbDMARDs missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant MTX (N (%))	0 (0.0%)	0 (0.0%)	474 (92.8%)	4399 (93.3%)

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Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=724)	bDMARD (n=4371)	Tofacitinib (n=511)	bDMARD (n=4716)
Concomitant MTX missing N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant oral steroids (N (%))	387 (53.5%)	2097 (48.7%)	271 (53.1%)	2343 (50.6%)
Concomitant oral steroids missing (N (%))	1 (0.1%)	66 (1.5%)	1 (0.2%)	85 (1.8%)
Dose of concomitant Glucocorticoids (N (%))				
<5 mg/d	393 (54.4%)	2672 (62.1%)	297 (58.2%)	2879 (62.2%)
5-<10 mg/d	269 (37.2%)	1244 (28.9%)	167 (32.7%)	1370 (29.6%)
≥ 10 mg/d	61 (8.4%)	389 (9.0%)	46 (9.0%)	382 (8.2%)
Dose of concomitant Glucocorticoids missing (N (%))	1 (0.1%)	66 (1.5%)	1 (0.2%)	85 (1.8%)
Concomitant NSAIDs (N (%))	186 (25.7%)	1107 (25.4%)	144 (28.2%)	1400 (29.8%)
Concomitant NSAIDs missing (N (%))	1 (0.1%)	10 (0.2%)	1 (0.2%)	11 (0.2%)
Global Health (NRS 0 to 10) (mean (SD))	5.8 (2.1)	5.4 (2.3)	5.5 (2.2)	5.3 (2.1)
Global Health missing (N (%))	13 (1.8%)	105 (2.4%)	7 (1.4%)	103 (2.2%)
Pain (NRS 0 to 10) (mean (SD))	5.9 (2.3)	5.4 (2.5)	5.6 (2.3)	5.2 (2.4)
Pain missing (N (%))	10 (1.4%)	86 (2.0%)	7 (1.4%)	89 (1.9%)
FFbH (median [Q1, Q3])	63.9 [41.7, 83.3]	69.4 [50.0, 86.1]	66.7 [47.2, 83.3]	72.2 [52.8, 88.2]
FFbH missing (N (%))	13 (1.8%)	125 (2.9%)	10 (2.0%)	127 (2.7%)
28 Tender Joint Count (median [Q1, Q3])	5.0 [1.0, 10.0]	4.0 [1.0, 9.0]	5.0 [2.0, 10.0]	4.0 [1.0, 8.0]
28 Tender Joint Count missing (N (%))	5 (0.7%)	29 (0.7%)	3 (0.6%)	26 (0.6%)
28 Swollen Joint Count (median [Q1, Q3])	3.0 [0.0, 6.0]	2.0 [0.0, 5.0]	3.0 [0.0, 6.0]	2.0 [0.0, 5.0]
28 Swollen Joint Count missing (N (%))	5 (0.7%)	26 (0.6%)	2 (0.4%)	26 (0.6%)
CRP (mg/liter) (median [Q1, Q3])	5.0 [1.9, 12.7]	4.3 [1.8, 12.0]	6.5 [2.7, 14.2]	4.9 [2.0, 12.2]
CRP missing (N (%))	62 (8.6%)	432 (9.9%)	43 (8.4%)	352 (7.5%)
ESR (mm/1h) (median [Q1, Q3])	19.0 [8.0, 34.0]	18.0 [8.0, 32.0]	18.0 [9.0, 34.0]	16.0 [8.0, 30.0]
ESR missing (N (%))	74 (10.2%)	642 (14.7%)	36 (7.0%)	496 (10.5%)

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Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=724)	bDMARD (n=4371)	Tofacitinib (n=511)	bDMARD (n=4716)
Smoking				
Current (N (%))	167 (23.8%)	1089 (25.8%)	157 (31.2%)	1406 (30.7%)
Previous (N (%))	251 (35.7%)	1474 (34.9%)	154 (30.6%)	1568 (34.3%)
Never (N (%))	285 (40.5%)	1666 (39.4%)	192 (38.2%)	1604 (35.0%)
Missing (N (%))	21 (2.9%)	142 (3.2%)	8 (1.6%)	138 (2.9%)
Disease history				
Malignancies (N (%))	30 (4.1%)	238 (5.4%)	17 (3.3%)	239 (5.1%)
Lymphoma (N (%))	3 (0.4%)	21 (0.5%)	2 (0.4%)	30 (0.6%)
Tuberculosis (N (%))	16 (2.2%)	95 (2.2%)	8 (1.6%)	125 (2.7%)
Joint replacement surgery (N (%))	96 (13.4%)	467 (10.8%)	64 (12.6%)	481 (10.3%)
Joint replacement surgery missing (N (%))	6 (0.8%)	40 (0.9%)	3 (0.6%)	48 (1.0%)
COPD (N (%))	42 (5.8%)	264 (6.0%)	30 (5.9%)	289 (6.1%)
Diabetes mellitus (N (%))	119 (16.4%)	618 (14.1%)	63 (12.3%)	555 (11.8%)
Hypertension (N (%))	353 (48.8%)	2029 (46.4%)	222 (43.4%)	2049 (43.4%)
CHD/CAD (N (%))	66 (9.1%)	389 (8.9%)	36 (7.0%)	321 (6.8%)
CKD (N (%))	73 (10.1%)	445 (10.2%)	21 (4.1%)	173 (3.7%)
Heart failure (incl. CHF) (N (%))	28 (3.9%)	163 (3.7%)	7 (1.4%)	78 (1.7%)
Comorbidities				
Number of comorbidities (mean (SD))	3.0 (2.5)	2.9 (2.6)	2.6 (2.3)	2.6 (2.3)
No comorbidity (N (%))	134 (18.5%)	976 (22.3%)	121 (23.7%)	1061 (22.5%)
One comorbidity (N (%))	105 (14.5%)	592 (13.5%)	67 (13.1%)	735 (15.6%)
Two comorbidities (N (%))	113 (15.6%)	654 (15.0%)	86 (16.8%)	832 (17.6%)
Three or more comorbidities (N (%))	372 (51.4%)	2149 (49.2%)	237 (46.4%)	2088 (44.3%)

Abbreviations: ACR, American College of Rheumatology; bDMARDs, biologic disease modifying antirheumatic drugs; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DAS28,

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Table 12. Baseline Characteristics for therapy starts index date (II), stratified by monotherapy vs. combination therapy with concomitant nbDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=724)	bDMARD (n=4371)	Tofacitinib (n=511)	bDMARD (n=4716)

disease activity score 28; DMARDs, disease modifying antirheumatic drugs, ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; HAQ, health assessment questionnaire, MTX, methotrexate; N, Number; nbDMARDs, non-biologic disease modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, numerical rating scale; SD, standard deviation; mg, milligram; mm/1h, millimeter / 1 hour; Q1, first quartile; Q3, third quartile; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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10.3. Outcome Data

IRs: On-drug approach

The on-drug approach analysis was restricted to therapy episodes with at least one RABBIT cohort follow-up visit (see Table 21 for visit schedule) after initiation of the drug. For the on-drug approach, the possible maximum number of therapy episodes and the maximum mean total time at risk were 1,208 and 2,341.33 patient years (PYs) for the tofacitinib cohort, 8,795 and 17,507.14 PYs for the bDMARD cohort, and 3,511 and 5,393,07 PYs for the b/tsDMARD naive nbDMARD cohort, respectively. The maximum mean time and maximum median time (Q1, Q3) in PYs in the on-drug analysis was 1.95 and 1.18 (0.50, 2.96) for the tofacitinib cohort, 2.33 and 1.73 (0.75, 3.47) for the bDMARD cohort and 1.77 and 1.05 (0.44, 2.56) for the nbDMARD cohort, respectively. For the subgroup without prior b/tsDMARDs, the maximum mean time and maximum median time (Q1, Q3) in PYs in the on-drug analysis was 2.45 and 1.95 (0.70, 3.99) for the tofacitinib cohort, 2.32 and 1.64 (0.73, 3.50) for the bDMARD cohort and 1.77 and 1.05 (0.44, 2.56) for the nbDMARD cohort, respectively.

When stratifying by patient sex, the respective numbers of episodes and PYs for females and males were 929 (1769.14 PYs) and 279 (572.19 PYs) for the tofacitinib cohort, 6456 (12800.59 PYs) and 2339 (4706.55 PYs) for the bDMARD cohort and 2503 (3906.68 PYs) and 1008 (1486.39 PYs) for the nbDMARD cohort, respectively. The numbers decreased accordingly when an event occurred, as only the first event per patient per exposure group was considered.

Crude and age- and sex-standardized IRs for the tofacitinib and bDMARD cohorts for all outcomes are presented in Table 13. While all results for stratified comparisons are given in the tables, some subgroups with few episodes and events are not discussed in the text (e.g. the subgroup with at least one other prior JAKi, therapy start on or after 30-JUNE-2021). Stratified crude and age- and sex-standardized IRs, including for the b/tsDMARD naive nbDMARD cohort, are shown in Table 14. Generally, crude and age- and sex-standardized IRs were very similar across outcomes, and only the crude IRs are discussed in the text.

1. Serious infections (excluding TB)

   Overall: As seen in Table 13, there were 55 events in the tofacitinib cohort and 361 events in the bDMARD cohort. The crude IR in the tofacitinib cohort was elevated relative to the bDMARD cohort (24.03 per 1000 PYs (95% CI: 18.10, 31.28) versus 21.18 per 1000 PYs (95% CI: 19.05, 23.48) for the bDMARD cohort.. For females, the crude IR was 20.74 per 1000 PYs (95% CI: 14.53, 28.72) (36 events) in the tofacitinib and 18.98 per 1000 PYs (95% CI: 16.64, 21.56) (237 events) in the bDMARD cohort. For males, the crude IR was 34.35 per 1000 PYs (95% CI: 20.68, 53.64) (19 events) in the tofacitinib and 27.22 per 1000 PYs (95% CI: 22.64, 32.45) (124 events) in the bDMARD cohort (data not shown).

- Stratified: Results for the stratified analyses are shown in Table 14.
  - For the subgroup without prior b/tsDMARDs, there were 14 events in the tofacitinib cohort, 158 events in the bDMARD cohort, and 59 events in the nbDMARD cohort. The crude IR was 18.59 per 1000 PYs (95% CI: 10.16, 31.18) for the tofacitinib, 17.62

per 1000 PYs (95% CI: 14.98, 20.59) for the bDMARD and 11.11 per 1000 PYs (95% CI: 8.46, 14.33) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARD, the crude IR was 24.22 per 1000 PYs (95% CI: 13.85, 39.34) (16 events) for the tofacitinib and 21.14 per 1000 PYs (95% CI: 16.76, 26.31) (80 events) for the bDMARD cohort.
- For the subgroup with at least two prior b/tsDMARDs, the crude IR was 28.58 per 1000 PYs (95% CI: 18.49, 42.18) (25 events) for the tofacitinib and 28.67 per 1000 PYs (95% CI: 23.83, 34.21) (123 events) for the bDMARD cohort.
- For the subgroup with no other prior JAKi, the crude IR was 24.75 per 1000 PYs (95% CI: 18.59, 32.29) (54 events) for the tofacitinib and 20.35 per 1000 PYs (95% CI: 13.85, 39.34) (313 events) for the bDMARD cohort.
- For the subgroup of patients using monotherapy, the crude IR was 25.46 per 1000 PYs (95% CI: 17.30, 36.14) (31 events) for the tofacitinib and 22.86 per 1000 PYs (95% CI: 19.55, 26.58) (169 events) for the bDMARD cohort. For the subgroup of patients on combination therapy with a nbDMARD, the crude IR was 22.40 per 1000 PYs (95% CI: 14.35, 33.33) (24 events) for the tofacitinib and 19.89 per 1000 PYs (95% CI: 17.18, 22.92) (192 events) for the bDMARD cohort. For the subgroup on combination therapy with MTX, the crude IR was 21.62 per 1000 PYs (95% CI: 13.55, 32.73) (22 events) for the tofacitinib and 18.99 per 1000 PYs (95% CI: 16.26, 22.05) (172) events for the bDMARD cohort.
- For the subgroup of patients aged below 65 years, the crude IR was 13.41 per 1000 PYs (95% CI: 8.30, 20.50) (21 events) for the tofacitinib, 13.08 per 1000 PYs (95% CI: 11.09, 15.31) (154 events) for the bDMARD and 7.51 per 1000 PYs (95% CI: 4.90, 11.00) (26 events) for the nbDMARD cohort. For the subgroup of patients aged at least 65 years, the crude IR was 47.06 per 1000 PYs (95% CI: 32.59, 65.76) (34 events) for the tofacitinib, 39.30 per 1000 PYs (95% CI: 34.13, 45.03) (207 events) for the bDMARD and 17.86 per 1000 PYs (95% CI: 12.29, 25.08) (33 events) for the nbDMARD cohort.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Pneumonia: There were 17 events in the tofacitinib and 87 events in the bDMARD cohort. The crude IR was higher for the tofacitinib cohort (7.31 per 1000 PYs; 95% CI: 4.26, 11.71) relative to that of the bDMARD cohort (5.00 per 1000 PYs; 95% CI: 4.00, 6.16).

Other infections of the respiratory system: There was one event in the tofacitinib cohort and there were 38 events in the bDMARD cohort. The crude IR was 0.43 per 1000 PYs (95% CI: 0.01, 2.38) for the tofacitinib cohort and 2.18 per 1000 PYs (95% CI: 1.54, 2.99) for the bDMARD cohort.

Infections of the central nervous system (CNS): There were no events in the tofacitinib cohort and there were 7 events (crude IR 0.40 per 1000 PYs (95% CI: 0.16, 0.82)) in the bDMARD cohort.

Sepsis: There were 9 events in the tofacitinib cohort and 50 events in the bDMARD cohort. The crude IR was 3.86 per 1000 PYs (95% CI: 1.76, 7.33) for the tofacitinib cohort and 2.86 per 1000 PYs (95% CI: 2.12, 3.77) for the bDMARD cohort.

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Bone or joint infections: There was one event in the tofacitinib cohort and there were 14 events in the bDMARD cohort. The crude IR was 0.43 per 1000 PYs (95% CI: 0.01, 2.38) for the tofacitinib and 0.80 per 1000 PYs (95% CI: 0.44, 1.34) for the bDMARD cohort.

Opportunistic infections: There were 3 events in the tofacitinib cohort and 8 events in the bDMARD cohort. The crude IR was 1.28 per 1000 PYs (95% CI: 0.26, 3.75) for the tofacitinib cohort and 0.46 per 1000 PYs (95% CI: 0.20, 0.90) for the bDMARD cohort.

Other infections: There were 26 events in the tofacitinib cohort and 187 events in the bDMARD cohort. The crude IR was 11.24 per 1000 PYs (95% CI: 7.34, 16.46) for the tofacitinib and 10.84 per 1000 PYs (95% CI: 9.34, 12.51) for the bDMARD cohort.

2. TB: There were no events in the tofacitinib and nbDMARD cohorts, and only one event in the bDMARD cohort. No stratified analyses were conducted.

3. HZ:

Overall: There were 49 events in the tofacitinib cohort and 143 events in the bDMARD cohort. The crude IR was higher for the tofacitinib cohort as compared to the bDMARD cohort (21.69 per 1000 PYs (95% CI: 16.05, 28.68) vs. 8.28 per 1000 PYs (95% CI: 6.98, 9.76), respectively). For females, the crude IR was 23.61 per 1000 PYs (95% CI: 16.87, 32.15) (40 events) in the tofacitinib cohort and 10.25 per 1000 PYs (95% CI: 8.56, 12.18) (129 events) in the bDMARD cohort. For males, the crude IR was 15.94 per 1000 PYs (95% CI: 7.29, 30.26) (9 events) in the tofacitinib and 2.99 per 1000 PYs (95% CI: 1.63, 5.01) (14 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 15 events in the tofacitinib cohort, 70 events in the bDMARD cohort, and 23 events in the nbDMARD cohort. The crude IR was 20.51 per 1000 PYs (95% CI: 11.48, 33.82) for the tofacitinib cohort, 7.76 per 1000 PYs (95% CI: 6.05, 9.80) for the bDMARD cohort and 4.30 per 1000 PYs (95% CI: 2.73, 6.45) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARD, the crude IR was 11.96 per 1000 PYs (95% CI: 5.16, 23.56) (8 events) for the tofacitinib cohort and 9.90 per 1000 PYs (95% CI: 7.00, 13.58) (38 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 30.29 per 1000 PYs (95% CI: 19.79, 44.39) (26 events) for the tofacitinib cohort and 7.95 per 1000 PYs (95% CI: 5.54, 11.05) (35 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 21.34 per 1000 PYs (95% CI: 15.63, 28.47) (46 events) for the tofacitinib cohort and 8.48 per 1000 PYs (95% CI: 7.10, 10.06) (132 events) for the bDMARD cohort.
- For the subgroup of patients using monotherapy, the crude IR was 19.89 per 1000 PYs (95% CI: 12.75, 29.60) (24 events) for the tofacitinib cohort and 7.83 per 1000 PYs (95% CI: 5.96, 10.11) (59 events) for the bDMARD cohort. For the subgroup of patients on combination therapy with a nbDMARD, the crude IR was 23.76 per 1000 PYs (95% CI: 15.37, 35.07) (25 events) for the tofacitinib cohort and 8.63 per 1000 PYs (95% CI: 6.88, 10.68) (84 events) for the bDMARD cohort. For the subgroup on combination therapy with MTX, the crude IR was 23.02 per 1000 PYs (95% CI: 14.59,

34.54) (23 events) for the tofacitinib cohort and 8.22 per 1000 PYs (95% CI: 6.46, 10.30) (75 events) for the bDMARD cohort.

- For the subgroup of patients aged below 65 years, the crude IR was 19.48 per 1000 PYs (95% CI: 13.15, 27.81) (30 events) for the tofacitinib, 8.30 per 1000 PYs (95% CI: 6.74, 10.11) (98 events) for the bDMARD and 3.17 per 1000 PYs (95% CI: 1.58, 5.68) (11 events) for the nbDMARD cohort. For the subgroup of patients aged at least 65 years, the crude IR was 26.43 per 1000 PYs (95% CI: 15.91, 41.27) (19 events) for the tofacitinib cohort, 8.24 per 1000 PYs (95% CI: 6.01, 11.03) (45 events) for the bDMARD cohort and 6.37 per 1000 PYs (95% CI: 3.29, 11.13) (12 events) for the nbDMARD cohort.

4. Fractures:

Overall: There were 48 events in the tofacitinib cohort and 306 events in the bDMARD cohort. The crude IR was 21.23 per 1000 PYs (95% CI: 15.66, 28.15) for the tofacitinib and 18.02 per 1000 PYs (95% CI: 16.06, 20.16) for the bDMARD cohort. For females, the crude IR was 25.43 per 1000 PYs (95% CI: 18.41, 34.36) (43 events) in the tofacitinib cohort and 20.35 per 1000 PYs (95% CI: 17.91, 23.02) (252 events) in the bDMARD cohort. In contrast, for males, the crude IR was 8.77 per 1000 PYs (95% CI: 2.85, 20.47) (5 events) in the tofacitinib cohort and 11.75 per 1000 PYs (95% CI: 8.83, 15.34) (54 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 19 events in the tofacitinib cohort, 154 events in the bDMARD cohort, and 51 events in the nbDMARD cohort. The crude IR was 25.86 per 1000 PYs (95% CI: 15.57, 40.39) for the tofacitinib cohort, 17.32 per 1000 PYs (95% CI: 14.70, 20.29) for the bDMARD cohort and 9.61 per 1000 PYs (95% CI: 7.15, 12.63) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARD, the crude IR was 15.21 per 1000 PYs (95% CI: 7.29, 27.97) (10 events) for the tofacitinib cohort and 18.04 per 1000 PYs (95% CI: 14.01, 22.88) (68 events for the bDMARD cohort). For the subgroup with at least two prior b/tsDMARDs, the crude IR was 21.87 per 1000 PYs (95% CI: 13.17, 34.16) (19 events) for the tofacitinib cohort and 19.44 per 1000 PYs (95% CI: 15.50, 24.06) (84 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 20.40 per 1000 PYs (95% CI: 14.83, 27.39) (44 events) for the tofacitinib cohort and 17.92 per 1000 PYs (95% CI: 15.86, 20.17) (274 events) for the bDMARD cohort.
- For the subgroup using monotherapy, the crude IR was 18.21 per 1000 PYs (95% CI: 11.41, 27.57) (22 events) for the tofacitinib cohort and 17.56 per 1000 PYs (95% CI: 14.67, 20.85) (130 events) for the bDMARD cohort. For the subgroup using combination therapy with a nbDMARD, the crude IR was 24.70 per 1000 PYs (95% CI: 16.14, 36.20) (26 events) for the tofacitinib cohort and 18.38 per 1000 PYs (95% CI: 15.77, 21.31) (176 events) for the bDMARD cohort. For the subgroup using combination therapy with MTX, the crude IR was 26.06 per 1000 PYs (95% CI: 17.02, 38.19) (26 events) for the tofacitinib cohort and 18.26 per 1000 PYs (95% CI: 15.57, 21.27) (164 events) for the bDMARD cohort.
- For the subgroup of patients aged below 65 years, the crude IR was 15.56 per 1000 PYs (95% CI: 9.97, 23.15) (24 events) for the tofacitinib cohort, 14.11 per 1000 PYs

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(95% CI: 12.04, 16.43) (165 events) for the bDMARD and 5.50 per 1000 PYs (95% CI: 3.31, 8.59) (19 events) for the nbDMARD cohort. For the subgroup of patients aged at least 65 years, the crude IR was 33.42 per 1000 PYs (95% CI: 21.41, 49.72) (24 events) for the tofacitinib cohort, 26.68 per 1000 PYs (95% CI: 22.46, 31.47) (141 events) for the bDMARD cohort and 17.25 per 1000 PYs (95% CI: 11.80, 24.35) (32 events) for the nbDMARD cohort.

5. Cardiac disorders:

Overall: There were 41 events in the tofacitinib cohort and 232 events in the bDMARD cohort. The crude IR was 17.90 per 1000 PYs (95% CI: 12.85, 24.28) for the tofacitinib cohort and 13.49 per 1000 PYs (95% CI: 11.81, 15.34) for the bDMARD cohort. For females, the crude IR was 15.01 per 1000 PYs (95% CI: 9.80, 21.99) (26 events) in the tofacitinib cohort and 11.01 per 1000 PYs (95% CI: 9.26, 13.01) (139 events) in the bDMARD cohort. For males, the crude IR was 26.89 per 1000 PYs (95% CI: 15.05, 44.34) (15 events) in the tofacitinib cohort and 20.32 per 1000 PYs (95% CI: 16.40, 24.89) (93 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 13 events in the tofacitinib cohort, 112 events in the bDMARD cohort, and 33 events in the nbDMARD cohort. The crude IR was 17.26 per 1000 PYs (95% CI: 9.19, 29.52) for the tofacitinib cohort, 12.43 per 1000 PYs (95% CI: 10.24, 14.96) for the bDMARD cohort and 6.17 per 1000 PYs (95% CI: 4.25, 8.67) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARD, the crude IR was 19.72 per 1000 PYs (95% CI: 10.50, 33.72) (13 events) for the tofacitinib cohort and 13.36 per 1000 PYs (95% CI: 9.94, 17.56) (51 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 17.08 per 1000 PYs (95% CI: 9.56, 28.17) (15 events) for the tofacitinib cohort and 15.80 per 1000 PYs (95% CI: 12.29, 19.99) (69 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 17.85 per 1000 PYs (95% CI: 12.70, 24.41) (39 events) for the tofacitinib cohort and 13.61 per 1000 PYs (95% CI: 11.84, 15.58) (211 events) for the bDMARD cohort. For the subgroup on monotherapy, the crude IR was 20.55 per 1000 PYs (95% CI: 13.30, 30.33) (25 events) for the tofacitinib cohort and 15.53 per 1000 PYs (95% CI: 12.83, 18.63) (116 events) for the bDMARD cohort. For the subgroup on combination therapy with a nbDMARD, the crude IR was 14.90 per 1000 PYs (95% CI: 8.52, 24.20) (16 events) for the tofacitinib cohort and 11.92 per 1000 PYs (95% CI: 9.85, 14.30) (116 events) for the bDMARD cohort. For the subgroup on combination therapy with MTX, the crude IR was 15.70 per 1000 PYs (95% CI: 8.97, 25.50) (16 events) for the tofacitinib cohort and 11.85 per 1000 PYs (95% CI: 9.72, 14.30) (108 events) for the bDMARD cohort.
- For the subgroup of patients with aged below 65 years, the crude IR was 11.56 per 1000 PYs (95% CI: 6.85, 18.26) (18 events) for the tofacitinib cohort, 7.85 per 1000 PYs (95% CI: 6.33, 9.61) (93 events) for the bDMARD cohort and 3.46 per 1000 PYs (95% CI: 1.79, 6.04) (12 events) for the nbDMARD cohort. For the subgroup of patients aged at least 65 years, the crude IR was 31.38 per 1000 PYs (95% CI: 19.89, 47.09) (23 events) for the tofacitinib cohort, 26.01 per 1000 PYs (95% CI:

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21.87, 30.71) (139 events) for the bDMARD cohort and 11.18 per 1000 PYs (95% CI: 6.92, 17.09) (21 events) for the nbDMARD cohort.

- For the subgroup of patients without CV risk factors, the crude IR was 6.08 per 1000 PYs (95% CI: 1.98, 14.20) (5 events) for the tofacitinib cohort, 4.25 per 1000 PYs (95% CI: 2.89, 6.04) (31 events) for the bDMARD cohort and 0.93 per 1000 PYs (95% CI: 0.11, 3.34) (2 events) for the nbDMARD cohort. For the subgroup of patients with CV risk factors, the crude IR was 24.51 per 1000 PYs (95% CI: 17.17, 33.93) (36 events) for the tofacitinib cohort, 20.28 per 1000 PYs (95% CI: 17.58, 23.29) (201 events) for the bDMARD cohort and 9.73 per 1000 PYs (95% CI: 6.61, 13.81) (31 events) for the b/tsDMARD naive nbDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 16.99 per 1000 PYs (95% CI: 12.02, 23.32) (38 events) for the tofacitinib cohort, 12.88 per 1000 PYs (95% CI: 11.01, 14.97) (169 events) for the bDMARD cohort and 5.85 per 1000 PYs (95% CI: 3.82, 8.58) (26 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, the crude IR was 55.51 per 1000 PYs (95% CI: 11.45, 162.21) (3 events) for the tofacitinib cohort, 15.47 per 1000 PYs (95% CI: 11.89, 19.80) (63 events) for the bDMARD cohort and 7.72 per 1000 PYs (95% CI: 3.10, 15.91) (7 events) for the nbDMARD cohort.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Heart failure: There were 10 events in the tofacitinib cohort and 60 events in the bDMARD cohort. The crude IR was 4.28 per 1000 PYs (95% CI: 2.05, 7.87) for the tofacitinib cohort and 3.44 per 1000 PYs (95% CI: 2.62, 4.42) for the bDMARD cohort.

Coronary artery disease: There were 7 events in the tofacitinib cohort and 63 events in the bDMARD cohort. The crude IR was 3.00 per 1000 PYs (95% CI: 1.21, 6.18) for the tofacitinib cohort and 3.62 per 1000 PYs (95% CI: 2.78, 4.63) for the bDMARD cohort.

Myocardial infarction: There were 11 events in the tofacitinib cohort and 47 events in the bDMARD cohort. The crude IR was 4.72 per 1000 PYs (95% CI: 2.36, 8.45) for the tofacitinib cohort and 2.70 per 1000 PYs (95% CI: 1.98, 3.58) for the bDMARD cohort. For episodes without CV risk factors, the crude IR was 3.64 per 1000 PYs (95% CI: 0.75, 10.63) (3 events) for tofacitinib and 0.82 per 1000 PYs (95% CI: 0.30, 1.78) (6 events) for bDMARD. For episodes with CV risk factors, the crude IR was 5.32 per 1000 PYs (95% CI: 2.30, 10.48) (8 events) for the tofacitinib cohort and 4.05 per 1000 PYs (95% CI: 2.91, 5.50) (41 events) for the bDMARD cohort. For other stratifications see Table 14.

Cardiovascular risk (MACE):

Overall:There were 20 events in the tofacitinib and 91 events in the bDMARD cohort. The crude IR was 8.60 per 1000 PYs (95% CI: 5.26, 13.29) for the tofacitinib and 5.23 per 1000 PYs (95% CI: 4.21, 6.42) for the bDMARD cohort. For females, the crude IR was 5.68 per 1000 PYs (95% CI: 2.72, 10.44) (10 events) in the tofacitinib and 3.93 per 1000 PYs (95% CI: 2.91, 5.18) (50 events) in the bDMARD cohort. For males, the crude IR was

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17.77 per 1000 PYs (95% CI: 8.52, 32.67) (10 events) in the tofacitinib and 8.80 per 1000 PYs (95% CI: 6.31, 11.93) (41 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 7 events in the tofacitinib, 48 events in the bDMARD, and 18 events in the nbDMARD cohort. The crude IR was 9.12 per 1000 PYs (95% CI: 3.67, 18.80) for the tofacitinib, 5.28 per 1000 PYs (95% CI: 3.89, 7.00) for the bDMARD and 3.36 per 1000 PYs (95% CI: 1.99, 5.31) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 7.44 per 1000 PYs (95% CI: 2.42, 17.37) (5 events) for the tofacitinib and 5.43 per 1000 PYs (95% CI: 3.36, 8.29) (21 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDst, the crude IR was 9.03 per 1000 PYs (95% CI: 3.90, 17.80) (8 events) for the tofacitinib and 4.96 per 1000 PYs (95% CI: 3.11, 7.51) (22 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 8.56 per 1000 PYs (95% CI: 5.16, 13.38) (19 events) for the tofacitinib and 5.11 per 1000 PYs (95% CI: 4.05, 6.36) (80 events) for the bDMARD cohort. For the subgroup monotherapy, the crude IR was 10.49 per 1000 PYs (95% CI: 5.59, 17.94) (13 events) for the tofacitinib and 5.82 per 1000 PYs (95% CI: 4.23, 7.81) (44 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 6.45 per 1000 PYs (95% CI: 2.59, 13.29) (7 events) for the tofacitinib and 4.78 per 1000 PYs (95% CI: 3.51, 6.36) (47 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 6.79 per 1000 PYs (95% CI: 2.73, 13.99) (7 events) for the tofacitinib and 4.56 per 1000 PYs (95% CI: 3.29, 6.16) (42 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, there were in the tofacitinib, in the bDMARD, and in the nbDMARD cohort. The crude IR was 6.97 per 1000 PYs (95% CI: 3.48, 12.46) (11 events) for the tofacitinib, 3.35 per 1000 PYs (95% CI: 2.40, 4.57) (40 events) for the bDMARD and 2.02 per 1000 PYs (95% CI: 0.81, 4.16) (7 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 12.07 per 1000 PYs (95% CI: 5.52, 22.92) (9 events) for the tofacitinib, 9.33 per 1000 PYs (95% CI: 6.95, 12.27) (51 events) for the bDMARD and 5.83 per 1000 PYs (95% CI: 2.91, 10.44) (11 events) for the nbDMARD cohort.

- For the subgroup of patients without CV risk factors, the crude IR was 3.64 per 1000 PYs (95% CI: 0.75, 10.63) (3 events) for the tofacitinib, 1.09 per 1000 PYs (95% CI: 0.47, 2.15) (8 events) for the bDMARD and 0.46 per 1000 PYs (95% CI: 0.01, 2.57) (1 event) for the nbDMARD cohort. For the subgroup of patients with CV risk factors, the crude IR was 11.34 per 1000 PYs (95% CI: 6.60, 18.15) (17 events) for the tofacitinib, 8.24 per 1000 PYs (95% CI: 6.56, 10.21) (83 events) for the bDMARD and 5.33 per 1000 PYs (95% CI: 3.10, 8.53) (17 events) for the nbDMARD cohort. For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 8.37 per 1000 PYs (95% CI: 5.04, 13.08) (19 events) for the tofacitinib, 4.98 per 1000 PYs (95% CI: 3.85, 6.33) (66 events) for the bDMARD and 3.38 per 1000 PYs (95% CI: 1.89, 5.57) (15 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, the crude IR was 18.01 per 1000 PYs (95% CI: 0.46, 100.34) (1 event) for the tofacitinib cohort, 6.05 per 1000 PYs (95%

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CI: 3.91, 8.93) (25 events) for the bDMARD cohort and 3.28 per 1000 PYs (95% CI: 0.68, 9.59) (3 events) for the nbDMARD cohort.

Other cardiac disorders: There were 21 events in the tofacitinib cohort and 117 events in the bDMARD cohort. The crude IR was 9.09 per 1000 PYs (95% CI: 5.63, 13.89) for the tofacitinib cohort and 6.75 per 1000 PYs (95% CI: 5.58, 8.09) for the bDMARD cohort.

6. Hematologic disorders:

Overall: There were 7 events in the tofacitinib and 48 events in the bDMARD cohort. The crude IR was 3.00 per 1000 PYs (95% CI: 1.21, 6.18) for the tofacitinib and 2.75 per 1000 PYs (95% CI: 2.03, 3.64) for the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, the crude IR was 3.92 per 1000 PYs (95% CI: 0.81, 11.46) (3 events) for the tofacitinib, 2.74 per 1000 PYs (95% CI: 1.77, 4.05) (25 events) for the bDMARD and 1.86 per 1000 PYs (95% CI: 0.89, 3.42) (10 events) for the nbDMARD cohort.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Bone marrow depression and hypoplastic anaemia: There was no event in the tofacitinib cohort and there were 7 events in the bDMARD (crude IR 0.40 per 1000 PYs; 95% CI: 0.16, 0.82). No stratified analyses were done.

Decreased white blood cells: There was 1 event in the tofacitinib cohort and there were 8 events in the bDMARD cohort. The crude IR was 0.43 per 1000 PYs (95% CI: 0.01, 2.38) for the tofacitinib and 0.46 per 1000 PYs (95% CI: 0.20, 0.90) for the bDMARD cohort. No stratified analyses were done.

Platelet disorders: There was no event in the tofacitinib cohort and there were 4 events (crude IR 0.23 per 1000 PYs; 95% CI: 0.06, 0.59) in the bDMARD cohort. No stratified analyses were done.

Other blood dyscrasia: There were 6 events in the tofacitinib cohort and 31 events in the bDMARD cohort. The crude IR was 2.57 per 1000 PYs (95% CI: 0.94, 5.60) for the tofacitinib and 1.77 per 1000 PYs (95% CI: 1.21, 2.52) for the bDMARD cohort.

7. Disorders of the nervous system (excluding infections):

Overall: There were 36 events in the tofacitinib and 235 events in the bDMARD cohort. The crude IR was 15.64 per 1000 PYs (95% CI: 10.96, 21.66) for the tofacitinib and 13.70 per 1000 PYs (95% CI: 12.01, 15.57) for the bDMARD cohort. For females, the crude IR was 14.33 per 1000 PYs (95% CI: 9.27, 21.25) (25 events) in the tofacitinib and 13.55 per 1000 PYs (95% CI: 11.59, 15.75) (170 events) in the bDMARD cohort. For males, the crude IR was 19.78 per 1000 PYs (95% CI: 9.88, 35.40) (11 events) in the tofacitinib and 14.12 per 1000 PYs (95% CI: 10.90, 18.00) (65 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

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- For the subgroup without prior b/tsDMARDs, there were 6 events in the tofacitinib, 109 events in the bDMARD, and 34 events in the nbDMARD cohort. The crude IR was 7.81 per 1000 PYs (95% CI: 2.87, 17.00) for the tofacitinib, 12.12 per 1000 PYs (95% CI: 9.95, 14.62) for the bDMARD and 6.38 per 1000 PYs (95% CI: 4.42, 8.91) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 10.53 per 1000 PYs (95% CI: 4.23, 21.69) (7 events) for the tofacitinib and 10.97 per 1000 PYs (95% CI: 7.90, 14.82) (42 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 26.49 per 1000 PYs (95% CI: 16.80, 39.75) (23 events) for the tofacitinib and 19.41 per 1000 PYs (95% CI: 15.48, 24.03) (84 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 14.53 per 1000 PYs (95% CI: 9.94, 20.52) (32 events) for the tofacitinib and 12.99 per 1000 PYs (95% CI: 11.26, 14.92) (201 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 20.43 per 1000 PYs (95% CI: 13.22, 30.16) (25 events) for the tofacitinib and 14.08 per 1000 PYs (95% CI: 11.52, 17.05) (105 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 10.21 per 1000 PYs (95% CI: 5.10, 18.26) (11 events) for the tofacitinib and 13.41 per 1000 PYs (95% CI: 11.21, 15.93) (130 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 9.78 per 1000 PYs (95% CI: 4.69, 17.98) (10 events) for the tofacitinib and 13.10 per 1000 PYs (95% CI: 10.85, 15.67) (119 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 9.57 per 1000 PYs (95% CI: 5.36, 15.79) (15 events) for the tofacitinib, 10.34 per 1000 PYs (95% CI: 8.59, 12.35) (122 events) for the bDMARD and 4.04 per 1000 PYs (95% CI: 2.21, 6.77) (14 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 28.59 per 1000 PYs (95% CI: 17.70, 43.71) (21 events) for the tofacitinib, 21.11 per 1000 PYs (95% CI: 17.40, 25.38) (113 events) for the bDMARD and 10.72 per 1000 PYs (95% CI: 6.55, 16.56) (20 events) for the nbDMARD cohort.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Stroke: There were 14 events in the tofacitinib and 64 events in the bDMARD cohort. The crude IR was 6.02 per 1000 PYs (95% CI: 3.29, 10.10) for the tofacitinib and 3.67 per 1000 PYs (95% CI: 2.83, 4.69) for the bDMARD cohort.

Central demyelination: There was no event in the tofacitinib cohort and only one event in the bDMARD cohort. No stratified analyses were done.

Other disorders of the CNS: There were 16 events in the tofacitinib and 105 events in the bDMARD cohort. The crude IR was 6.87 per 1000 PYs (95% CI: 3.93, 11.16) for the tofacitinib and 6.05 per 1000 PYs (95% CI: 4.95, 7.33) for the bDMARD cohort.

Disorders of the peripheral nervous system: There were 5 events in the tofacitinib and 45 events in the bDMARD cohort. The crude IR was 2.14 per 1000 PYs (95% CI: 0.70, 5.00) for the tofacitinib and 2.58 per 1000 PYs (95% CI: 1.88, 3.45) for the bDMARD cohort.

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Psychiatric disorders: There were 5 events in the tofacitinib and 49 events in the bDMARD cohort. The crude IR was 2.14 per 1000 PYs (95% CI: 0.70, 5.00) for the tofacitinib and 2.81 per 1000 PYs (95% CI: 2.08, 3.72) for the bDMARD cohort.

8. PML: There was no event in the tofacitinib cohort and only one event in the bDMARD cohort. No stratified analyses were done.

9. Allergic conditions and hypersensitivity: There were 3 events in the tofacitinib cohort and 23 events in the bDMARD cohort. The crude IR was 1.28 per 1000 PYs (95% CI: 0.26, 3.75) for the tofacitinib and 1.32 per 1000 PYs (95% CI: 0.83, 1.97) for the bDMARD cohort. Due to the small number of events no further analyses were done.

10. Hepatic failure: There were no events in the tofacitinib cohort, there were 7 events in the bDMARD cohort (crude IR 0.40 per 1000 PYs; 95% CI: 0.16, 0.82), and one event in the nbDMARD cohort (crude IR 0.19 per 1000 PYs; 95% CI: 0.00, 1.03). No stratified analyses were conducted.

11. GI perforations

Overall: There were 5 events in the tofacitinib and 44 events in the bDMARD cohort. The crude IR was 2.14 per 1000 PYs (95% CI: 0.69, 4.99) for the tofacitinib and 2.52 per 1000 PYs (95% CI: 1.83, 3.39) for the bDMARD cohort.

Stratified:

- For the subgroup without prior b/tsDMARDs, there was no event in the tofacitinib cohort. 16 events occurred in the bDMARD cohort (crude IR 1.75; 95% CI: 1.00, 2.85) and 14 events in the nbDMARD cohort (crude IR 2.60; 95% CI: 1.42, 4.37). Further results for the stratified analyses are shown in Table 14.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Lower intestinal perforations: There was no event in the tofacitinib cohort and there were 13 events in the bDMARD cohort (crude IR 0.74; 95% CI: 0.40, 1.27). No stratified analyses were done.

Other intestinal perforations: There were 5 events in the tofacitinib and 37 events in the bDMARD cohort. The crude IR was 2.14 per 1000 PYs (95% CI: 0.69, 4.99) for the tofacitinib and 2.12 per 1000 PYs (95% CI: 1.49, 2.92) for the bDMARD cohort.

12. Pregnancy: Please see end of section 10.4.

13. Embolic and thrombotic events, venous or vessel type unspecified:

Overall: There were 7 events in the tofacitinib and 41 events in the bDMARD cohort. The crude IR was 2.99 per 1000 PYs (95% CI: 1.20, 6.17) for the tofacitinib and 2.35 per 1000 PYs (95% CI: 1.69, 3.19) for the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

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- For the subgroup without prior b/tsDMARDs, the crude IR was 2.61 per 1000 PYs (95% CI: 0.32, 9.41) (2 events) for the tofacitinib, 2.30 per 1000 PYs (95% CI: 1.42, 3.52) (21 events) for the bDMARD and 0.74 per 1000 PYs (95% CI: 0.20, 1.90) (4 events) for the nbDMARD cohort.
- For the subgroup with one prior b/tsDMARDs, the crude IR was 2.95 per 1000 PYs (95% CI: 0.36, 10.66) (2 events) for the tofacitinib and 2.31 per 1000 PYs (95% CI: 1.06, 4.39) (9 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 3.36 per 1000 PYs (95% CI: 0.69, 9.82) (3 events) for the tofacitinib and 2.48 per 1000 PYs (95% CI: 1.24, 4.44) (11 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 3.14 per 1000 PYs (95% CI: 1.26, 6.47) (7 events) for the tofacitinib and 2.29 per 1000 PYs (95% CI: 1.60, 3.17) (36 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 4.82 per 1000 PYs (95% CI: 1.77, 10.49) (6 events) for the tofacitinib and 2.37 per 1000 PYs (95% CI: 1.40, 3.75) (18 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 0.92 per 1000 PYs (95% CI: 0.02, 5.10) (one event) for the tofacitinib and 2.33 per 1000 PYs (95% CI: 1.48, 3.50) (23 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 0.96 per 1000 PYs (95% CI: 0.02, 5.27) (one event) for the tofacitinib and 2.38 per 1000 PYs (95% CI: 1.49, 3.60) (22 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 1.26 per 1000 PYs (95% CI: 0.15, 4.54) (2 events) for the tofacitinib, 1.25 per 1000 PYs (95% CI: 0.70, 2.07) (15 events) for the bDMARD and 0.29 per 1000 PYs (95% CI: 0.01, 1.60) (1 event) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 6.69 per 1000 PYs (95% CI: 2.17, 15.60) (5 events) for the tofacitinib, 4.74 per 1000 PYs (95% CI: 3.10, 6.94) (26 events) for the bDMARD and 1.58 per 1000 PYs (95% CI: 0.33, 4.62) (3 events) for the nbDMARD cohort.

- For episodes without VTE risk factors, the crude IR was 1.14 per 1000 PYs (95% CI: 0.03, 6.34) (1 event) for tofacitinib and 1.19 per 1000 PYs (95% CI: 0.54, 2.26) (9 events) for bDMARD. For episodes with VTE risk factors, the crude IR was 4.11 per 1000 PYs (95% CI: 1.51, 8.95) (6 events) for tofacitinib and 3.23 per 1000 PYs (95% CI: 2.21, 4.57) (32 events) for bDMARD. For episodes before 31-JAN-2020, the crude IR was 3.57 per 1000 PYs (95% CI: 1.43, 7.35) (7 events) for tofacitinib and 2.22 per 1000 PYs (95% CI: 1.39, 3.36) (22 events) for bDMARD. For episodes on or after 31-JAN-2020, there was no event within the tofacitinib cohort and 19 events within the bDMARD cohort (crude IR 2.52 per 1000 PYs; 95% CI: 1.52, 3.93).

Results for the stratified analyses of the following outcomes are shown in Table 14.

VTE: There were 6 events in the tofacitinib and 41 events in the bDMARD cohort. The crude IR was 2.57 per 1000 PYs (95% CI: 0.94, 5.58) for the tofacitinib and 2.35 per 1000 PYs (95% CI: 1.69, 3.19) for the bDMARD cohort. For episodes without VTE risk factors, the crude IR was 1.14 per 1000 PYs (95% CI: 0.03, 6.34) (1 event) for tofacitinib and 1.19 per 1000 PYs (95% CI: 0.54, 2.26) (9 events) for bDMARD. For episodes with VTE risk factors, the crude IR was 3.43 per 1000 PYs (95% CI: 1.11, 7.99) (5 events) for tofacitinib and 3.23 per 1000 PYs (95% CI: 2.21, 4.57) (32 events) for bDMARD.

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DVT: There were 2 events in the tofacitinib and 18 events in the bDMARD cohort. The crude IR was 0.85 per 1000 PYs (95% CI: 0.10, 3.09) for the tofacitinib and 1.03 per 1000 PYs (95% CI: 0.61, 1.63) for the bDMARD cohort. Boths events in the tofacitinib cohort occurred in the subgroup with VTE risk factors and age at least 65 years.

PE: There were 6 events in the tofacitinib and 31 events in the bDMARD cohort. The crude IR was 2.57 per 1000 PYs (95% CI: 0.94, 5.58) for the tofacitinib and 1.78 per 1000 PYs (95% CI: 1.21, 2.52) for the bDMARD cohort. For episodes without VTE risk factors, the crude IR was 1.14 per 1000 PYs (95% CI: 0.03, 6.34) (1 event) for tofacitinib and 0.66 per 1000 PYs (95% CI: 0.21, 1.54) (5 events) for bDMARD. For episodes with VTE risk factors, the crude IR was 3.43 per 1000 PYs (95% CI: 1.11, 7.99) (5 events) for tofacitinib and 2.62 per 1000 PYs (95% CI: 1.71, 3.85) (26 events) for bDMARD.

14. Operations and hospitalizations:

Overall: There were 34 events in the tofacitinib and 235 events in the bDMARD cohort. The crude IR was 14.82 per 1000 PYs (95% CI: 10.27, 20.72) for the tofacitinib and 13.72 per 1000 PYs (95% CI: 12.02, 15.59) for the bDMARD cohort. For females, the crude IR was 16.81 per 1000 PYs (95% CI: 11.26, 24.15) (29 events) in the tofacitinib and 13.73 per 1000 PYs (95% CI: 11.75, 15.94) (172 events) in the bDMARD cohort. For males, the crude IR was 8.79 per 1000 PYs (95% CI: 2.85, 20.52) (5 events) in the tofacitinib and 13.68 per 1000 PYs (95% CI: 10.51, 17.50) (63 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14

- For the subgroup without prior b/tsDMARDs use, there were 10 events in the tofacitinib, 97 events in the bDMARD, and 31 events in the nbDMARD cohort. The crude IR was 13.31 per 1000 PYs (95% CI: 6.38, 24.48) for the tofacitinib, 10.78 per 1000 PYs (95% CI: 8.74, 13.15) for the bDMARD and 5.81 per 1000 PYs (95% CI: 3.95, 8.24) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 11.96 per 1000 PYs (95% CI: 5.16, 23.57) (8 events) for the tofacitinib and 17.71 per 1000 PYs (95% CI: 13.72, 22.49) (67 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 18.32 per 1000 PYs (95% CI: 10.47, 29.76) (16 events) for the tofacitinib and 16.32 per 1000 PYs (95% CI: 12.75, 20.58) (71 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 14.17 per 1000 PYs (95% CI: 9.63, 20.11) (31 events) for the tofacitinib and 13.14 per 1000 PYs (95% CI: 11.39, 15.07) (203 events) for the bDMARD cohort.
- For the subgroup monotherapy the crude IR was 14.73 per 1000 PYs (95% CI: 8.73, 23.28) (18 events) for the tofacitinib and 14.50 per 1000 PYs (95% CI: 11.90, 17.51) (108 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 14.93 per 1000 PYs (95% CI: 8.53, 24.25) (16 events) for the tofacitinib and 13.11 per 1000 PYs (95% CI: 10.93, 1.60) (127 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 15.74 per 1000 PYs (95% CI: 8.99, 25.56) (16 events) for the tofacitinib and 12.65 per 1000 PYs (95% CI: 10.45, 15.19) (115 events) for the bDMARD cohort.

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- For the subgroup of patients with age below 65 years, the crude IR was 11.59 per 1000 PYs (95% CI: 6.87, 18.31) (18 events) for the tofacitinib, 11.91 per 1000 PYs (95% CI: 10.02, 14.05) (140 events) for the bDMARD and 3.17 per 1000 PYs (95% CI: 1.58, 5.68) (11 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 21.62 per 1000 PYs (95% CI: 12.36, 35.11) (16 events) for the tofacitinib, 17.66 per 1000 PYs (95% CI: 14.29, 21.59) (95 events) for the bDMARD and 10.68 per 1000 PYs (95% CI: 6.52, 16.49) (20 events) for the nbDMARD cohort.

Results for the stratified analyses of the following outcomes are shown in Table 14.

Bone and joint surgery and other joint therapeutic procedures: There were 25 events in the tofacitinib and 196 events in the bDMARD cohort. The crude IR was 10.81 per 1000 PYs (95% CI: 7.00, 15.96) for the tofacitinib and 11.41 per 1000 PYs (95% CI: 9.87, 13.12) for the bDMARD cohort.

Other operations and (major) therapeutic procedures that lead to hospitalization: There were 9 events in the tofacitinib and 44 events in the bDMARD cohort. The crude IR was 3.88 per 1000 PYs (95% CI: 1.77, 7.36) for the tofacitinib and 2.52 per 1000 PYs (95% CI: 1.83, 3.39) for the bDMARD cohort.

15. Other serious diagnoses, symptoms, and syndromes

Overall: There were 166 events in the tofacitinib and 1134 events in the bDMARD cohort. The crude IR was 78.89 per 1000 PYs (95% CI: 67.35, 91.85) for the tofacitinib and 72.39 per 1000 PYs (95% CI: 68.24, 76.73) for the bDMARD cohort. For females, the crude IR was 83.26 per 1000 PYs (95% CI: 69.61, 98.80) (131 events) in the tofacitinib and 72.85 per 1000 PYs (95% CI: 67.99, 77.96) (835 events) in the bDMARD cohort. For males, the crude IR was 65.94 per 1000 PYs (95% CI: 45.93, 91.71) (35 events) in the tofacitinib and 71.16 per 1000 PYs (95% CI: 63.32, 79.70) (299 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 49 events in the tofacitinib, 533 events in the bDMARD, and 183 events in the nbDMARD cohort. The crude IR was 71.94 per 1000 PYs (95% CI: 53.22, 95.11) for the tofacitinib, 63.90 per 1000 PYs (95% CI: 58.59, 69.56) for the bDMARD and 35.86 per 1000 PYs (95% CI: 30.85, 41.45) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 63.99 per 1000 PYs (95% CI: 45.50, 87.48) (39 events) for the tofacitinib and 76.69 per 1000 PYs (95% CI: 67.70, 86.54) (263 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 95.87 per 1000 PYs (95% CI: 75.78, 119.65) (78 events) for the tofacitinib and 86.80 per 1000 PYs (95% CI: 77.79, 96.57) (338 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 75.12 per 1000 PYs (95% CI: 63.62, 88.11) (151 events) for the tofacitinib and 70.39 per 1000 PYs (95% CI: 66.09, 74.90) (999 events) for the bDMARD cohort.

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- For the subgroup monotherapy, the crude IR was 79.26 per 1000 PYs (95% CI: 63.65, 97.54) (89 events) for the tofacitinib and 77.64 per 1000 PYs (95% CI: 71.15, 84.57) (526 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 78.47 per 1000 PYs (95% CI: 61.93, 98.07) (77 events) for the tofacitinib and 68.40 per 1000 PYs (95% CI: 63.07, 74.05) (608 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 81.95 per 1000 PYs (95% CI: 64.57, 102.57) (76 events) for the tofacitinib and 68.27 per 1000 PYs (95% CI: 62.77, 74.11) (569 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 61.53 per 1000 PYs (95% CI: 49.41, 75.72) (89 events) for the tofacitinib, 60.36 per 1000 PYs (95% CI: 55.83, 65.16) (656 events) for the bDMARD and 27.54 per 1000 PYs (95% CI: 22.20, 33.78) (92 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 117.06 per 1000 PYs (95% CI: 92.39, 146.31) (77 events) for the tofacitinib, 99.68 per 1000 PYs (95% CI: 90.94, 109.03) (478 events) for the bDMARD and 51.62 per 1000 PYs (95% CI: 41.56, 63.38) (91 events) for the nbDMARD cohort.

16. NMSC:

Overall: There were 12 events in the tofacitinib and 41 events in the bDMARD cohort. The crude IR was 5.16 per 1000 PYs (95% CI: 2.67, 9.02) for the tofacitinib and 2.35 per 1000 PYs (95% CI: 1.69, 3.19) for the bDMARD cohort. For females, the crude IR was 5.13 per 1000 PYs (95% CI: 2.34, 9.73) (9 events) in the tofacitinib and 2.04 per 1000 PYs (95% CI: 1.33, 2.99) (26 events) in the bDMARD cohort. For males, the crude IR was 5.27 per 1000 PYs (95% CI: 1.09, 15.39) (3 events) in the tofacitinib and 3.21 per 1000 PYs (95% CI: 1.79, 5.29) (15 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 4 events in the tofacitinib, 18 events in the bDMARD, and 9 events in the nbDMARD cohort. The crude IR was 5.25 per 1000 PYs (95% CI: 1.43, 13.44) for the tofacitinib, 1.97 per 1000 PYs (95% CI: 1.17, 3.12) for the bDMARD and 1.68 per 1000 PYs (95% CI: 0.77, 3.18) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 2.96 per 1000 PYs (95% CI: 0.36, 10.69) (2 events) for the tofacitinib and 3.61 per 1000 PYs (95% CI: 1.97, 6.05) (14 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 6.77 per 1000 PYs (95% CI: 2.48, 14.73) (6 events) for the tofacitinib and 2.03 per 1000 PYs (95% CI: 0.93, 3.85) (9 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 5.41 per 1000 PYs (95% CI: 2.80, 9.46) (12 events) for the tofacitinib and 2.29 per 1000 PYs (95% CI: 1.61, 3.17) (36 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 3.21 per 1000 PYs (95% CI: 0.88, 8.23) (4 events) for the tofacitinib and 2.90 per 1000 PYs (95% CI: 1.82, 4.39) (22 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 7.40 per 1000 PYs (95% CI: 3.20, 14.59) (8 events) for the tofacitinib and 1.93 per 1000 PYs (95% CI: 1.16, 3.01) (19 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 7.80 per

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1000 PYs (95% CI: 3.37, 15.37) (8 events) for the tofacitinib and 2.06 per 1000 PYs (95% CI: 1.24, 3.21) (19 events) for the bDMARD cohort.

- For the subgroup of patients with age below 65 years, the crude IR was 2.52 per 1000 PYs (95% CI: 0.69, 6.46) (4 events) for the tofacitinib, 1.34 per 1000 PYs (95% CI: 0.76, 2.17) (16 events) for the bDMARD and 0.29 per 1000 PYs (95% CI: 0.01, 1.60) (1 event) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 10.84 per 1000 PYs (95% CI: 4.68, 21.35) (8 events) for the tofacitinib, 4.57 per 1000 PYs (95% CI: 2.96, 6.74) (25 events) for the bDMARD and 4.24 per 1000 PYs (95% CI: 1.83, 8.36) (8 events) for the nbDMARD cohort.

- For the subgroup of patients without malignancy risk factors, the crude IR was 7.20 per 1000 PYs (95% CI: 2.34, 16.80) (5 events) for the tofacitinib, 2.51 per 1000 PYs (95% CI: 1.34, 4.29) (13 events) for the bDMARD and 2.68 per 1000 PYs (95% CI: 0.73, 6.86) (4 events) for the nbDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 4.29 per 1000 PYs (95% CI: 1.73, 8.85) (7 events) for the tofacitinib, 2.29 per 1000 PYs (95% CI: 1.52, 3.31) (28 events) for the bDMARD and 1.29 per 1000 PYs (95% CI: 0.42, 3.01) (5 events) for the nbDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 4.47 per 1000 PYs (95% CI: 2.15, 8.23) (10 events) for the tofacitinib, 2.16 per 1000 PYs (95% CI: 1.51, 2.99) (36 events) for the bDMARD and 1.35 per 1000 PYs (95% CI: 0.54, 2.79) (7 events) for the nbDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 5.29 per 1000 PYs (95% CI: 2.73, 9.24) (12 events) for the tofacitinib, 2.18 per 1000 PYs (95% CI: 1.46, 3.13) (29 events) for the bDMARD and 1.57 per 1000 PYs (95% CI: 0.63, 3.23) (7 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was no event in the tofacitinib cohort, but only based on 55 episodes.

17. Malignancies (overall, excluding NMSC):

Overall: There were 23 events in the tofacitinib and 160 events in the bDMARD cohort. The crude IR was 9.88 per 1000 PYs (95% CI: 6.26, 14.83) for the tofacitinib and 9.22 per 1000 PYs (95% CI: 7.85, 10.76) for the bDMARD cohort. For females, the crude IR was 9.10 per 1000 PYs (95% CI: 5.20, 14.78) (16 events) in the tofacitinib and 7.96 per 1000 PYs (95% CI: 6.48, 9.67) (101 events) in the bDMARD cohort. For males, the crude IR was 12.30 per 1000 PYs (95% CI: 4.95, 25.34) (7 events) in the tofacitinib and 12.65 per 1000 PYs (95% CI: 9.63, 16.32) (59 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14

- For the subgroup without prior b/tsDMARDs, there were 8 events in the tofacitinib, 82 events in the bDMARD, and 30 events in the nbDMARD cohort. The crude IR was 10.48 per 1000 PYs (95% CI: 4.52, 20.65) for the tofacitinib, 9.03 per 1000 PYs (95%

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CI: 7.18, 11.21) for the bDMARD and 5.60 per 1000 PYs (95% CI: 3.78, 7.99) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 8.91 per 1000 PYs (95% CI: 3.27, 19.38) (6 events) for the tofacitinib and 9.84 per 1000 PYs (95% CI: 6.96, 13.50) (38 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 10.11 per 1000 PYs (95% CI: 4.62, 19.20) (9 events) for the tofacitinib and 9.06 per 1000 PYs (95% CI: 6.48, 12.34) (40 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 9.01 per 1000 PYs (95% CI: 5.50, 13.92) (20 events) for the tofacitinib and 8.95 per 1000 PYs (95% CI: 7.53, 10.56) (140 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 10.49 per 1000 PYs (95% CI: 5.58, 17.93) (13 events) for the tofacitinib and 9.13 per 1000 PYs (95% CI: 7.10, 11.55) (69 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 9.19 per 1000 PYs (95% CI: 4.41, 16.91) (10 events) for the tofacitinib and 9.29 per 1000 PYs (95% CI: 7.48, 11.40) (91 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 8.71 per 1000 PYs (95% CI: 3.98, 16.54) (9 events) for the tofacitinib and 9.36 per 1000 PYs (95% CI: 7.49, 11.56) (86 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 6.32 per 1000 PYs (95% CI: 3.03, 11.63) (10 events) for the tofacitinib, 6.98 per 1000 PYs (95% CI: 5.56, 8.65) (83 events) for the bDMARD and 4.61 per 1000 PYs (95% CI: 2.64, 7.49) (16 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 17.44 per 1000 PYs (95% CI: 9.29, 29.82) (13 events) for the tofacitinib, 14.09 per 1000 PYs (95% CI: 11.12, 17.61) (77 events) for the bDMARD and 7.41 per 1000 PYs (95% CI: 4.05, 12.43) (14 events) for the nbDMARD cohort.

- For the subgroup of patients without malignancy risk factors, the crude IR was 8.64 per 1000 PYs (95% CI: 3.17, 18.80) (6 events) for the tofacitinib, 7.17 per 1000 PYs (95% CI: 5.05, 9.88) (37 events) for the bDMARD and 4.02 per 1000 PYs (95% CI: 1.48, 8.75) (6 events) for the nbDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 10.41 per 1000 PYs (95% CI: 6.07, 16.67) (17 events) for the tofacitinib, 10.11 per 1000 PYs (95% CI: 8.41, 12.07) (123 events) for the bDMARD and 6.22 per 1000 PYs (95% CI: 3.98, 9.25) (24 events) for the nbDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 8.48 per 1000 PYs (95% CI: 5.11, 13.25) (19 events) for the tofacitinib, 8.19 per 1000 PYs (95% CI: 6.87, 9.96) (136 events) for the bDMARD and 4.85 per 1000 PYs (95% CI: 3.14, 7.16) (25 events) for the nbDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 10.12 per 1000 PYs (95% CI: 6.42, 15.19) (23 events) for the tofacitinib, 8.76 per 1000 PYs (95% CI: 7.24, 10.51) (116 events) for the bDMARD and 4.72 per 1000 PYs (95% CI: 2.92, 7.21) (21 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was no event in the tofacitinib cohort, but based on only 55 episodes. The crufe IR was 10.69 per 1000 PYs (95% CI: 7.76, 14.35) (44 events) for the bDMARD and 9.91 per 1000 PYs (95% CI: 4.53, 18.81) (9 events) for the nbDMARD cohort.

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18. Lymphoma (overall): There were 2 events in the tofacitinib and 6 events in the bDMARD cohort. The crude IR was 0.85 per 1000 PYs (95% CI: 0.10, 3.09) for the tofacitinib and 0.34 per 1000 PYs (95% CI: 0.13, 0.75) for the bDMARD cohort. No stratified analyses were done.

Non-Hodgkin lymphoma: There was one event in the tofacitinib cohort (crude IR 0.43; 95% CI: 0.01, 2.38) and no event in the bDMARD and nbDMARD cohort. No stratified analyses were done.

Hodgkin lymphoma: There was no event in the tofacitinib cohort, one event in the nbDMARD cohort (crude IR 0.19; 95% CI: 0.00, 1.03) and 4 events in the bDMARD cohort (0.23; 95% CI: 0.06, 0.59). No stratified analyses were done.

Chronic lymphatic leukemia: There was one event in the tofacitinib cohort (crude IR 0.43; 95% CI: 0.01, 2.38), 2 events in the bDMARD cohort (crude IR 0.11; 95% CI: 0.01, 0.41) and no event in the nbDMARD cohort. No stratified analyses were done

19. Lung cancer:

Overall: There were 6 events in the tofacitinib and 23 events in the bDMARD cohort. The crude IR was 2.57 per 1000 PYs (95% CI: 0.94, 5.58) for the tofacitinib and 1.31 per 1000 PYs (95% CI: 0.83, 1.97) for the bDMARD cohort. For females, the crude IR was 1.70 per 1000 PYs (95% CI: 0.35, 4.96) (3 events) in the tofacitinib and 0.55 per 1000 PYs (95% CI: 0.22, 1.13) (7 events) in the bDMARD cohort. For males, the crude IR was 5.26 per 1000 PYs (95% CI: 1.08, 15.36) (3 events) in the tofacitinib and 3.40 per 1000 PYs (95% CI: 1.94, 5.52) (16 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there was one event in the tofacitinib, there were 12 events in the bDMARD, and 5 events in the nbDMARD cohort. The crude IR was 1.30 per 1000 PYs (95% CI: 0.03, 7.24) for the tofacitinib, 1.31 per 1000 PYs (95% CI: 0.68, 2.29) for the bDMARD and 0.93 per 1000 PYs (95% CI: 0.30, 2.17) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 1.48 per 1000 PYs (95% CI: 0.04, 8.22) (one event) for the tofacitinib and 1.80 per 1000 PYs (95% CI: 0.72, 3.70) (7 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 4.49 per 1000 PYs (95% CI: 1.22, 11.49) (4 events) for the tofacitinib and 0.90 per 1000 PYs (95% CI: 0.24, 2.30) (4 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 2.69 per 1000 PYs (95% CI: 0.99. 5.86) (6 events) for the tofacitinib and 1.33 per 1000 PYs (95% CI: 0.82, 2.04) (21 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 1.60 per 1000 PYs (95% CI: 0.19, 5.79) (2 events) for the tofacitinib and 0.52 per 1000 PYs (95% CI: 0.14, 1.34) (4 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 3.67 per 1000 PYs (95% CI: 1.00, 9.39) (4 events) for the tofacitinib and 1.92 per 1000 PYs (95% CI: 1.16, 3.00) (19 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was

2.30 per 1000 PYs (95% CI: 0.48, 6.73) (3 events) for the tofacitinib and 0.49 per 1000 PYs (95% CI: 0.13, 1.24) (4 events) for the bDMARD cohort.

- For the subgroup of patients with age below 65 years, the crude IR was 1.89 per 1000 PYs (95% CI: 0.39, 5.52) (3 events) for the tofacitinib, 0.75 per 1000 PYs (95% CI: 0.34, 1.43) (9 events) for the bDMARD and 0.29 per 1000 PYs (95% CI: 0.01, 1.60) (one event) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 4.00 per 1000 PYs (95% CI: 0.83, 11.69) (3 events) for the tofacitinib, 2.54 per 1000 PYs (95% CI: 1.39, 4.25) (14 events) for the bDMARD and 2.11 per 1000 PYs (95% CI: 0.57, 5.39) (4 events) for the nbDMARD cohort.

- For the subgroup of patients without malignancy risk factors, the crude IR was 1.43 per 1000 PYs (95% CI: 0.04, 7.96) (one event) for the tofacitinib, 0.19 per 1000 PYs (95% CI: 0.00, 1.07) (one event) for the bDMARD cohort, while there were no events for the nbDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 3.05 per 1000 PYs (95% CI: 0.99, 7.12) (5 events) for the tofacitinib, 1.79 per 1000 PYs (95% CI: 1.12, 2.71) (22 events) for the bDMARD and 1.29 per 1000 PYs (95% CI: 0.42, 3.01) (5 events) for the nbDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 2.22 per 1000 PYs (95% CI: 0.72, 5.19) (5 events) for the tofacitinib, 1.20 per 1000 PYs (95% CI: 0.73, 1.85) (20 events) for the bDMARD and 0.96 per 1000 PYs (95% CI: 0.31, 2.25) (5 events) for the nbDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 2.63 per 1000 PYs (95% CI: 0.96, 5.72) (6 events) for the tofacitinib, 1.20 per 1000 PYs (95% CI: 0.68, 1.95) (16 events) for the bDMARD and 0.45 per 1000 PYs (95% CI: 0.05, 1.61) (2 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was no event in the tofacitinib cohort, but based on only 55 episodes. The crufe IR was 1.69 per 1000 PYs (95% CI: 0.68, 3.48) (7 events) for the bDMARD and 3.29 per 1000 PYs (95% CI: 0.68, 9.60) (3 events) for the nbDMARD cohort.

20. All-cause Mortality:

Overall: There were 15 events in the tofacitinib and 102 events in the bDMARD cohort. The crude IR was 6.41 per 1000 PYs (95% CI: 3.59, 10.57) for the tofacitinib and 5.83 per 1000 PYs (95% CI: 4.75, 7.07) for the bDMARD cohort. For females, the crude IR was 6.78 per 1000 PYs (95% CI: 3.50, 11.85) (12 events) in the tofacitinib and 4.37 per 1000 PYs (95% CI: 3.30, 5.68) (56 events) in the bDMARD cohort. For males, the crude IR was 5.24 per 1000 PYs (95% CI: 1.08, 15.32) (3 events) in the tofacitinib and 9.77 per 1000 PYs (95% CI: 7.16, 13.04) (46 events) in the bDMARD cohort.

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Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 5 events in the tofacitinib, 56 events in the bDMARD, and 15 events in the nbDMARD cohort. The crude IR was 6.50 per 1000 PYs (95% CI: 2.11, 15.16) for the tofacitinib, 6.12 per 1000 PYs (95% CI: 4.62, 7.95) for the bDMARD and 2.78 per 1000 PYs (95% CI: 1.56, 4.59) for the nbDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 2.95 per 1000 PYs (95% CI: 0.36, 10.65) (2 events) for the tofacitinib and 5.90 per 1000 PYs (95% CI: 3.74, 8.85) (23 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 8.96 per 1000 PYs (95% CI: 3.87, 17.65) (8 events) for the tofacitinib and 5.16 per 1000 PYs (95% CI: 3.27, 7.74) (23 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 6.27 per 1000 PYs (95% CI: 3.43, 10.52) (14 events) for the tofacitinib and 6.02 per 1000 PYs (95% CI: 4.87, 7.36) (95 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 6.41 per 1000 PYs (95% CI: 2.77, 12.62) (8 events) for the tofacitinib and 6.82 per 1000 PYs (95% CI: 5.09, 8.95) (52 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 6.41 per 1000 PYs (95% CI: 2.58, 13.20) (7 events) for the tofacitinib and 5.06 per 1000 PYs (95% CI: 3.75, 6.67) (50 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 6.74 per 1000 PYs (95% CI: 2.71, 13.90) (7 events) for the tofacitinib and 5.18 per 1000 PYs (95% CI: 3.82, 6.87) (48 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 1.89 per 1000 PYs (95% CI: 0.39, 5.51) (3 events) for the tofacitinib, 1.75 per 1000 PYs (95% CI: 1.08, 2.68) (21 events) for the bDMARD and 0.29 per 1000 PYs (95% CI: 0.01, 1.60) (1 event) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 15.97 per 1000 PYs (95% CI: 8.25, 27.90) (12 events) for the tofacitinib, 14.67 per 1000 PYs (95% CI: 11.65, 18.23) (81 events) for the bDMARD and 7.35 per 1000 PYs (95% CI: 4.02, 12.34) (14 events) for the nbDMARD cohort.

21. Leukaemia (excl. B-CLL): There was no event in the tofacitinib cohort, no event in the nbDMARD cohort and only 3 events in the bDMARD cohort (crude IR 0.17; 95% CI: 0.04, 0.50). No stratified analyses were done.

22. Other haematopietic neoplasms (malignant and benign): There was no event in the tofacitinib cohort, one event in the nbDMARD cohort (crude IR 0.19; 95% CI: 0.00, 1.03) and only 3 events in the bDMARD cohort (crude IR 0.17; 95% CI: 0.04, 0.50). No stratified analyses were done.

23. Solid malignancies:

Overall: There were 20 events in the tofacitinib and 131 events in the bDMARD cohort. The crude IR was 8.59 per 1000 PYs (95% CI: 5.25, 13.26) for the tofacitinib and 7.54 per 1000 PYs (95% CI: 6.30, 8.94) for the bDMARD cohort. For females, the crude IR was 7.39 per 1000 PYs (95% CI: 3.93, 12.63) (13 events) in the tofacitinib and 6.21 per 1000 PYs (95% CI: 4.92, 7.74) (79 events) in the bDMARD cohort. For males, the crude IR was 12.30 per

1000 PYs (95% CI: 4.95, 25.34) (7 events) in the tofacitinib and 11.14 per 1000 PYs (95% CI: 8.32, 14.60) (52 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 14.

- For the subgroup without prior b/tsDMARDs, there were 6 events in the tofacitinib, 66 events in the bDMARD, and 29 events in the nbDMARD cohort. The crude IR was 7.86 per 1000 PYs (95% CI: 2.88, 17.10) for the tofacitinib, 7.26 per 1000 PYs (95% CI: 5.61, 9.23) for the bDMARD and 5.41 per 1000 PYs (95% CI: 3.62, 7.77) for the nbDMARD cohort.
- For the subgroup with one prior b/tsDMARDs, the crude IR was 7.41 per 1000 PYs (95% CI: 2.41, 17.29) (5 events) for the tofacitinib and 8.28 per 1000 PYs (95% CI: 5.66, 11.69) (32 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 10.11 per 1000 PYs (95% CI:4.62, 19.20) (9 events) for the tofacitinib and 7.46 per 1000 PYs (95% CI: 5.13, 10.47) (33 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 7.65 per 1000 PYs (95% CI: 4.46, 12.25) (17 events) for the tofacitinib and 7.34 per 1000 PYs (95% CI: 6.06, 8.81) (115 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 9.68 per 1000 PYs (95% CI: 5.00, 16.91) (12 events) for the tofacitinib and 7.26 per 1000 PYs (95% CI: 5.47, 9.46) (55 events) for the bDMARD cohort. For the subgroup combination therapy with a nbDMARD, the crude IR was 7.35 per 1000 PYs (95% CI: 3.17, 14.47) (8 events) for the tofacitinib and 7.74 per 1000 PYs (95% CI: 6.10, 9.69) (76 events) for the bDMARD cohort. For the subgroup combination therapy with MTX, the crude IR was 10.05 per 1000 PYs (95% CI: 5.35, 17.18) (13 events) for the tofacitinib and 7.21 per 1000 PYs (95% CI: 5.49, 9.30) (59 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 6.32 per 1000 PYs (95% CI: 3.03, 11.63) (10 events) for the tofacitinib, 5.96 per 1000 PYs (95% CI: 4.66, 7.52) (71 events) for the bDMARD and 4.33 per 1000 PYs (95% CI: 2.42, 7.13) (15 events) for the nbDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 13.39 per 1000 PYs (95% CI: 6.42, 24.62) (10 events) for the tofacitinib, 10.96 per 1000 PYs (95% CI: 8.36, 14.11) (60 events) for the bDMARD and 7.40 per 1000 PYs (95% CI: 4.05, 12.42) (14 events) for the nbDMARD cohort.

- For the subgroup of patients without malignancy risk factors, the crude IR was 8.64 per 1000 PYs (95% CI: 3.17, 18.80) (6 events) for the tofacitinib, 5.99 per 1000 PYs (95% CI: 4.07, 8.51) (31 events) for the bDMARD and 4.02 per 1000 PYs (95% CI: 1.47, 8.74) (6 events) for the nbDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 8.57 per 1000 PYs (95% CI: 4.68, 14.37) (14 events) for the tofacitinib, 8.21 per 1000 PYs (95% CI: 6.68, 9.99) (100 events) for the bDMARD and 5.96 per 1000 PYs (95% CI: 3.78, 8.94) (23 events) for the nbDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 7.59 per 1000 PYs (95% CI: 4.42, 12.15) (17 events) for the tofacitinib, 6.92 per 1000 PYs (95% CI: 5.71, 8.31) (115 events) for the bDMARD and 4.65 per 1000 PYs (95% CI: 2.98, 6.93) (24 events) for the nbDMARD cohort.

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- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 8.80 per 1000 PYs (95% CI: 5.37, 13.59) (20 events) for the tofacitinib, 7.16 per 1000 PYs (95% CI: 5.80, 8.76) (95 events) for the bDMARD and 4.49 per 1000 PYs (95% CI: 2.75, 6.94) (20 events) for the nbDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was no event in the tofacitinib cohort, but based on only 55 episodes. The crufe IR was 8.73 per 1000 PYs (95% CI: 6.11, 12.09) (36 events) for the bDMARD and 9.91 per 1000 PYs (95% CI: 4.53, 18.81) (9 events) for the nbDMARD cohort.

24. Glioblastoma: There were no events.

25. Benign neoplasms: There were 10 events in the tofacitinib and 55 events in the bDMARD cohort. The crude IR was 4.29 per 1000 PYs (95% CI: 2.06, 7.89) for the tofacitinib and 3.16 per 1000 PYs (95% CI: 2.38, 4.11) for the bDMARD cohort.

26. Unspecified neoplasms and precanceroses: There was no event in the tofacitinib and there were 19 events in the bDMARD cohort. The crude IR was 1.09 per 1000 PYs (95% CI: 0.65, 1.70) for the bDMARD cohort. No stratified analyses were done.

27. Metastases, cancer related and morbidities and associated syndromes: There was no event in the tofacitinib cohort, 3 events in the nbDMARD cohort (crude IR 0.56; 95% CI: 0.11, 1.63) and 6 events in the bDMARD cohort (crude IR 0.34; 95% CI: 0.13, 0.75). No stratified analyses were done.

28. Interstitial lung disease: There were 3 events in the tofacitinib cohort and 45 events in the bDMARD cohort. The crude IR was 1.28 per 1000 PYs (95% CI: 0.26, 3.75) for the tofacitinib and 2.58 per 1000 PYs (95% CI: 1.88, 3.45) for the bDMARD cohort. For the subgroup without prior b/tsDMARDs, there was 1 event in the tofacitinib and there were 26 events in the bDMARD and 7 events in the nbDMARD cohort. The crude IR was 1.30 per 1000 PYs (95% CI: 0.03, 7.25) for the tofacitinib, 2.85 per 1000 PYs (95% CI: 1.86, 4.17) for the bDMARD and 1.30 per 1000 PYs (95% CI: 0.52, 2.68) for the nbDMARD cohort.

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
1. Serious infections (excluding TB)												
Tofacitinib	55	2288.71	36	1735.55	19	553.16	24.03	18.10	31.28	24.03	18.10	31.28
bDMARD	361	17043.12	237	12487.21	124	4555.91	21.18	19.05	23.48	21.18	19.04	23.48
Pneumonia												
Tofacitinib	17	2324.33	9	1761.28	8	563.05	7.31	4.26	11.71	7.36	4.29	11.79
bDMARD	87	17407.55	56	12731.54	31	4676.01	5.00	4.00	6.16	5.06	4.05	6.24
Other infections of the respiratory system												
Tofacitinib	1	2341.21	1	1769.01	0	572.19	0.43	0.01	2.38	0.43	0.01	2.39
bDMARD	38	17454.03	26	12768.22	12	4685.81	2.18	1.54	2.99	2.19	1.55	3.01
Infections of the CNS												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.58
bDMARD	7	17500.90	5	12795.67	2	4705.23	0.40	0.16	0.82	0.40	0.16	0.83
Sepsis												
Tofacitinib	9	2332.13	5	1766.60	4	565.53	3.86	1.76	7.33	3.91	1.79	7.42
bDMARD	50	17468.35	34	12771.84	16	4696.52	2.86	2.12	3.77	2.91	2.16	3.83
Bone or joint infections												
Tofacitinib	1	2341.04	1	1768.84	0	572.19	0.43	0.01	2.38	0.43	0.01	2.41
bDMARD	14	17495.21	8	12793.72	6	4701.50	0.80	0.44	1.34	0.81	0.44	1.36
Opportunistic infections												
Tofacitinib	3	2340.66	2	1768.72	1	571.95	1.28	0.26	3.75	1.29	0.27	3.76

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years		LCL	UCL		LCL	UCL
bDMARD	8	17500.82	5	12797.87	3	4702.95	0.46	0.20	0.90	0.46	0.20	0.92
Other infections												
Tofacitinib	26	2313.95	19	1746.76	7	567.19	11.24	7.34	16.46	11.36	7.42	16.65
bDMARD	187	17251.04	119	12634.78	68	4616.26	10.84	9.34	12.51	10.96	9.45	12.65
2. TB												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.79
bDMARD	1	17506.33	0	12800.59	1	4705.75	0.06	0.00	0.32	0.06	0.00	0.31
3. HZ												
Tofacitinib	49	2258.75	40	1694.16	9	564.58	21.69	16.05	28.68	21.35	15.79	28.22
bDMARD	143	17267.16	129	12580.71	14	4686.45	8.28	6.98	9.76	8.30	6.99	9.77
4. Fractures												
Tofacitinib	48	2260.70	43	1690.79	5	569.91	21.23	15.66	28.15	21.18	15.62	28.09
bDMARD	306	16979.65	252	12385.64	54	4594.01	18.02	16.06	20.16	18.11	16.14	20.26
5. Cardiac disorders (overall)												
Tofacitinib	41	2290.53	26	1732.62	15	557.91	17.90	12.85	24.28	18.14	13.01	24.61
bDMARD	232	17196.91	139	12619.77	93	4577.14	13.49	11.81	15.34	13.66	11.96	15.54
Heart failure												
Tofacitinib	10	2335.72	7	1763.96	3	571.76	4.28	2.05	7.87	4.32	2.07	7.94
bDMARD	60	17454.19	45	12761.62	15	4692.57	3.44	2.62	4.42	3.50	2.67	4.51
Coronary artery dis-ease												
Tofacitinib	7	2333.72	5	1761.95	2	571.77	3.00	1.21	6.18	3.04	1.22	6.27
bDMARD	63	17420.37	36	12754.22	27	4666.15	3.62	2.78	4.63	3.65	2.81	4.68

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
Myocardial infarction												
Tofacitinib	11	2329.56	7	1762.08	4	567.48	4.72	2.36	8.45	4.89	2.44	8.75
bDMARD	47	17435.85	23	12762.41	24	4673.44	2.70	1.98	3.58	2.69	1.98	3.58
MACE												
Tofacitinib	20	2324.69	10	1761.82	10	562.87	8.60	5.26	13.29	8.83	5.39	13.64
bDMARD	91	17392.01	50	12731.31	41	4660.69	5.23	4.21	6.42	5.28	4.25	6.48
Other cardiac disorders												
Tofacitinib	21	2310.63	14	1747.40	7	563.23	9.09	5.63	13.89	9.18	5.68	14.04
bDMARD	117	17341.08	70	12694.31	47	4646.76	6.75	5.58	8.09	6.85	5.67	8.21
6. Hematologic disorders (overall)												
Tofacitinib	7	2333.87	6	1762.94	1	570.93	3.00	1.21	6.18	3.00	1.21	6.18
bDMARD	48	17464.20	36	12767.79	12	4696.41	2.75	2.03	3.64	2.78	2.05	3.69
Bone marrow depression and hypoplastic anaemia												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.58
bDMARD	7	17505.38	6	12798.90	1	4706.48	0.40	0.16	0.82	0.40	0.16	0.83
Decreased white blood cells												
Tofacitinib	1	2341.08	1	1768.89	0	572.19	0.43	0.01	2.38	0.41	0.01	2.31
bDMARD	8	17497.19	7	12791.13	1	4706.07	0.46	0.20	0.90	0.46	0.20	0.91
Platelet disorders												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.54

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
bDMARD	4	17505.30	3	12799.34	1	4705.96	0.23	0.06	0.59	0.23	0.06	0.59
Other blood dyscrasia												
Tofacitinib	6	2334.12	5	1763.19	1	570.93	2.57	0.94	5.60	2.59	0.95	5.64
bDMARD	31	17477.20	21	12779.93	10	4697.27	1.77	1.21	2.52	1.80	1.22	2.55
7. Disorders of the nervous system (excluding infections) (overall)												
Tofacitinib	36	2301.15	25	1745.10	11	556.05	15.64	10.96	21.66	15.69	10.99	21.72
bDMARD	235	17149.13	170	12545.93	65	4603.19	13.70	12.01	15.57	13.81	12.10	15.69
Stroke												
Tofacitinib	14	2324.91	8	1762.78	6	562.12	6.02	3.29	10.10	6.10	3.33	10.23
bDMARD	64	17422.14	39	12747.71	25	4674.43	3.67	2.83	4.69	3.72	2.86	4.75
Central demyelination												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.50
bDMARD	1	17506.88	1	12800.18	0	4706.71	0.06	0.00	0.32	0.06	0.00	0.32
Other disorders of the CNS												
Tofacitinib	16	2328.11	13	1757.39	3	570.72	6.87	3.93	11.16	6.88	3.93	11.18
bDMARD	105	17342.13	77	12677.96	28	4664.18	6.05	4.95	7.33	6.09	4.98	7.37
Disorders of the peripheral nervous system												
Tofacitinib	5	2335.66	3	1767.07	2	568.59	2.14	0.70	5.00	2.12	0.69	4.95

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
bDMARD	45	17437.54	37	12747.80	8	4689.74	2.58	1.88	3.45	2.61	1.91	3.50
Psychiatric disorders												
Tofacitinib	5	2334.78	4	1763.64	1	571.14	2.14	0.70	5.00	2.15	0.70	5.01
bDMARD	49	17427.73	36	12744.39	13	4683.35	2.81	2.08	3.72	2.81	2.08	3.71
8. PML												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.50
bDMARD	1	17506.88	1	12800.18	0	4706.71	0.06	0.00	0.32	0.06	0.00	0.32
9. Allergic conditions and hypersensitivity												
Tofacitinib	3	2340.58	3	1768.39	0	572.19	1.28	0.26	3.75	1.28	0.26	3.73
bDMARD	23	17474.57	18	12772.44	5	4702.13	1.32	0.83	1.97	1.32	0.84	1.98
10. Hepatic failure												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.62
bDMARD	7	17497.54	2	12795.84	5	4701.70	0.40	0.16	0.82	0.40	0.16	0.82
11.GI perforations (overall)												
Tofacitinib	5	2340.53	3	1768.56	2	571.96	2.14	0.69	4.99	2.17	0.70	5.05
bDMARD	44	17441.75	32	12752.07	12	4689.68	2.52	1.83	3.39	2.54	1.84	3.41
Lower intestinal perforations												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.61
bDMARD	13	17495.06	10	12789.10	3	4705.96	0.74	0.40	1.27	0.75	0.40	1.28

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
Other GI perforations												
Tofacitinib	5	2340.53	3	1768.56	2	571.96	2.14	0.69	4.99	2.15	0.70	5.01
bDMARD	37	17451.04	30	12752.56	7	4698.48	2.12	1.49	2.92	2.14	1.50	2.95
13. Embolic / thrombotic events, venous / vessel type unspecified (overall)												
Tofacitinib	7	2337.83	5	1765.90	2	571.93	2.99	1.20	6.17	3.01	1.21	6.20
bDMARD	41	17450.20	28	12753.84	13	4696.36	2.35	1.69	3.19	2.38	1.71	3.23
VTE												
Tofacitinib	6	2338.90	4	1766.97	2	571.93	2.57	0.94	5.58	2.58	0.95	5.61
bDMARD	41	17450.20	28	12753.84	13	4696.36	2.35	1.69	3.19	2.38	1.71	3.23
DVT												
Tofacitinib	2	2340.85	1	1768.86	1	571.99	0.85	0.10	3.09	0.86	0.10	3.10
bDMARD	18	17479.19	12	12779.33	6	4699.86	1.03	0.61	1.63	1.04	0.62	1.64
PE												
Tofacitinib	6	2338.90	4	1766.97	2	571.93	2.57	0.94	5.58	2.59	0.95	5.64
bDMARD	31	17463.67	20	12766.51	11	4697.15	1.78	1.21	2.52	1.81	1.23	2.56
14. Operations and hospitalizations (overall)												
Tofacitinib	34	2293.48	29	1724.72	5	568.76	14.82	10.27	20.72	14.79	10.24	14.79
bDMARD	235	17134.34	172	12528.35	63	4605.99	13.72	12.02	15.59	13.78	12.07	13.78
Bone and joint surgery and other joint												

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
therapeutic procedures												
Tofacitinib	25	2312.30	22	1742.67	3	569.63	10.81	7.00	15.96	10.80	6.99	15.94
bDMARD	196	17180.38	143	12561.70	53	4618.68	11.41	9.87	13.12	11.45	9.90	13.17
Other operations and therapeutic procedures that lead to hospitalization												
Tofacitinib	9	2322.51	7	1751.19	2	571.32	3.88	1.77	7.36	3.86	1.76	7.32
bDMARD	44	17448.36	31	12762.08	13	4686.28	2.52	1.83	3.39	2.55	1.85	3.42
15. Other serious diagnoses, symptoms and syndromes												
Tofacitinib	166	2104.17	131	1573.39	35	530.78	78.89	67.35	91.85	78.89	67.35	91.85
bDMARD	1134	15664.28	835	11462.35	299	4201.93	72.39	68.24	76.73	72.55	68.38	76.90
16. NMSC												
Tofacitinib	12	2324.79	9	1755.10	3	569.69	5.16	2.67	9.02	5.19	2.68	9.06
bDMARD	41	17438.22	26	12758.28	15	4679.94	2.35	1.69	3.19	2.39	1.71	3.24
17. Malignancies (overall, excluding NMSC)												
Tofacitinib	23	2327.22	16	1758.16	7	569.06	9.88	6.26	14.83	9.95	6.30	14.93
bDMARD	160	17356.00	101	12691.32	59	4664.68	9.22	7.85	10.76	9.30	7.92	10.86
18. Lymphoma (overall)												
Tofacitinib	2	2340.07	2	1767.87	0	572.19	0.85	0.10	3.09	0.90	0.11	3.26

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years		LCL	UCL		LCL	UCL
bDMARD	6	17497.28	2	12795.22	4	4702.06	0.34	0.13	0.75	0.34	0.13	0.75
Non-Hodgkin lymphoma												
Tofacitinib	1	2341.33	1	1769.14	0	572.19	0.43	0.01	2.38	0.43	0.01	2.39
bDMARD	0	17507.29	0	12800.59	0	4706.71	0.00	0.00	0.21	0.00	0.00	0.21
Hodgkin lymphoma												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.68
bDMARD	4	17498.55	1	12796.18	3	4702.37	0.23	0.06	0.59	0.23	0.06	0.58
Chronic lymphatic leukemia												
Tofacitinib	1	2340.07	1	1767.87	0	572.19	0.43	0.01	2.38	0.45	0.01	2.49
bDMARD	2	17506.03	1	12799.63	1	4706.39	0.11	0.01	0.41	0.11	0.01	0.41
19. Lung Cancer												
Tofacitinib	6	2338.51	3	1767.78	3	570.73	2.57	0.94	5.58	2.63	0.97	5.73
bDMARD	23	17503.09	7	12798.29	16	4704.80	1.31	0.83	1.97	1.34	0.85	2.01
20. All-cause Mortality												
Tofacitinib	15	2341.33	12	1769.14	3	572.19	6.41	3.59	10.57	6.50	3.63	10.71
bDMARD	102	17507.14	56	12800.59	46	4706.55	5.83	4.75	7.07	5.96	4.86	7.23
21. Leukaemia (excl. B-CLL)												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.59
bDMARD	3	17505.54	2	12800.33	1	4705.22	0.17	0.04	0.50	0.18	0.04	0.52

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
22. Other haematopietic neoplasms (malignant and benign)												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.63
bDMARD	3	17505.29	3	12798.58	0	4706.71	0.17	0.04	0.50	0.17	0.04	0.50
23. Solid malignancies (overall)												
Tofacitinib	20	2328.73	13	1759.68	7	569.06	8.59	5.25	13.26	8.63	5.27	13.33
bDMARD	131	17383.96	79	12714.13	52	4669.83	7.54	6.30	8.94	7.61	6.36	9.03
24. Glioblastoma												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	NA	NA	NA
bDMARD	0	17507.29	0	12800.59	0	4706.71	0.00	0.00	0.21	NA	NA	NA
25. Benign neoplasms												
Tofacitinib	10	2330.15	6	1763.85	4	566.30	4.29	2.06	7.89	4.25	2.03	7.81
bDMARD	55	17417.24	46	12722.54	9	4694.70	3.16	2.38	4.11	3.19	2.40	4.15
26. Unspecified neoplasms and precanceroses												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.57
bDMARD	19	17492.00	15	12785.90	4	4706.10	1.09	0.65	1.70	1.10	0.66	1.72
27. Metastases, cancer related and morbidities and associated syndromes												
Tofacitinib	0	2341.33	0	1769.14	0	572.19	0.00	0.00	1.58	0.00	0.00	1.59

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Table 13. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Total Crude IR per 1000 PYs	Total Crude 95% CI		Total Std. IR per 1000 PYs	Total Std. IR 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
bDMARD	6	17505.20	4	12798.86	2	4706.33	0.34	0.13	0.75	0.35	0.13	0.76
28. Interstitial lung disease												
Tofacitinib	3	2338.90	0	1769.14	3	569.77	1.28	0.26	3.75	1.31	0.27	3.83
bDMARD	45	17453.79	29	12766.07	16	4687.72	2.58	1.88	3.45	2.59	1.89	3.47

Standardized IRs were calculated based on direct standardization if there were at least five events in each of the standardization groups (women <65 years, men <65 years, women ≥ 65 years, men ≥ 65 years), and based on indirect standardization otherwise. For the subgroups Age <65 years and Age ≥65 years no standardized IRs could be calculated by definition. If within a considered subgroup, any of the standardization groups did not contain patients, no standardized IRs could be calculated. If no standardized IR was available for one of these reasons or if there were no events across all cohorts, NA is given instead of a standardized IR.
Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; CNS, central nervous system; DVT, deep vein thrombosis; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate; LCL, lower confidence limit; MACE, major cardiovascular events; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PML, progressive multifocal leukoencephalopathy; PY, patient year; std., standardized by age/sex; TB, tuberculosis; UCL: upper confidence limit; VTE, venous thromboembolism.

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
1. Serious infection (excluding TB)									
No previous b/tsDMARD	Tofacitinib	14	753.29	18.59	10.16	31.18	18.23	9.96	30.59
	bDMARD	158	8968.18	17.62	14.98	20.59	17.96	15.27	20.98
	nbDMARD	59	5310.65	11.11	8.46	14.33	10.80	8.22	13.93
One previous b/tsDMARD	Tofacitinib	16	660.55	24.22	13.85	39.34	26.27	15.00	42.66
	bDMARD	80	3784.98	21.14	16.76	26.31	20.85	16.53	25.95
At least 2 previous b/tsDMARD	Tofacitinib	25	874.87	28.58	18.49	42.18	28.74	18.59	42.43
	bDMARD	123	4289.96	28.67	23.83	34.21	28.64	23.80	34.17
No prior non-tofacitinib JAKi use	Tofacitinib	54	2182.08	24.75	18.59	32.29	24.75	18.59	32.29
	bDMARD	313	15382.01	20.35	18.16	22.73	20.35	18.16	22.74
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	106.62	9.38	0.24	52.26	10.03	0.25	55.89
	bDMARD	48	1661.11	28.90	21.31	38.31	28.78	21.22	38.15
Monotherapy	Tofacitinib	31	1217.39	25.46	17.30	36.14	25.41	17.26	36.07
	bDMARD	169	7392.18	22.86	19.55	26.58	22.87	19.55	26.59
Combination Therapy with a nbDMARD	Tofacitinib	24	1071.32	22.40	14.35	33.33	22.99	14.73	34.21
	bDMARD	192	9650.94	19.89	17.18	22.92	20.32	17.55	23.41
Combination Therapy with MTX	Tofacitinib	22	1017.58	21.62	13.55	32.73	22.39	14.02	33.90
	bDMARD	172	9055.50	18.99	16.26	22.05	19.15	16.39	22.23
Age <65 years	Tofacitinib	21	1566.22	13.41	8.30	20.50	NA	NA	NA
	bDMARD	154	11776.03	13.08	11.09	15.31	NA	NA	NA
	nbDMARD	26	3462.79	7.51	4.90	11.00	NA	NA	NA
Age ≥65 years	Tofacitinib	34	722.48	47.06	32.59	65.76	NA	NA	NA
	bDMARD	207	5267.09	39.30	34.13	45.03	NA	NA	NA
	nbDMARD	33	1847.86	17.86	12.29	25.08	NA	NA	NA
Pneumonia									
No previous b/tsDMARD	Tofacitinib	6	766.58	7.83	2.87	17.04	7.73	2.84	16.82
	bDMARD	46	9100.53	5.05	3.70	6.74	5.15	3.77	6.87
	nbDMARD	19	5367.74	3.54	2.13	5.53	3.44	2.07	5.37
One previous b/tsDMARD	Tofacitinib	6	668.30	8.98	3.29	19.54	9.76	3.58	21.24
	bDMARD	15	3876.21	3.87	2.17	6.38	3.82	2.13	6.30

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least 2 previous b/tsDMARD	Tofacitinib	5	889.45	5.62	1.83	13.12	5.35	1.74	12.48
	bDMARD	26	4430.81	5.87	3.83	8.60	5.93	3.87	8.69
No prior non-tofacitinib JAKi use	Tofacitinib	17	2216.07	7.67	4.47	12.28	7.72	4.49	12.36
	bDMARD	77	15688.42	4.91	3.87	6.13	4.96	3.92	6.20
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	36.04
	bDMARD	10	1719.12	5.82	2.79	10.70	5.80	2.78	10.66
Monotherapy	Tofacitinib	7	1241.43	5.64	2.27	11.62	5.60	2.25	11.55
	bDMARD	32	7576.39	4.22	2.89	5.96	4.23	2.89	5.97
Combination Therapy with a nbDMARD	Tofacitinib	10	1082.90	9.23	4.43	16.98	9.45	4.52	17.37
	bDMARD	55	9831.15	5.59	4.21	7.28	5.72	4.31	7.45
Combination Therapy with MTX	Tofacitinib	9	1028.37	8.75	4.00	16.61	9.02	4.12	17.11
	bDMARD	50	9218.88	5.42	4.03	7.15	5.47	4.06	7.21
Age <65 years	Tofacitinib	7	1581.19	4.43	1.78	9.12	NA	NA	NA
	bDMARD	39	11947.88	3.26	2.32	4.46	NA	NA	NA
	nbDMARD	6	3473.02	1.73	0.63	3.76	NA	NA	NA
Age ≥65 years	Tofacitinib	10	743.14	13.46	6.45	24.75	NA	NA	NA
	bDMARD	48	5459.67	8.79	6.48	11.66	NA	NA	NA
	nbDMARD	13	1881.65	6.91	3.68	11.81	NA	NA	NA
Other infections of the respiratory system									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.79
	bDMARD	15	9128.21	1.64	0.92	2.71	1.66	0.93	2.73
	nbDMARD	6	5385.54	1.11	0.41	2.42	1.10	0.40	2.39
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.83
	bDMARD	6	3890.95	1.54	0.57	3.36	1.52	0.56	3.32
At least 2 previous b/tsDMARD	Tofacitinib	1	892.85	1.12	0.03	6.24	1.12	0.03	6.26
	bDMARD	17	4434.88	3.83	2.23	6.14	3.83	2.23	6.13
No prior non-tofacitinib JAKi use	Tofacitinib	1	2232.94	0.45	0.01	2.50	0.45	0.01	2.50
	bDMARD	33	15719.64	2.10	1.45	2.95	2.11	1.45	2.97
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	38.11

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	5	1734.39	2.88	0.94	6.73	2.86	0.93	6.68
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.95
	bDMARD	19	7595.08	2.50	1.51	3.91	2.50	1.51	3.91
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.50	0.92	0.02	5.10	0.94	0.02	5.22
	bDMARD	19	9858.96	1.93	1.16	3.01	1.93	1.16	3.02
Combination Therapy with MTX	Tofacitinib	1	1037.69	0.96	0.02	5.37	0.97	0.02	5.41
	bDMARD	17	9243.44	1.84	1.07	2.94	1.84	1.07	2.94
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	22	11956.49	1.84	1.15	2.79	NA	NA	NA
	nbDMARD	2	3487.52	0.57	0.07	2.07	NA	NA	NA
Age ≥65 years	Tofacitinib	1	751.21	1.33	0.03	7.42	NA	NA	NA
	bDMARD	16	5497.55	2.91	1.66	4.73	NA	NA	NA
	nbDMARD	4	1898.02	2.11	0.57	5.40	NA	NA	NA
Infections of the central nervous system (CNS)									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.54
	bDMARD	3	9147.11	0.33	0.07	0.96	0.34	0.07	1.00
	nbDMARD	1	5392.94	0.19	0.00	1.03	0.18	0.00	0.98
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.37
	bDMARD	1	3898.15	0.26	0.01	1.43	0.26	0.01	1.43
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.06
	bDMARD	3	4455.64	0.67	0.14	1.97	0.68	0.14	1.97
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.65
	bDMARD	6	15764.47	0.38	0.14	0.83	0.38	0.14	0.83
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	33.57
	bDMARD	1	1736.43	0.58	0.01	3.21	0.58	0.01	3.21
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.94
	bDMARD	4	7618.25	0.53	0.14	1.34	0.53	0.14	1.35
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.29
	bDMARD	3	9882.64	0.30	0.06	0.89	0.31	0.06	0.92

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.55
	bDMARD	3	9266.21	0.32	0.07	0.95	0.33	0.07	0.97
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	3	11982.31	0.25	0.05	0.73	NA	NA	NA
	nbDMARD	1	3489.18	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	4	5518.59	0.72	0.20	1.86	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
Sepsis									
No previous b/tsDMARD	Tofacitinib	1	769.71	1.30	0.03	7.24	1.23	0.03	6.86
	bDMARD	23	9136.07	2.52	1.60	3.78	2.60	1.65	3.90
	nbDMARD	5	5388.02	0.93	0.30	2.17	0.89	0.29	2.07
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.15
	bDMARD	11	3885.92	2.83	1.41	5.06	2.77	1.38	4.96
At least 2 previous b/tsDMARD	Tofacitinib	8	883.84	9.05	3.91	17.83	9.00	3.89	17.74
	bDMARD	16	4446.36	3.60	2.06	5.84	3.60	2.06	5.85
No prior non-tofacitinib JAKi use	Tofacitinib	8	2225.50	3.59	1.55	7.08	3.63	1.57	7.16
	bDMARD	47	15734.05	2.99	2.19	3.97	3.04	2.23	4.04
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	106.62	9.38	0.24	52.26	9.12	0.23	50.80
	bDMARD	3	1734.30	1.73	0.36	5.06	1.73	0.36	5.06
Monotherapy	Tofacitinib	5	1241.84	4.03	1.31	9.40	4.05	1.31	9.45
	bDMARD	28	7605.27	3.68	2.45	5.32	3.68	2.44	5.32
Combination Therapy with a nbDMARD	Tofacitinib	4	1090.29	3.67	1.00	9.39	3.80	1.04	9.73
	bDMARD	22	9863.08	2.23	1.40	3.38	2.31	1.45	3.50
Combination Therapy with MTX	Tofacitinib	4	1035.48	3.86	1.05	9.89	4.02	1.09	10.28
	bDMARD	20	9249.09	2.16	1.32	3.34	2.18	1.33	3.37
Age <65 years	Tofacitinib	2	1589.86	1.26	0.15	4.54	NA	NA	NA
	bDMARD	16	11970.39	1.34	0.76	2.17	NA	NA	NA
	nbDMARD	1	3489.18	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	7	742.27	9.43	3.79	19.43	NA	NA	NA
	bDMARD	34	5497.96	6.18	4.28	8.64	NA	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	4	1898.84	2.11	0.57	5.39	NA	NA	NA
Bone or joint infections									
No previous b/tsDMARD	Tofacitinib	1	769.49	1.30	0.03	7.24	1.31	0.03	7.30
	bDMARD	5	9148.66	0.55	0.18	1.28	0.56	0.18	1.30
	nbDMARD	3	5388.63	0.56	0.11	1.63	0.54	0.11	1.58
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.72
	bDMARD	5	3892.59	1.28	0.42	3.00	1.27	0.41	2.97
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.95
	bDMARD	4	4453.97	0.90	0.24	2.30	0.87	0.24	2.23
No prior non-tofacitinib JAKi use	Tofacitinib	1	2232.77	0.45	0.01	2.50	0.45	0.01	2.49
	bDMARD	11	15761.87	0.70	0.35	1.25	0.71	0.35	1.27
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	49.22
	bDMARD	3	1733.35	1.73	0.36	5.06	1.70	0.35	4.96
Monotherapy	Tofacitinib	1	1248.41	0.80	0.02	4.46	0.80	0.02	4.45
	bDMARD	7	7616.63	0.92	0.37	1.89	0.92	0.37	1.89
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.41
	bDMARD	7	9878.59	0.71	0.28	1.46	0.72	0.29	1.48
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.70
	bDMARD	7	9262.15	0.76	0.30	1.56	0.76	0.31	1.58
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	6	11982.06	0.50	0.18	1.09	NA	NA	NA
	nbDMARD	2	3486.25	0.57	0.07	2.07	NA	NA	NA
Age ≥65 years	Tofacitinib	1	751.04	1.33	0.03	7.42	NA	NA	NA
	bDMARD	8	5513.16	1.45	0.63	2.86	NA	NA	NA
	nbDMARD	1	1902.38	0.53	0.01	2.93	NA	NA	NA
Opportunistic infections									

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.51
	bDMARD	3	9146.61	0.33	0.07	0.96	0.33	0.07	0.98
	nbDMARD	3	5392.48	0.56	0.11	1.63	0.54	0.11	1.59
One previous b/tsDMARD	Tofacitinib	1	678.33	1.47	0.04	8.21	1.59	0.04	8.85
	bDMARD	2	3896.21	0.51	0.06	1.85	0.51	0.06	1.83
At least 2 previous b/tsDMARD	Tofacitinib	2	892.55	2.24	0.27	8.09	2.22	0.27	8.02
	bDMARD	3	4457.99	0.67	0.14	1.97	0.67	0.14	1.97
No prior non-tofacitinib JAKi use	Tofacitinib	3	2232.39	1.34	0.28	3.93	1.35	0.28	3.94
	bDMARD	7	15765.32	0.44	0.18	0.91	0.45	0.18	0.93
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	86.50
	bDMARD	1	1735.50	0.58	0.01	3.21	0.56	0.01	3.09
Monotherapy	Tofacitinib	2	1248.28	1.60	0.19	5.79	1.59	0.19	5.74
	bDMARD	2	7619.93	0.26	0.03	0.95	0.26	0.03	0.95
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.38	0.92	0.02	5.10	0.94	0.02	5.22
	bDMARD	6	9880.88	0.61	0.22	1.32	0.64	0.23	1.39
Combination Therapy with MTX	Tofacitinib	1	1037.57	0.96	0.02	5.37	0.98	0.02	5.45
	bDMARD	6	9264.45	0.65	0.24	1.41	0.66	0.24	1.43
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	2	11979.57	0.17	0.02	0.60	NA	NA	NA
	nbDMARD	2	3489.10	0.57	0.07	2.07	NA	NA	NA
Age ≥65 years	Tofacitinib	3	750.66	4.00	0.82	11.68	NA	NA	NA
	bDMARD	6	5521.25	1.09	0.40	2.37	NA	NA	NA
	nbDMARD	1	1903.38	0.53	0.01	2.93	NA	NA	NA
Other infections									
No previous b/tsDMARD	Tofacitinib	5	758.16	6.59	2.14	15.39	6.49	2.11	15.16
	bDMARD	72	9060.74	7.95	6.22	10.01	8.09	6.33	10.19
	nbDMARD	26	5361.21	4.85	3.17	7.11	4.72	3.08	6.91

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
One previous b/tsDMARD	Tofacitinib	9	671.07	13.41	6.13	25.46	14.38	6.58	27.30
	bDMARD	48	3829.94	12.53	9.24	16.62	12.39	9.13	16.42
At least 2 previous b/tsDMARD	Tofacitinib	12	884.71	13.56	7.01	23.69	13.72	7.08	23.96
	bDMARD	67	4360.36	15.37	11.91	19.51	15.33	11.88	19.47
No prior non-tofacitinib JAKi use	Tofacitinib	26	2205.68	11.79	7.70	17.27	11.91	7.78	17.45
	bDMARD	157	15563.55	10.09	8.57	11.79	10.20	8.66	11.92
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	36.19
	bDMARD	30	1687.48	17.78	11.99	25.38	17.71	11.95	25.28
Monotherapy	Tofacitinib	17	1229.79	13.82	8.05	22.13	13.79	8.03	22.08
	bDMARD	84	7495.75	11.21	8.94	13.87	11.21	8.94	13.88
Combination Therapy with a nbDMARD	Tofacitinib	9	1084.16	8.30	3.80	15.76	8.51	3.89	16.16
	bDMARD	103	9755.29	10.56	8.62	12.81	10.82	8.83	13.13
Combination Therapy with MTX	Tofacitinib	8	1030.14	7.77	3.35	15.30	8.08	3.49	15.91
	bDMARD	93	9144.89	10.17	8.21	12.46	10.28	8.30	12.59
Age <65 years	Tofacitinib	11	1575.92	6.98	3.48	12.49	NA	NA	NA
	bDMARD	74	11865.64	6.24	4.90	7.83	NA	NA	NA
	nbDMARD	16	3473.49	4.61	2.63	7.48	NA	NA	NA
Age ≥65 years	Tofacitinib	15	738.03	20.32	11.38	33.52	NA	NA	NA
	bDMARD	113	5385.39	20.98	17.29	25.23	NA	NA	NA
	nbDMARD	10	1887.72	5.30	2.54	9.74	NA	NA	NA
2. TB									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	NA	NA	NA
	bDMARD	0	9149.44	0.00	0.00	0.40	NA	NA	NA
	nbDMARD	0	5393.07	0.00	0.00	0.68	NA	NA	NA
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.38	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	5.54
	bDMARD	1	4458.52	0.22	0.01	1.25	0.21	0.01	1.19
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	NA	NA	NA
	bDMARD	0	15770.61	0.00	0.00	0.23	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	64.38
	bDMARD	1	1735.72	0.58	0.01	3.21	0.56	0.01	3.12
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.87
	bDMARD	1	7621.91	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	NA	NA	NA
	bDMARD	0	9884.42	0.00	0.00	0.37	NA	NA	NA
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	NA	NA	NA
	bDMARD	0	9267.99	0.00	0.00	0.40	NA	NA	NA
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	1	11983.79	0.08	0.00	0.46	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	0	5522.55	0.00	0.00	0.67	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
3. HZ									
No previous b/tsDMARD	Tofacitinib	15	731.50	20.51	11.48	33.82	20.33	11.37	33.53
	bDMARD	70	9023.38	7.76	6.05	9.80	7.81	6.09	9.87
	nbDMARD	23	5350.12	4.30	2.73	6.45	4.25	2.70	6.38
One previous b/tsDMARD	Tofacitinib	8	668.94	11.96	5.16	23.56	11.80	5.09	23.25
	bDMARD	38	3839.90	9.90	7.00	13.58	9.92	7.02	13.62
At least 2 previous b/tsDMARD	Tofacitinib	26	858.31	30.29	19.79	44.39	30.62	20.00	44.87
	bDMARD	35	4403.88	7.95	5.54	11.05	7.93	5.52	11.03
No prior non-tofacitinib JAKi use	Tofacitinib	46	2155.14	21.34	15.63	28.47	21.01	15.38	28.02
	bDMARD	132	15557.00	8.48	7.10	10.06	8.51	7.12	10.09
At least one prior non-tofacitinib JAKi use	Tofacitinib	3	103.61	28.96	5.97	84.62	27.93	5.76	81.61
	bDMARD	11	1710.15	6.43	3.21	11.51	6.45	3.21	11.54
Monotherapy	Tofacitinib	24	1206.38	19.89	12.75	29.60	20.04	12.84	29.82
	bDMARD	59	7531.18	7.83	5.96	10.11	7.82	5.96	10.09
Combination Therapy with a nbDMARD	Tofacitinib	25	1052.37	23.76	15.37	35.07	23.34	15.10	34.46

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	84	9735.97	8.63	6.88	10.68	8.75	6.98	10.83
Combination Therapy with MTX	Tofacitinib	23	999.28	23.02	14.59	34.54	22.39	14.19	33.59
	bDMARD	75	9128.35	8.22	6.46	10.30	8.24	6.48	10.33
Age <65 years	Tofacitinib	30	1539.80	19.48	13.15	27.81	NA	NA	NA
	bDMARD	98	11808.22	8.30	6.74	10.11	NA	NA	NA
	nbDMARD	11	3467.08	3.17	1.58	5.68	NA	NA	NA
Age ≥65 years	Tofacitinib	19	718.95	26.43	15.91	41.27	NA	NA	NA
	bDMARD	45	5458.94	8.24	6.01	11.03	NA	NA	NA
	nbDMARD	12	1883.03	6.37	3.29	11.13	NA	NA	NA
4. Fractures									
No previous b/tsDMARD	Tofacitinib	19	734.60	25.86	15.57	40.39	24.54	14.77	38.32
	bDMARD	154	8889.47	17.32	14.70	20.29	17.70	15.02	20.73
	nbDMARD	51	5309.41	9.61	7.15	12.63	9.34	6.95	12.28
One previous b/tsDMARD	Tofacitinib	10	657.40	15.21	7.29	27.97	15.64	7.49	28.76
	bDMARD	68	3768.49	18.04	14.01	22.88	17.96	13.95	22.77
At least 2 previous b/tsDMARD	Tofacitinib	19	868.69	21.87	13.17	34.16	22.04	13.26	34.42
	bDMARD	84	4321.69	19.44	15.50	24.06	19.41	15.48	24.03
No prior non-tofacitinib JAKi use	Tofacitinib	44	2156.41	20.40	14.83	27.39	20.37	14.80	27.35
	bDMARD	274	15290.19	17.92	15.86	20.17	18.03	15.96	20.30
At least one prior non-tofacitinib JAKi use	Tofacitinib	4	104.29	38.35	10.45	98.20	38.53	10.50	98.65
	bDMARD	32	1689.46	18.94	12.96	26.74	18.94	12.95	26.73
Monotherapy	Tofacitinib	22	1208.23	18.21	11.41	27.57	18.19	11.40	27.54
	bDMARD	130	7405.08	17.56	14.67	20.85	17.56	14.67	20.85
Combination Therapy with a nbDMARD	Tofacitinib	26	1052.46	24.70	16.14	36.20	25.55	16.69	37.44
	bDMARD	176	9574.56	18.38	15.77	21.31	18.78	16.11	21.77
Combination Therapy with MTX	Tofacitinib	26	997.65	26.06	17.02	38.19	26.78	17.49	39.24
	bDMARD	164	8983.44	18.26	15.57	21.27	18.26	15.57	21.28
Age <65 years	Tofacitinib	24	1542.52	15.56	9.97	23.15	NA	NA	NA
	bDMARD	165	11695.74	14.11	12.04	16.43	NA	NA	NA
	nbDMARD	19	3454.53	5.50	3.31	8.59	NA	NA	NA
Age ≥65 years	Tofacitinib	24	718.18	33.42	21.41	49.72	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	141	5283.91	26.68	22.46	31.47	NA	NA	NA
	nbDMARD	32	1854.88	17.25	11.80	24.35	NA	NA	NA
5. Cardiac disorders									
No previous b/tsDMARD	Tofacitinib	13	752.98	17.26	9.19	29.52	16.55	8.80	28.31
	bDMARD	112	9010.22	12.43	10.24	14.96	12.82	10.55	15.42
	nbDMARD	33	5347.46	6.17	4.25	8.67	5.91	4.07	8.30
One previous b/tsDMARD	Tofacitinib	13	659.20	19.72	10.50	33.72	21.17	11.26	36.20
	bDMARD	51	3818.57	13.36	9.94	17.56	13.20	9.83	17.36
At least 2 previous b/tsDMARD	Tofacitinib	15	878.36	17.08	9.56	28.17	17.68	9.89	29.16
	bDMARD	69	4368.11	15.80	12.29	19.99	15.69	12.21	19.86
No prior non-tofacitinib JAKi use	Tofacitinib	39	2184.36	17.85	12.70	24.41	18.02	12.81	24.64
	bDMARD	211	15498.34	13.61	11.84	15.58	13.79	12.00	15.79
At least one prior non-tofacitinib JAKi use	Tofacitinib	2	106.17	18.84	2.28	68.05	23.64	2.86	85.39
	bDMARD	21	1698.56	12.36	7.65	18.90	12.21	7.55	18.66
Monotherapy	Tofacitinib	25	1216.63	20.55	13.30	30.33	20.32	13.15	30.00
	bDMARD	116	7469.27	15.53	12.83	18.63	15.56	12.86	18.66
Combination Therapy with a nbDMARD	Tofacitinib	16	1073.90	14.90	8.52	24.20	15.57	8.89	25.28
	bDMARD	116	9727.63	11.92	9.85	14.30	12.12	10.01	14.53
Combination Therapy with MTX	Tofacitinib	16	1019.09	15.70	8.97	25.50	16.54	9.45	26.86
	bDMARD	108	9116.50	11.85	9.72	14.30	11.89	9.75	14.35
Age <65 years	Tofacitinib	18	1557.58	11.56	6.85	18.26	NA	NA	NA
	bDMARD	93	11853.31	7.85	6.33	9.61	NA	NA	NA
	nbDMARD	12	3468.76	3.46	1.79	6.04	NA	NA	NA
Age ≥65 years	Tofacitinib	23	732.95	31.38	19.89	47.09	NA	NA	NA
	bDMARD	139	5343.60	26.01	21.87	30.71	NA	NA	NA
	nbDMARD	21	1878.71	11.18	6.92	17.09	NA	NA	NA
No CV risk factor	Tofacitinib	5	821.84	6.08	1.98	14.20	NA	NA	NA
	bDMARD	31	7287.91	4.25	2.89	6.04	NA	NA	NA
	nbDMARD	2	2161.44	0.93	0.11	3.34	NA	NA	NA
At least one CV risk factor	Tofacitinib	36	1468.69	24.51	17.17	33.93	25.56	17.90	35.39
	bDMARD	201	9908.99	20.28	17.58	23.29	20.35	17.63	23.36

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	31	3186.03	9.73	6.61	13.81	9.46	6.43	13.43
Therapy start before 30-JUNE-2021	Tofacitinib	38	2236.48	16.99	12.02	23.32	16.88	11.95	23.18
	bDMARD	169	13125.19	12.88	11.01	14.97	13.17	11.26	15.31
	nbDMARD	26	4441.00	5.85	3.82	8.58	5.51	3.60	8.08
Therapy start on or after 30-JUNE-2021	Tofacitinib	3	54.05	55.51	11.45	162.21	67.15	13.85	196.25
	bDMARD	63	4071.71	15.47	11.89	19.80	15.47	11.89	19.80
	nbDMARD	7	906.47	7.72	3.10	15.91	7.64	3.07	15.75
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	33	1435.05	23.00	15.83	32.29	23.63	16.26	33.19
	bDMARD	146	7441.17	19.62	16.57	23.07	19.80	16.72	23.29
	nbDMARD	24	2641.77	9.08	5.82	13.52	8.73	5.59	12.99
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	3	33.63	89.19	18.39	260.67	105.79	21.82	309.16
	bDMARD	55	2467.82	22.29	16.79	29.01	22.27	16.78	28.99
	nbDMARD	7	544.25	12.86	5.17	26.50	12.78	5.14	26.34
Heart failure									
No previous b/tsDMARD	Tofacitinib	1	769.78	1.30	0.03	7.24	1.21	0.03	6.74
	bDMARD	27	9135.45	2.96	1.95	4.30	3.09	2.03	4.49
	nbDMARD	6	5385.24	1.11	0.41	2.43	1.05	0.39	2.28
One previous b/tsDMARD	Tofacitinib	4	675.41	5.92	1.61	15.16	7.00	1.91	17.91
	bDMARD	12	3877.31	3.09	1.60	5.41	3.01	1.56	5.27
At least 2 previous b/tsDMARD	Tofacitinib	5	890.53	5.61	1.82	13.10	5.75	1.87	13.42
	bDMARD	21	4441.43	4.73	2.93	7.23	4.71	2.91	7.19
No prior non-tofacitinib JAKi use	Tofacitinib	9	2227.62	4.04	1.85	7.67	4.07	1.86	7.72
	bDMARD	53	15724.73	3.37	2.52	4.41	3.43	2.57	4.49
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	108.10	9.25	0.23	51.54	10.76	0.27	59.94
	bDMARD	7	1729.46	4.05	1.63	8.34	4.01	1.61	8.27
Monotherapy	Tofacitinib	8	1244.28	6.43	2.78	12.67	6.42	2.77	12.65
	bDMARD	35	7589.92	4.61	3.21	6.41	4.61	3.21	6.42

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with a nbDMARD	Tofacitinib	2	1091.44	1.83	0.22	6.62	1.93	0.23	6.98
	bDMARD	25	9864.27	2.53	1.64	3.74	2.66	1.72	3.93
Combination Therapy with MTX	Tofacitinib	2	1036.63	1.93	0.23	6.97	2.02	0.25	7.31
	bDMARD	21	9249.05	2.27	1.41	3.47	2.30	1.42	3.51
Age <65 years	Tofacitinib	3	1588.48	1.89	0.39	5.52	NA	NA	NA
	bDMARD	12	11964.45	1.00	0.52	1.75	NA	NA	NA
	nbDMARD	1	3484.50	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	7	747.24	9.37	3.77	19.30	NA	NA	NA
	bDMARD	48	5489.74	8.74	6.45	11.59	NA	NA	NA
	nbDMARD	5	1900.74	2.63	0.85	6.14	NA	NA	NA
No CV risk factor	Tofacitinib	1	827.48	1.21	0.03	6.73	NA	NA	NA
	bDMARD	2	7318.86	0.27	0.03	0.99	NA	NA	NA
	nbDMARD	0	2153.74	0.00	0.00	1.71	NA	NA	NA
At least one CV risk factor	Tofacitinib	9	1508.24	5.97	2.73	11.33	6.30	2.88	11.96
	bDMARD	58	10135.33	5.72	4.35	7.40	5.76	4.38	7.45
	nbDMARD	6	3217.47	1.86	0.68	4.06	1.78	0.65	3.87
Therapy start before 30-JUNE-2021	Tofacitinib	7	2281.67	3.07	1.23	6.32	3.02	1.21	6.22
	bDMARD	39	13323.97	2.93	2.08	4.00	3.01	2.14	4.12
	nbDMARD	5	4470.43	1.12	0.36	2.61	1.04	0.34	2.42
Therapy start on or after 30-JUNE-2021	Tofacitinib	3	54.05	55.51	11.45	162.21	74.76	15.42	218.47
	bDMARD	21	4130.22	5.08	3.15	7.77	5.05	3.13	7.72
	nbDMARD	1	914.81	1.09	0.03	6.09	1.11	0.03	6.17
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	6	1474.60	4.07	1.49	8.86	4.20	1.54	9.13
	bDMARD	37	7615.56	4.86	3.42	6.70	4.93	3.47	6.79
	nbDMARD	5	2664.88	1.88	0.61	4.38	1.78	0.58	4.14
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	3	33.63	89.19	18.39	260.67	115.96	23.91	338.88
	bDMARD	21	2519.77	8.33	5.16	12.74	8.30	5.14	12.69
	nbDMARD	1	552.59	1.81	0.05	10.08	1.82	0.05	10.11

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Coronary artery disease									
No previous b/tsDMARD	Tofacitinib	3	767.45	3.91	0.81	11.42	3.81	0.78	11.12
	bDMARD	31	9109.11	3.40	2.31	4.83	3.48	2.36	4.94
	nbDMARD	18	5360.72	3.36	1.99	5.31	3.25	1.93	5.14
One previous b/tsDMARD	Tofacitinib	3	673.93	4.45	0.92	13.01	4.67	0.96	13.65
	bDMARD	16	3871.28	4.13	2.36	6.71	4.10	2.34	6.66
At least 2 previous b/tsDMARD	Tofacitinib	1	892.33	1.12	0.03	6.24	1.19	0.03	6.65
	bDMARD	16	4439.98	3.60	2.06	5.85	3.56	2.03	5.78
No prior non-tofacitinib JAKi use	Tofacitinib	7	2225.45	3.15	1.26	6.48	3.17	1.28	6.54
	bDMARD	58	15690.57	3.70	2.81	4.78	3.74	2.84	4.83
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	53.61
	bDMARD	5	1729.79	2.89	0.94	6.75	2.83	0.92	6.60
Monotherapy	Tofacitinib	5	1242.10	4.03	1.31	9.39	4.01	1.30	9.36
	bDMARD	31	7580.32	4.09	2.78	5.80	4.09	2.78	5.81
Combination Therapy with a nbDMARD	Tofacitinib	2	1091.61	1.83	0.22	6.62	1.92	0.23	6.93
	bDMARD	32	9840.05	3.25	2.22	4.59	3.30	2.25	4.65
Combination Therapy with MTX	Tofacitinib	2	1036.81	1.93	0.23	6.97	2.05	0.25	7.40
	bDMARD	30	9225.16	3.25	2.19	4.64	3.26	2.20	4.66
Age <65 years	Tofacitinib	4	1583.79	2.53	0.69	6.47	NA	NA	NA
	bDMARD	28	11937.28	2.35	1.56	3.39	NA	NA	NA
	nbDMARD	7	3476.36	2.01	0.81	4.15	NA	NA	NA
Age ≥65 years	Tofacitinib	3	749.92	4.00	0.82	11.69	NA	NA	NA
	bDMARD	35	5483.09	6.38	4.45	8.88	NA	NA	NA
	nbDMARD	11	1884.36	5.84	2.91	10.44	NA	NA	NA
No CV risk factor	Tofacitinib	1	827.09	1.21	0.03	6.74	NA	NA	NA
	bDMARD	7	7319.63	0.96	0.38	1.97	NA	NA	NA
	nbDMARD	1	2164.85	0.46	0.01	2.57	NA	NA	NA
At least one CV risk factor	Tofacitinib	6	1506.62	3.98	1.46	8.67	4.13	1.51	8.98
	bDMARD	56	10100.73	5.54	4.19	7.20	5.55	4.19	7.21
	nbDMARD	17	3195.87	5.32	3.10	8.52	5.22	3.04	8.36

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Therapy start before 30-JUNE-2021	Tofacitinib	7	2278.13	3.07	1.24	6.33	3.05	1.23	6.28
	bDMARD	51	13287.90	3.84	2.86	5.05	3.92	2.92	5.16
	nbDMARD	16	4450.17	3.60	2.06	5.84	3.39	1.93	5.50
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	75.00
	bDMARD	12	4132.47	2.90	1.50	5.07	2.92	1.51	5.10
	nbDMARD	2	910.55	2.20	0.27	7.93	2.14	0.26	7.71
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	6	1471.46	4.08	1.50	8.88	4.18	1.54	9.11
	bDMARD	46	7576.71	6.07	4.44	8.10	6.12	4.48	8.16
	nbDMARD	15	2647.53	5.67	3.17	9.34	5.46	3.05	9.01
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	35.17	0.00	0.00	104.90	0.00	0.00	114.07
	bDMARD	10	2524.02	3.96	1.90	7.29	3.97	1.90	7.30
	nbDMARD	2	548.33	3.65	0.44	13.18	3.60	0.44	13.01
Myocardial infarction									
No previous b/tsDMARD	Tofacitinib	4	767.53	5.21	1.42	13.34	5.16	1.40	13.20
	bDMARD	24	9112.48	2.63	1.69	3.92	2.65	1.70	3.95
	nbDMARD	6	5378.02	1.12	0.41	2.43	1.10	0.41	2.40
One previous b/tsDMARD	Tofacitinib	5	671.63	7.44	2.42	17.37	7.64	2.48	17.82
	bDMARD	12	3878.25	3.09	1.60	5.40	3.08	1.59	5.38
At least 2 previous b/tsDMARD	Tofacitinib	2	890.40	2.25	0.27	8.11	2.58	0.31	9.31
	bDMARD	11	4445.11	2.47	1.24	4.43	2.41	1.20	4.32
No prior non-tofacitinib JAKi use	Tofacitinib	10	2223.22	4.50	2.16	8.27	4.62	2.21	8.50
	bDMARD	41	15708.33	2.61	1.87	3.54	2.61	1.87	3.54
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	106.33	9.40	0.24	52.40	13.25	0.34	73.84
	bDMARD	6	1727.51	3.47	1.27	7.56	3.41	1.25	7.43
Monotherapy	Tofacitinib	7	1243.80	5.63	2.26	11.60	5.60	2.25	11.54
	bDMARD	25	7585.39	3.30	2.13	4.87	3.30	2.13	4.87

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with a nbDMARD	Tofacitinib	4	1085.75	3.68	1.00	9.43	3.92	1.07	10.04
	bDMARD	22	9850.46	2.23	1.40	3.38	2.17	1.36	3.28
Combination Therapy with MTX	Tofacitinib	4	1030.95	3.88	1.06	9.93	4.33	1.18	11.09
	bDMARD	21	9234.29	2.27	1.41	3.48	2.25	1.39	3.44
Age <65 years	Tofacitinib	8	1579.75	5.06	2.19	9.98	NA	NA	NA
	bDMARD	27	11940.76	2.26	1.49	3.29	NA	NA	NA
	nbDMARD	4	3476.81	1.15	0.31	2.95	NA	NA	NA
Age ≥65 years	Tofacitinib	3	749.81	4.00	0.83	11.69	NA	NA	NA
	bDMARD	20	5495.09	3.64	2.22	5.62	NA	NA	NA
	nbDMARD	2	1901.21	1.05	0.13	3.80	NA	NA	NA
No CV risk factor	Tofacitinib	3	824.92	3.64	0.75	10.63	NA	NA	NA
	bDMARD	6	7317.13	0.82	0.30	1.78	NA	NA	NA
	nbDMARD	1	2164.35	0.46	0.01	2.57	NA	NA	NA
At least one CV risk factor	Tofacitinib	8	1504.64	5.32	2.30	10.48	5.43	2.35	10.70
	bDMARD	41	10118.72	4.05	2.91	5.50	4.02	2.88	5.45
	nbDMARD	5	3213.67	1.56	0.51	3.63	1.58	0.51	3.70
Therapy start before 30-JUNE-2021	Tofacitinib	11	2273.98	4.84	2.41	8.66	4.96	2.47	8.87
	bDMARD	33	13301.21	2.48	1.71	3.48	2.48	1.71	3.48
	nbDMARD	6	4462.44	1.34	0.49	2.93	1.33	0.49	2.90
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	78.54
	bDMARD	14	4134.64	3.39	1.85	5.68	3.42	1.87	5.74
	nbDMARD	0	0	915.58	0.00	0.00	0.00	0.00	3.83
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	8	1469.47	5.44	2.35	10.73	5.50	2.37	10.84
	bDMARD	28	7593.64	3.69	2.45	5.33	3.65	2.43	5.28
	nbDMARD	5	2660.30	1.88	0.61	4.39	1.92	0.62	4.48
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	35.17	0.00	0.00	104.90	0.00	0.00	121.08
	bDMARD	13	2525.07	5.15	2.74	8.80	5.17	2.75	8.84
	nbDMARD	0	553.37	0.00	0.00	6.67	0.00	0.00	6.49

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
MACE									
No previous b/tsDMARD	Tofacitinib	7	767.27	9.12	3.67	18.80	8.83	3.55	18.20
	bDMARD	48	9088.08	5.28	3.89	7.00	5.39	3.97	7.14
	nbDMARD	18	5354.67	3.36	1.99	5.31	3.27	1.94	5.17
One previous b/tsDMARD	Tofacitinib	5	671.63	7.44	2.42	17.37	7.84	2.54	18.28
	bDMARD	21	3870.85	5.43	3.36	8.29	5.38	3.33	8.22
At least 2 previous b/tsDMARD	Tofacitinib	8	885.79	9.03	3.90	17.80	9.07	3.91	17.86
	bDMARD	22	4433.07	4.96	3.11	7.51	4.96	3.11	7.51
No prior non-tofacitinib JAKi use	Tofacitinib	19	2218.36	8.56	5.16	13.38	8.75	5.27	13.67
	bDMARD	80	15665.56	5.11	4.05	6.36	5.15	4.08	6.41
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	106.33	9.40	0.24	52.40	11.67	0.30	65.05
	bDMARD	11	1726.45	6.37	3.18	11.40	6.30	3.14	11.27
Monotherapy	Tofacitinib	13	1239.18	10.49	5.59	17.94	10.47	5.57	17.91
	bDMARD	44	7563.95	5.82	4.23	7.81	5.82	4.23	7.81
Combination Therapy with a nbDMARD	Tofacitinib	7	1085.52	6.45	2.59	13.29	6.77	2.72	13.95
	bDMARD	47	9828.06	4.78	3.51	6.36	4.77	3.50	6.34
Combination Therapy with MTX	Tofacitinib	7	1030.71	6.79	2.73	13.99	7.29	2.93	15.03
	bDMARD	42	9213.85	4.56	3.29	6.16	4.56	3.28	6.16
Age <65 years	Tofacitinib	11	1579.30	6.97	3.48	12.46	NA	NA	NA
	bDMARD	40	11928.49	3.35	2.40	4.57	NA	NA	NA
	nbDMARD	7	3468.57	2.02	0.81	4.16	NA	NA	NA
Age ≥65 years	Tofacitinib	9	745.39	12.07	5.52	22.92	NA	NA	NA
	bDMARD	51	5463.52	9.33	6.95	12.27	NA	NA	NA
	nbDMARD	11	1886.10	5.83	2.91	10.44	NA	NA	NA
No CV risk factor	Tofacitinib	3	824.92	3.64	0.75	10.63	NA	NA	NA
	bDMARD	8	7315.99	1.09	0.47	2.15	NA	NA	NA
	nbDMARD	1	2164.35	0.46	0.01	2.57	NA	NA	NA
At least one CV risk factor	Tofacitinib	17	1499.78	11.34	6.60	18.15	11.84	6.89	18.96
	bDMARD	83	10076.02	8.24	6.56	10.21	8.22	6.55	10.19
	nbDMARD	17	3190.32	5.33	3.10	8.53	5.26	3.06	8.42

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Therapy start before 30-JUNE-2021	Tofacitinib	19	2269.17	8.37	5.04	13.08	8.42	5.07	13.15
	bDMARD	66	13259.18	4.98	3.85	6.33	5.06	3.91	6.43
	nbDMARD	15	4440.54	3.38	1.89	5.57	3.22	1.80	5.31
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	55.53	18.01	0.46	100.34	22.16	0.56	123.48
	bDMARD	25	4132.82	6.05	3.91	8.93	6.07	3.92	8.96
	nbDMARD	3	914.13	3.28	0.68	9.59	3.20	0.66	9.36
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	16	1464.67	10.92	6.24	17.74	11.21	6.40	18.20
	bDMARD	61	7551.62	8.08	6.18	10.38	8.10	6.19	10.40
	nbDMARD	14	2638.40	5.31	2.90	8.90	5.20	2.84	8.73
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	1	35.11	28.48	0.72	158.68	36.54	0.93	203.61
	bDMARD	22	2524.40	8.71	5.46	13.19	8.71	5.46	13.18
	nbDMARD	3	551.92	5.44	1.12	15.89	5.38	1.11	15.73
Other cardiac disorders									
No previous b/tsDMARD	Tofacitinib	6	756.73	7.93	2.91	17.26	7.63	2.80	16.61
	bDMARD	54	9071.97	5.95	4.47	7.77	6.19	4.65	8.07
	nbDMARD	15	5381.86	2.79	1.56	4.60	2.63	1.47	4.34
One previous b/tsDMARD	Tofacitinib	2	672.98	2.97	0.36	10.74	3.25	0.39	11.75
	bDMARD	26	3862.42	6.73	4.40	9.86	6.63	4.33	9.72
At least 2 previous b/tsDMARD	Tofacitinib	13	880.93	14.76	7.86	25.24	15.03	7.99	25.70
	bDMARD	37	4406.68	8.40	5.91	11.57	8.37	5.89	11.53
No prior non-tofacitinib JAKi use	Tofacitinib	20	2202.53	9.08	5.55	14.02	9.14	5.58	14.11
	bDMARD	106	15626.60	6.78	5.55	8.20	6.90	5.65	8.34
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	108.10	9.25	0.23	51.54	11.69	0.30	65.15
	bDMARD	11	1714.47	6.42	3.20	11.48	6.33	3.16	11.33
Monotherapy	Tofacitinib	12	1228.65	9.77	5.05	17.06	9.69	5.00	16.92
	bDMARD	54	7544.58	7.16	5.38	9.34	7.17	5.38	9.35

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		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with a nbDMARD	Tofacitinib	9	1081.98	8.32	3.80	15.79	8.66	3.96	16.44
	bDMARD	63	9796.50	6.43	4.94	8.23	6.63	5.09	8.48
Combination Therapy with MTX	Tofacitinib	9	1027.17	8.76	4.01	16.63	9.11	4.17	17.30
	bDMARD	59	9183.24	6.42	4.89	8.29	6.48	4.93	8.36
Age <65 years	Tofacitinib	7	1572.57	4.45	1.79	9.17	NA	NA	NA
	bDMARD	44	11938.56	3.69	2.68	4.95	NA	NA	NA
	nbDMARD	4	3485.12	1.15	0.31	2.94	NA	NA	NA
Age ≥65 years	Tofacitinib	14	738.06	18.97	10.37	31.83	NA	NA	NA
	bDMARD	73	5402.52	13.51	10.59	16.99	NA	NA	NA
	nbDMARD	11	1896.73	5.80	2.90	10.38	NA	NA	NA
No CV risk factor	Tofacitinib	2	824.66	2.43	0.29	8.76	NA	NA	NA
	bDMARD	20	7308.98	2.74	1.67	4.23	NA	NA	NA
	nbDMARD	0	2167.76	0.00	0.00	1.70	NA	NA	NA
At least one CV risk factor	Tofacitinib	19	1485.97	12.79	7.70	19.97	13.38	8.05	20.90
	bDMARD	97	10032.09	9.67	7.84	11.80	9.74	7.90	11.89
	nbDMARD	15	3214.67	4.67	2.61	7.70	4.47	2.50	7.37
Therapy start before 30-JUNE-2021	Tofacitinib	20	2255.22	8.87	5.42	13.70	8.76	5.35	13.54
	bDMARD	86	13233.39	6.50	5.20	8.03	6.68	5.34	8.25
	nbDMARD	10	10	4471.50	2.24	1.07	2.08	1.00	3.83
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	55.42	18.05	0.46	100.54	21.24	0.54	118.34
	bDMARD	31	4107.69	7.55	5.13	10.71	7.54	5.12	10.70
	nbDMARD	5	910.36	5.49	1.78	12.82	5.48	1.78	12.79
At least one CV risk factor and therapy start before 30-JUNE-2021	Tofacitinib	18	1450.97	12.41	7.35	19.61	12.77	7.57	20.19
	bDMARD	72	7529.31	9.56	7.48	12.04	9.72	7.60	12.24
	nbDMARD	10	2665.95	3.75	1.80	6.90	3.54	1.69	6.50
At least one CV risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	1	35.00	28.57	0.72	159.18	33.79	0.86	188.28
	bDMARD	25	2502.78	9.99	6.46	14.75	9.97	6.45	14.71
	nbDMARD	5	548.15	9.12	2.96	21.29	9.13	2.96	21.30

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
6. Hematologic disorders									
No previous b/tsDMARD	Tofacitinib	3	765.32	3.92	0.81	11.46	3.76	0.77	10.97
	bDMARD	25	9122.46	2.74	1.77	4.05	2.81	1.82	4.15
	nbDMARD	10	5383.26	1.86	0.89	3.42	1.79	0.86	3.30
One previous b/tsDMARD	Tofacitinib	1	677.42	1.48	0.04	8.22	1.61	0.04	8.95
	bDMARD	8	3892.09	2.06	0.89	4.05	2.03	0.88	3.99
At least 2 previous b/tsDMARD	Tofacitinib	3	891.14	3.37	0.69	9.84	3.27	0.68	9.57
	bDMARD	15	4449.65	3.37	1.89	5.56	3.39	1.90	5.59
No prior non-tofacitinib JAKi use	Tofacitinib	7	2225.61	3.15	1.26	6.48	3.14	1.26	6.47
	bDMARD	40	15730.85	2.54	1.82	3.46	2.57	1.84	3.51
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	40.54
	bDMARD	8	1733.35	4.62	1.99	9.09	4.57	1.97	9.00
Monotherapy	Tofacitinib	3	1245.02	2.41	0.50	7.04	2.41	0.50	7.04
	bDMARD	25	7598.42	3.29	2.13	4.86	3.29	2.13	4.86
Combination Therapy with a nbDMARD	Tofacitinib	4	1088.85	3.67	1.00	9.41	3.81	1.04	9.75
	bDMARD	23	9865.78	2.33	1.48	3.50	2.43	1.54	3.64
Combination Therapy with MTX	Tofacitinib	4	1034.05	3.87	1.05	9.90	3.96	1.08	10.14
	bDMARD	21	9249.48	2.27	1.41	3.47	2.29	1.41	3.49
Age <65 years	Tofacitinib	2	1588.32	1.26	0.15	4.55	NA	NA	NA
	bDMARD	18	11964.08	1.50	0.89	2.38	NA	NA	NA
	nbDMARD	5	3484.32	1.44	0.47	3.35	NA	NA	NA
Age ≥65 years	Tofacitinib	5	745.55	6.71	2.18	15.65	NA	NA	NA
	bDMARD	30	5500.12	5.45	3.68	7.79	NA	NA	NA
	nbDMARD	5	1898.94	2.63	0.85	6.14	NA	NA	NA
Bone marrow depression and hypoplastic anaemia									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.51
	bDMARD	3	9148.94	0.33	0.07	0.96	0.33	0.07	0.98
	nbDMARD	5	5387.93	0.93	0.30	2.17	0.91	0.29	2.12
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.46

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	1	3897.64	0.26	0.01	1.43	0.25	0.01	1.39
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	3.87
	bDMARD	3	4458.80	0.67	0.14	1.97	0.68	0.14	1.99
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.65
	bDMARD	5	15769.37	0.32	0.10	0.74	0.32	0.10	0.75
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	48.44
	bDMARD	2	1736.01	1.15	0.14	4.16	1.13	0.14	4.09
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.95
	bDMARD	2	7621.68	0.26	0.03	0.95	0.26	0.03	0.95
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.51
	bDMARD	5	9883.70	0.51	0.16	1.18	0.52	0.17	1.22
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.73
	bDMARD	5	9267.26	0.54	0.18	1.26	0.54	0.18	1.26
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	1	11983.84	0.08	0.00	0.46	NA	NA	NA
	nbDMARD	3	3484.34	0.86	0.18	2.52	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	6	5521.55	1.09	0.40	2.37	NA	NA	NA
	nbDMARD	2	1903.59	1.05	0.13	3.80	NA	NA	NA
Decreased white blood cells									
No previous b/tsDMARD	Tofacitinib	1	769.53	1.30	0.03	7.24	1.26	0.03	7.00
	bDMARD	4	9144.02	0.44	0.12	1.12	0.44	0.12	1.13
	nbDMARD	0	5393.07	0.00	0.00	0.68	0.00	0.00	0.67
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	4.89
	bDMARD	2	3897.16	0.51	0.06	1.85	0.52	0.06	1.89
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	3.42
	bDMARD	2	4456.01	0.45	0.05	1.62	0.47	0.06	1.69
No prior non-tofacitinib JAKi use	Tofacitinib	1	2232.82	0.45	0.01	2.50	0.44	0.01	2.43
	bDMARD	7	15760.75	0.44	0.18	0.92	0.45	0.18	0.92
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	28.79

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	1	1736.44	0.58	0.01	3.21	0.58	0.01	3.25
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.97
	bDMARD	5	7618.97	0.66	0.21	1.53	0.66	0.21	1.53
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.38	0.92	0.02	5.10	0.89	0.02	4.96
	bDMARD	3	9878.23	0.30	0.06	0.89	0.31	0.06	0.92
Combination Therapy with MTX	Tofacitinib	1	1037.57	0.96	0.02	5.37	0.93	0.02	5.20
	bDMARD	3	9261.79	0.32	0.07	0.95	0.33	0.07	0.96
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	6	11977.01	0.50	0.18	1.09	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	1	751.08	1.33	0.03	7.42	NA	NA	NA
	bDMARD	2	5520.18	0.36	0.04	1.31	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
Platelet disorders									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.63
	bDMARD	3	9148.51	0.33	0.07	0.96	0.33	0.07	0.97
	nbDMARD	2	5393.07	0.37	0.04	1.34	0.36	0.04	1.32
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.06	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	3.05
	bDMARD	1	4458.73	0.22	0.01	1.25	0.24	0.01	1.34
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.61
	bDMARD	3	15769.37	0.19	0.04	0.56	0.19	0.04	0.56
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	86.54
	bDMARD	1	1735.93	0.58	0.01	3.21	0.56	0.01	3.09
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.97
	bDMARD	3	7621.22	0.39	0.08	1.15	0.39	0.08	1.15
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.53
	bDMARD	1	9884.08	0.10	0.00	0.56	0.11	0.00	0.59
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.50

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	1	9267.64	0.11	0.00	0.60	0.11	0.00	0.60
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	2	11983.85	0.17	0.02	0.60	NA	NA	NA
	nbDMARD	1	3489.31	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	2	5521.45	0.36	0.04	1.31	NA	NA	NA
	nbDMARD	1	1903.76	0.53	0.01	2.93	NA	NA	NA
Other blood dyscrasia									
No previous b/tsDMARD	Tofacitinib	2	765.56	2.61	0.32	9.44	2.51	0.30	9.08
	bDMARD	16	9129.05	1.75	1.00	2.85	1.81	1.03	2.94
	nbDMARD	3	5388.39	0.56	0.11	1.63	0.53	0.11	1.55
One previous b/tsDMARD	Tofacitinib	1	677.42	1.48	0.04	8.22	1.70	0.04	9.48
	bDMARD	5	3894.36	1.28	0.42	3.00	1.26	0.41	2.93
At least 2 previous b/tsDMARD	Tofacitinib	3	891.14	3.37	0.69	9.84	3.39	0.70	9.91
	bDMARD	10	4453.79	2.25	1.08	4.13	2.24	1.07	4.12
No prior non-tofacitinib JAKi use	Tofacitinib	6	2225.85	2.70	0.99	5.87	2.71	0.99	5.90
	bDMARD	26	15742.95	1.65	1.08	2.42	1.68	1.10	2.46
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	41.23
	bDMARD	5	1734.25	2.88	0.94	6.73	2.85	0.93	6.66
Monotherapy	Tofacitinib	3	1245.02	2.41	0.50	7.04	2.40	0.50	7.03
	bDMARD	17	7604.15	2.24	1.30	3.58	2.24	1.30	3.58
Combination Therapy with a nbDMARD	Tofacitinib	3	1089.10	2.75	0.57	8.05	2.88	0.59	8.42
	bDMARD	14	9873.05	1.42	0.78	2.38	1.48	0.81	2.49
Combination Therapy with MTX	Tofacitinib	3	1034.30	2.90	0.60	8.48	2.98	0.61	8.69
	bDMARD	12	9256.75	1.30	0.67	2.26	1.30	0.67	2.28
Age <65 years	Tofacitinib	2	1588.32	1.26	0.15	4.55	NA	NA	NA
	bDMARD	10	11973.38	0.84	0.40	1.54	NA	NA	NA
	nbDMARD	1	3489.28	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	4	745.80	5.36	1.46	13.73	NA	NA	NA
	bDMARD	21	5503.82	3.82	2.36	5.83	NA	NA	NA
	nbDMARD	2	1899.11	1.05	0.13	3.80	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
7. Disorders of the nervous system (excluding infections)									
No previous b/tsDMARD	Tofacitinib	6	768.02	7.81	2.87	17.00	7.61	2.79	16.57
	bDMARD	109	8991.58	12.12	9.95	14.62	12.31	10.11	14.85
	nbDMARD	34	5333.07	6.38	4.42	8.91	6.24	4.32	8.71
One previous b/tsDMARD	Tofacitinib	7	665.01	10.53	4.23	21.69	10.95	4.40	22.56
	bDMARD	42	3829.98	10.97	7.90	14.82	10.89	7.85	14.72
At least 2 previous b/tsDMARD	Tofacitinib	23	868.11	26.49	16.80	39.75	26.54	16.82	39.83
	bDMARD	84	4327.56	19.41	15.48	24.03	19.40	15.48	24.02
No prior non-tofacitinib JAKi use	Tofacitinib	32	2201.98	14.53	9.94	20.52	14.59	9.98	20.59
	bDMARD	201	15470.97	12.99	11.26	14.92	13.10	11.35	15.04
At least one prior non-tofacitinib JAKi use	Tofacitinib	4	99.16	40.34	10.99	103.28	39.94	10.88	102.25
	bDMARD	34	1678.16	20.26	14.03	28.31	20.27	14.04	28.33
Monotherapy	Tofacitinib	25	1223.56	20.43	13.22	30.16	20.42	13.21	30.15
	bDMARD	105	7456.08	14.08	11.52	17.05	14.08	11.52	17.05
Combination Therapy with a nbDMARD	Tofacitinib	11	1077.59	10.21	5.10	18.26	10.36	5.17	18.55
	bDMARD	130	9693.04	13.41	11.21	15.93	13.60	11.36	16.15
Combination Therapy with MTX	Tofacitinib	10	1022.81	9.78	4.69	17.98	9.95	4.76	18.30
	bDMARD	119	9087.06	13.10	10.85	15.67	13.14	10.89	15.73
Age <65 years	Tofacitinib	15	1566.72	9.57	5.36	15.79	NA	NA	NA
	bDMARD	122	11796.74	10.34	8.59	12.35	NA	NA	NA
	nbDMARD	14	3467.64	4.04	2.21	6.77	NA	NA	NA
Age ≥65 years	Tofacitinib	21	734.43	28.59	17.70	43.71	NA	NA	NA
	bDMARD	113	5352.39	21.11	17.40	25.38	NA	NA	NA
	nbDMARD	20	1865.44	10.72	6.55	16.56	NA	NA	NA
Stroke									
No previous b/tsDMARD	Tofacitinib	4	769.01	5.20	1.42	13.32	5.05	1.38	12.92
	bDMARD	34	9111.93	3.73	2.58	5.21	3.82	2.64	5.33
	nbDMARD	12	5365.65	2.24	1.16	3.91	2.17	1.12	3.78
One previous b/tsDMARD	Tofacitinib	2	671.94	2.98	0.36	10.75	3.22	0.39	11.63

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	12	3878.42	3.09	1.60	5.40	3.05	1.58	5.34
At least 2 previous b/tsDMARD	Tofacitinib	8	883.96	9.05	3.91	17.83	8.63	3.73	17.01
	bDMARD	18	4431.79	4.06	2.41	6.42	4.10	2.43	6.48
No prior non-tofacitinib JAKi use	Tofacitinib	13	2219.57	5.86	3.12	10.02	5.94	3.16	10.16
	bDMARD	57	15691.71	3.63	2.75	4.71	3.68	2.78	4.76
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	105.34	9.49	0.24	52.89	8.47	0.21	47.20
	bDMARD	7	1730.43	4.05	1.63	8.33	4.08	1.64	8.40
Monotherapy	Tofacitinib	10	1233.97	8.10	3.89	14.90	8.10	3.88	14.90
	bDMARD	27	7583.36	3.56	2.35	5.18	3.56	2.35	5.18
Combination Therapy with a nbDMARD	Tofacitinib	4	1090.94	3.67	1.00	9.39	3.76	1.02	9.63
	bDMARD	37	9838.78	3.76	2.65	5.18	3.82	2.69	5.27
Combination Therapy with MTX	Tofacitinib	4	1036.13	3.86	1.05	9.88	3.96	1.08	10.15
	bDMARD	33	9228.07	3.58	2.46	5.02	3.60	2.48	5.05
Age <65 years	Tofacitinib	6	1580.65	3.80	1.39	8.26	NA	NA	NA
	bDMARD	28	11950.21	2.34	1.56	3.39	NA	NA	NA
	nbDMARD	3	3481.80	0.86	0.18	2.52	NA	NA	NA
Age ≥65 years	Tofacitinib	8	744.25	10.75	4.64	21.18	NA	NA	NA
	bDMARD	36	5471.93	6.58	4.61	9.11	NA	NA	NA
	nbDMARD	9	1883.85	4.78	2.18	9.07	NA	NA	NA
Central demyelination									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	NA	NA	NA
	bDMARD	0	9149.44	0.00	0.00	0.40	NA	NA	NA
	nbDMARD	0	5393.07	0.00	0.00	0.68	NA	NA	NA
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	4.89
	bDMARD	1	3897.96	0.26	0.01	1.43	0.26	0.01	1.46
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	NA	NA	NA
	bDMARD	0	4459.48	0.00	0.00	0.83	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.58
	bDMARD	1	15770.20	0.06	0.00	0.35	0.06	0.00	0.35
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.98
	bDMARD	1	7622.46	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	NA	NA	NA
	bDMARD	0	9884.42	0.00	0.00	0.37	NA	NA	NA
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	NA	NA	NA
	bDMARD	0	9267.99	0.00	0.00	0.40	NA	NA	NA
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	1	11984.34	0.08	0.00	0.46	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	0	5522.55	0.00	0.00	0.67	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
Other disorders of the CNS									
No previous b/tsDMARD	Tofacitinib	3	768.56	3.90	0.80	11.41	3.80	0.78	11.11
	bDMARD	52	9077.56	5.73	4.28	7.51	5.80	4.33	7.61
	nbDARD	16	5377.90	2.98	1.70	4.83	2.92	1.67	4.74
One previous b/tsDMARD	Tofacitinib	4	676.55	5.91	1.61	15.14	5.98	1.63	15.31
	bDMARD	13	3871.71	3.36	1.79	5.74	3.35	1.78	5.73
At least 2 previous b/tsDMARD	Tofacitinib	9	883.01	10.19	4.66	19.35	10.44	4.77	19.81
	bDMARD	40	4392.87	9.11	6.51	12.40	9.06	6.47	12.34
No prior non-tofacitinib JAKi use	Tofacitinib	14	2225.23	6.29	3.44	10.56	6.30	3.44	10.57
	bDMARD	88	15636.89	5.63	4.51	6.93	5.67	4.54	6.98
At least one prior non-tofacitinib JAKi use	Tofacitinib	2	102.88	19.44	2.35	70.22	20.44	2.48	73.85
	bDMARD	17	1705.24	9.97	5.81	15.96	9.94	5.79	15.92
Monotherapy	Tofacitinib	10	1244.34	8.04	3.85	14.78	8.04	3.85	14.78
	bDMARD	45	7541.52	5.97	4.35	7.98	5.97	4.35	7.98
Combination Therapy with a nbDMARD	Tofacitinib	6	1083.77	5.54	2.03	12.05	5.63	2.07	12.25
	bDMARD	60	9800.61	6.12	4.67	7.88	6.19	4.72	7.97
Combination Therapy with MTX	Tofacitinib	5	1028.99	4.86	1.58	11.34	4.95	1.61	11.55

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	55	9187.32	5.99	4.51	7.79	6.00	4.52	7.81
Age <65 years	Tofacitinib	6	1582.33	3.79	1.39	8.25	NA	NA	NA
	bDMARD	57	11885.12	4.80	3.63	6.21	NA	NA	NA
	nbDMARD	8	3481.74	2.30	0.99	4.53	NA	NA	NA
Age ≥65 years	Tofacitinib	10	745.78	13.41	6.43	24.66	NA	NA	NA
	bDMARD	48	5457.01	8.80	6.49	11.66	NA	NA	NA
	nbDMARD	8	1896.16	4.22	1.82	8.31	NA	NA	NA
Disorders of the peripheral nervous system									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.59
	bDMARD	22	9109.06	2.42	1.51	3.66	2.49	1.56	3.77
	nbDMARD	6	5380.51	1.12	0.41	2.43	1.07	0.39	2.33
One previous b/tsDMARD	Tofacitinib	1	677.39	1.48	0.04	8.23	1.60	0.04	8.90
	bDMARD	12	3884.54	3.09	1.60	5.40	3.05	1.57	5.33
At least 2 previous b/tsDMARD	Tofacitinib	4	888.49	4.50	1.23	11.53	4.24	1.15	10.85
	bDMARD	11	4443.93	2.48	1.24	4.43	2.51	1.25	4.48
No prior non-tofacitinib JAKi use	Tofacitinib	4	2228.19	1.80	0.49	4.60	1.78	0.49	4.56
	bDMARD	40	15707.64	2.55	1.82	3.47	2.58	1.84	3.52
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	107.48	9.30	0.24	51.84	8.44	0.21	47.01
	bDMARD	5	1729.90	2.89	0.94	6.75	2.91	0.94	6.79
Monotherapy	Tofacitinib	4	1243.09	3.22	0.88	8.24	3.23	0.88	8.27
	bDMARD	17	7602.60	2.24	1.30	3.58	2.23	1.30	3.58
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.57	0.92	0.02	5.10	0.92	0.02	5.15
	bDMARD	28	9834.94	2.85	1.89	4.11	2.94	1.96	4.26
Combination Therapy with MTX	Tofacitinib	1	1037.76	0.96	0.02	5.37	0.96	0.02	5.37
	bDMARD	25	9221.35	2.71	1.75	4.00	2.74	1.77	4.05
Age <65 years	Tofacitinib	1	1589.21	0.63	0.02	3.51	NA	NA	NA
	bDMARD	19	11956.97	1.59	0.96	2.48	NA	NA	NA
	nbDMARD	3	3485.82	0.86	0.18	2.52	NA	NA	NA
Age ≥65 years	Tofacitinib	4	746.45	5.36	1.46	13.72	NA	NA	NA
	bDMARD	26	5480.57	4.74	3.10	6.95	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	3	1894.69	1.58	0.33	4.63	NA	NA	NA
Psychiatric disorders									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	5.00
	bDMARD	17	9124.38	1.86	1.09	2.98	1.83	1.07	2.94
	nbDMARD	5	5381.18	0.93	0.30	2.17	0.95	0.31	2.22
One previous b/tsDMARD	Tofacitinib	1	674.09	1.48	0.04	8.27	1.47	0.04	8.18
	bDMARD	8	3884.95	2.06	0.89	4.06	2.06	0.89	4.06
At least 2 previous b/tsDMARD	Tofacitinib	4	890.90	4.49	1.22	11.50	4.65	1.27	11.91
	bDMARD	24	4418.39	5.43	3.48	8.08	5.39	3.45	8.03
No prior non-tofacitinib JAKi use	Tofacitinib	4	2227.12	1.80	0.49	4.60	1.80	0.49	4.60
	bDMARD	41	15710.04	2.61	1.87	3.54	2.61	1.87	3.53
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	107.66	9.29	0.24	51.75	9.45	0.24	52.63
	bDMARD	8	1717.70	4.66	2.01	9.18	4.65	2.01	9.17
Monotherapy	Tofacitinib	3	1247.25	2.41	0.50	7.03	2.40	0.49	7.01
	bDMARD	26	7574.66	3.43	2.24	5.03	3.43	2.24	5.03
Combination Therapy with a nbDMARD	Tofacitinib	2	1087.53	1.84	0.22	6.64	1.80	0.22	6.50
	bDMARD	23	9853.08	2.33	1.48	3.50	2.30	1.46	3.46
Combination Therapy with MTX	Tofacitinib	2	1032.72	1.94	0.23	7.00	1.91	0.23	6.89
	bDMARD	22	9237.01	2.38	1.49	3.61	2.38	1.49	3.60
Age <65 years	Tofacitinib	4	1583.68	2.53	0.69	6.47	NA	NA	NA
	bDMARD	33	11932.48	2.77	1.90	3.88	NA	NA	NA
	nbDMARD	4	3480.76	1.15	0.31	2.94	NA	NA	NA
Age ≥65 years	Tofacitinib	1	751.10	1.33	0.03	7.42	NA	NA	NA
	bDMARD	16	5495.25	2.91	1.66	4.73	NA	NA	NA
	nbDMARD	1	1900.42	0.53	0.01	2.93	NA	NA	NA
8. PML									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	NA	NA	NA
	bDMARD	0	9149.44	0.00	0.00	0.40	NA	NA	NA
	nbDMARD	0	5393.07	0.00	0.00	0.68	NA	NA	NA
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	4.89

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	1	3897.96	0.26	0.01	1.43	0.26	0.01	1.46
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	NA	NA	NA
	bDMARD	0	4459.48	0.00	0.00	0.83	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.58
	bDMARD	1	15770.20	0.06	0.00	0.35	0.06	0.00	0.35
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.98
	bDMARD	1	7622.46	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	NA	NA	NA
	bDMARD	0	9884.42	0.00	0.00	0.37	NA	NA	NA
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	NA	NA	NA
	bDMARD	0	9267.99	0.00	0.00	0.40	NA	NA	NA
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	1	11984.34	0.08	0.00	0.46	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	0	5522.55	0.00	0.00	0.67	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
9. Allergic conditions and hypersensitivity									
No previous b/tsDMARD	Tofacitinib	2	769.19	2.60	0.31	9.39	2.55	0.31	9.20
	bDMARD	13	9129.89	1.42	0.76	2.43	1.44	0.76	2.46
	nbDMARD	3	5388.80	0.56	0.11	1.63	0.55	0.11	1.61
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.12
	bDMARD	2	3895.24	0.51	0.06	1.85	0.52	0.06	1.88
At least 2 previous b/tsDMARD	Tofacitinib	1	892.81	1.12	0.03	6.24	1.10	0.03	6.16
	bDMARD	8	4449.45	1.80	0.78	3.54	1.80	0.78	3.55
No prior non-tofacitinib JAKi use	Tofacitinib	3	2232.32	1.34	0.28	3.93	1.34	0.28	3.91
	bDMARD	18	15744.28	1.14	0.68	1.81	1.15	0.68	1.81

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	38.16
	bDMARD	5	1730.29	2.89	0.94	6.74	2.87	0.93	6.70
Monotherapy	Tofacitinib	2	1248.12	1.60	0.19	5.79	1.61	0.19	5.80
	bDMARD	11	7610.25	1.45	0.72	2.59	1.44	0.72	2.59
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.47	0.92	0.02	5.10	0.93	0.02	5.17
	bDMARD	12	9864.33	1.22	0.63	2.12	1.23	0.63	2.14
Combination Therapy with MTX	Tofacitinib	1	1037.66	0.96	0.02	5.37	0.99	0.02	5.49
	bDMARD	11	9249.29	1.19	0.59	2.13	1.19	0.59	2.12
Age <65 years	Tofacitinib	1	1589.75	0.63	0.02	3.50	NA	NA	NA
	bDMARD	15	11962.56	1.25	0.70	2.07	NA	NA	NA
	nbDMARD	2	3486.81	0.57	0.07	2.07	NA	NA	NA
Age ≥65 years	Tofacitinib	2	750.83	2.66	0.32	9.62	NA	NA	NA
	bDMARD	8	5512.02	1.45	0.63	2.86	NA	NA	NA
	nbDMARD	1	1901.99	0.53	0.01	2.93	NA	NA	NA
10. Hepatic failure									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	5.07
	bDMARD	5	9141.56	0.55	0.18	1.28	0.54	0.18	1.27
	nbDMARD	1	5393.01	0.19	0.00	1.03	0.19	0.00	1.04
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	4.89
	bDMARD	1	3898.14	0.26	0.01	1.43	0.26	0.01	1.46
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	5.54
	bDMARD	1	4457.84	0.22	0.01	1.25	0.21	0.01	1.19
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.68
	bDMARD	6	15762.50	0.38	0.14	0.83	0.38	0.14	0.83
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	64.25
	bDMARD	1	1735.05	0.58	0.01	3.21	0.56	0.01	3.12
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.92
	bDMARD	7	7613.12	0.92	0.37	1.89	0.92	0.37	1.90
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.07

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	0	9884.42	0.00	0.00	0.37	0.00	0.00	0.37
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.17
	bDMARD	0	9267.99	0.00	0.00	0.40	0.00	0.00	0.40
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	5	11975.24	0.42	0.14	0.97	NA	NA	NA
	nbDMARD	1	3489.25	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	2	5522.30	0.36	0.04	1.31	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
11. GI perforations									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.50
	bDMARD	16	9126.89	1.75	1.00	2.85	1.79	1.02	2.91
	nbDMARD	14	5376.95	2.60	1.42	4.37	2.54	1.38	4.25
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.07
	bDMARD	12	3882.13	3.09	1.60	5.40	3.04	1.57	5.30
At least 2 previous b/tsDMARD	Tofacitinib	5	892.16	5.60	1.82	13.08	5.94	1.93	13.87
	bDMARD	16	4432.72	3.61	2.06	5.86	3.57	2.04	5.80
No prior non-tofacitinib JAKi use	Tofacitinib	5	2232.26	2.24	0.73	5.23	2.27	0.74	5.29
	bDMARD	40	15715.30	2.55	1.82	3.47	2.56	1.83	3.49
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	36.28
	bDMARD	4	1726.45	2.32	0.63	5.93	2.31	0.63	5.91
Monotherapy	Tofacitinib	3	1247.99	2.40	0.50	7.03	2.39	0.49	6.99
	bDMARD	25	7590.80	3.29	2.13	4.86	3.30	2.13	4.87
Combination Therapy with a nbDMARD	Tofacitinib	2	1092.54	1.83	0.22	6.61	1.92	0.23	6.92
	bDMARD	19	9850.95	1.93	1.16	3.01	1.96	1.18	3.07
Combination Therapy with MTX	Tofacitinib	2	1037.73	1.93	0.23	6.96	2.01	0.24	7.27
	bDMARD	15	9244.49	1.62	0.91	2.68	1.63	0.91	2.68
Age <65 years	Tofacitinib	2	1589.77	1.26	0.15	4.54	NA	NA	NA
	bDMARD	21	11952.40	1.76	1.09	2.69	NA	NA	NA
	nbDMARD	5	3485.42	1.43	0.47	3.35	NA	NA	NA
Age ≥65 years	Tofacitinib	3	750.76	4.00	0.82	11.68	NA	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

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		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	23	5489.35	4.19	2.66	6.29	NA	NA	NA
	nbDMARD	9	1891.53	4.76	2.18	9.03	NA	NA	NA
Lower intestinal perforations									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.28
	bDMARD	5	9146.54	0.55	0.18	1.28	0.57	0.18	1.32
	nbDMARD	2	5391.06	0.37	0.04	1.34	0.36	0.04	1.29
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.05
	bDMARD	3	3897.34	0.77	0.16	2.25	0.76	0.16	2.21
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.21
	bDMARD	5	4451.18	1.12	0.36	2.62	1.12	0.36	2.61
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.68
	bDMARD	13	15759.84	0.82	0.44	1.41	0.83	0.44	1.42
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1735.22	0.00	0.00	2.13	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.93
	bDMARD	9	7616.22	1.18	0.54	2.24	1.18	0.54	2.25
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.67
	bDMARD	4	9878.84	0.40	0.11	1.04	0.42	0.11	1.07
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.80
	bDMARD	3	9262.65	0.32	0.07	0.95	0.32	0.07	0.94
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	5	11978.47	0.42	0.14	0.97	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	8	5516.59	1.45	0.63	2.86	NA	NA	NA
	nbDMARD	2	1901.75	1.05	0.13	3.80	NA	NA	NA
Other GI perforations									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.51
	bDMARD	12	9129.87	1.31	0.68	2.30	1.35	0.70	2.35
	nbDMARD	12	5378.95	2.23	1.15	3.90	2.16	1.12	3.78

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.11
	bDMARD	10	3882.63	2.58	1.24	4.74	2.53	1.21	4.65
At least 2 previous b/tsDMARD	Tofacitinib	5	892.16	5.60	1.82	13.08	5.88	1.91	13.72
	bDMARD	15	4438.54	3.38	1.89	5.57	3.35	1.87	5.52
No prior non-tofacitinib JAKi use	Tofacitinib	5	2232.26	2.24	0.73	5.23	2.25	0.73	5.24
	bDMARD	33	15724.59	2.10	1.44	2.95	2.12	1.46	2.97
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	36.28
	bDMARD	4	1726.45	2.32	0.63	5.93	2.31	0.63	5.91
Monotherapy	Tofacitinib	3	1247.99	2.40	0.50	7.03	2.39	0.49	7.00
	bDMARD	23	7591.29	3.03	1.92	4.55	3.03	1.92	4.55
Combination Therapy with a nbDMARD	Tofacitinib	2	1092.54	1.83	0.22	6.61	1.88	0.23	6.79
	bDMARD	14	9859.75	1.42	0.78	2.38	1.45	0.79	2.44
Combination Therapy with MTX	Tofacitinib	2	1037.73	1.93	0.23	6.96	1.97	0.24	7.12
	bDMARD	12	9250.81	1.30	0.67	2.27	1.30	0.67	2.28
Age <65 years	Tofacitinib	2	1589.77	1.26	0.15	4.54	NA	NA	NA
	bDMARD	16	11961.20	1.34	0.76	2.17	NA	NA	NA
	nbDMARD	5	3485.42	1.43	0.47	3.35	NA	NA	NA
Age ≥65 years	Tofacitinib	3	750.76	4.00	0.82	11.68	NA	NA	NA
	bDMARD	21	5489.84	3.83	2.37	5.85	NA	NA	NA
	nbDMARD	7	1893.54	3.70	1.49	7.62	NA	NA	NA
13. Embolic and thrombotic events									
No previous b/tsDMARD	Tofacitinib	2	767.68	2.61	0.32	9.41	2.50	0.30	9.02
	bDMARD	21	9126.31	2.30	1.42	3.52	2.38	1.47	3.64
	nbDMARD	4	5385.48	0.74	0.20	1.90	0.71	0.19	1.81
One previous b/tsDMARD	Tofacitinib	2	677.45	2.95	0.36	10.66	3.38	0.41	12.23
	bDMARD	9	3889.84	2.31	1.06	4.39	2.26	1.03	4.30
At least 2 previous b/tsDMARD	Tofacitinib	3	892.70	3.36	0.69	9.82	3.42	0.71	10.00
	bDMARD	11	4434.04	2.48	1.24	4.44	2.47	1.23	4.42
No prior non-tofacitinib JAKi use	Tofacitinib	7	2229.56	3.14	1.26	6.47	3.16	1.27	6.51
	bDMARD	36	15733.14	2.29	1.60	3.17	2.32	1.63	3.22

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	31.25
	bDMARD	5	1717.05	2.91	0.95	6.80	2.93	0.95	6.83
Monotherapy	Tofacitinib	6	1245.26	4.82	1.77	10.49	4.82	1.77	10.50
	bDMARD	18	7593.76	2.37	1.40	3.75	2.37	1.40	3.75
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.57	0.92	0.02	5.10	0.94	0.02	5.24
	bDMARD	23	9856.44	2.33	1.48	3.50	2.38	1.51	3.58
Combination Therapy with MTX	Tofacitinib	1	1037.76	0.96	0.02	5.37	1.00	0.03	5.57
	bDMARD	22	9243.06	2.38	1.49	3.60	2.40	1.51	3.64
Age <65 years	Tofacitinib	2	1589.95	1.26	0.15	4.54	NA	NA	NA
	bDMARD	15	11963.58	1.25	0.70	2.07	NA	NA	NA
	nbDMARD	1	3487.46	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	5	747.88	6.69	2.17	15.60	NA	NA	NA
	bDMARD	26	5486.62	4.74	3.10	6.94	NA	NA	NA
	nbDMARD	3	1898.01	1.58	0.33	4.62	NA	NA	NA
No VTE risk factor	Tofacitinib	1	879.23	1.14	0.03	6.34	NA	NA	NA
	bDMARD	9	7555.96	1.19	0.54	2.26	NA	NA	NA
	nbDMARD	1	2195.60	0.46	0.01	2.54	NA	NA	NA
At least one VTE risk factor	Tofacitinib	6	1458.60	4.11	1.51	8.95	4.24	1.56	9.24
	bDMARD	32	9894.24	3.23	2.21	4.57	3.27	2.24	4.61
	nbDMARD	3	3189.88	0.94	0.19	2.75	0.90	0.19	2.62
Therapy start before 31-JAN-2020	Tofacitinib	7	1961.52	3.57	1.43	7.35	3.43	1.38	7.08
	bDMARD	22	9901.47	2.22	1.39	3.36	2.31	1.45	3.50
	nbDMARD	3	3442.85	0.87	0.18	2.55	0.80	0.16	2.33
Therapy start on or after 31-JAN-2020	Tofacitinib	0	376.31	0.00	0.00	9.80	0.00	0.00	10.06
	bDMARD	19	7548.73	2.52	1.52	3.93	2.52	1.52	3.93
	nbDMARD	1	1942.62	0.51	0.01	2.87	0.51	0.01	2.85
VTE									
No previous b/tsDMARD	Tofacitinib	2	767.68	2.61	0.32	9.41	2.50	0.30	9.02
	bDMARD	21	9126.31	2.30	1.42	3.52	2.38	1.47	3.64

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	4	5385.48	0.74	0.20	1.90	0.71	0.19	1.81
One previous b/tsDMARD	Tofacitinib	1	678.52	1.47	0.04	8.21	1.68	0.04	9.37
	bDMARD	9	3889.84	2.31	1.06	4.39	2.26	1.04	4.30
At least 2 previous b/tsDMARD	Tofacitinib	3	892.70	3.36	0.69	9.82	3.42	0.71	10.00
	bDMARD	11	4434.04	2.48	1.24	4.44	2.47	1.23	4.42
No prior non-tofacitinib JAKi use	Tofacitinib	6	2230.63	2.69	0.99	5.85	2.71	0.99	5.89
	bDMARD	36	15733.14	2.29	1.60	3.17	2.32	1.63	3.22
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	31.25
	bDMARD	5	1717.05	2.91	0.95	6.80	2.93	0.95	6.83
Monotherapy	Tofacitinib	5	1246.33	4.01	1.30	9.36	4.01	1.30	9.36
	bDMARD	18	7593.76	2.37	1.40	3.75	2.37	1.40	3.75
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.57	0.92	0.02	5.10	0.94	0.02	5.24
	bDMARD	23	9856.44	2.33	1.48	3.50	2.38	1.51	3.58
Combination Therapy with MTX	Tofacitinib	1	1037.76	0.96	0.02	5.37	1.00	0.03	5.57
	bDMARD	22	9243.06	2.38	1.49	3.60	2.40	1.51	3.64
Age <65 years	Tofacitinib	2	1589.95	1.26	0.15	4.54	NA	NA	NA
	bDMARD	15	11963.58	1.25	0.70	2.07	NA	NA	NA
	nbDMARD	1	3487.46	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	4	748.95	5.34	1.46	13.67	NA	NA	NA
	bDMARD	26	5486.62	4.74	3.10	6.94	NA	NA	NA
	nbDMARD	3	1898.01	1.58	0.33	4.62	NA	NA	NA
No VTE risk factor	Tofacitinib	1	879.23	1.14	0.03	6.34	NA	NA	NA
	bDMARD	9	7555.96	1.19	0.54	2.26	NA	NA	NA
	nbDMARD	1	2195.60	0.46	0.01	2.54	NA	NA	NA
At least one VTE risk factor	Tofacitinib	5	1459.67	3.43	1.11	7.99	3.53	1.15	8.24
	bDMARD	32	9894.24	3.23	2.21	4.57	3.27	2.24	4.62
	nbDMARD	3	3189.88	0.94	0.19	2.75	0.90	0.19	2.62
Therapy start before 31-JAN-2020	Tofacitinib	6	1962.59	3.06	1.12	6.65	2.94	1.08	6.41
	bDMARD	22	9901.47	2.22	1.39	3.36	2.32	1.45	3.51
	nbDMARD	3	3442.85	0.87	0.18	2.55	0.80	0.16	2.33

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Therapy start on or after 31-JAN-2020	Tofacitinib	0	376.31	0.00	0.00	9.80	0.00	0.00	10.06
	bDMARD	19	7548.73	2.52	1.52	3.93	2.52	1.52	3.93
	nbDMARD	1	1942.62	0.51	0.01	2.87	0.51	0.01	2.85
At least one VTE risk factor and therapy start before 31-JAN-2020	Tofacitinib	5	1247.90	4.01	1.30	9.35	4.04	1.31	9.44
	bDMARD	19	5398.50	3.52	2.12	5.50	3.61	2.17	5.64
	nbDMARD	3	2039.42	1.47	0.30	4.30	1.37	0.28	4.01
DVT									
No previous b/tsDMARD	Tofacitinib	1	769.58	1.30	0.03	7.24	1.31	0.03	7.31
	bDMARD	9	9133.41	0.99	0.45	1.87	0.99	0.45	1.88
	nbDMARD	0	5393.07	0.00	0.00	0.68	0.00	0.00	0.68
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.46
	bDMARD	4	3895.93	1.03	0.28	2.63	1.00	0.27	2.56
At least 2 previous b/tsDMARD	Tofacitinib	1	892.70	1.12	0.03	6.24	1.16	0.03	6.47
	bDMARD	5	4449.85	1.12	0.36	2.62	1.12	0.36	2.60
No prior non-tofacitinib JAKi use	Tofacitinib	2	2232.59	0.90	0.11	3.24	0.90	0.11	3.26
	bDMARD	16	15749.85	1.02	0.58	1.65	1.02	0.59	1.66
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	30.95
	bDMARD	2	1729.35	1.16	0.14	4.18	1.16	0.14	4.20
Monotherapy	Tofacitinib	2	1248.23	1.60	0.19	5.79	1.61	0.19	5.80
	bDMARD	9	7605.28	1.18	0.54	2.25	1.18	0.54	2.25
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.42
	bDMARD	9	9873.92	0.91	0.42	1.73	0.90	0.41	1.71
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.67
	bDMARD	9	9257.48	0.97	0.44	1.85	0.97	0.45	1.85
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	10	11970.89	0.84	0.40	1.54	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	2	750.85	2.66	0.32	9.62	NA	NA	NA
	bDMARD	8	5508.30	1.45	0.63	2.86	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No VTE risk factor	Tofacitinib	0	879.29	0.00	0.00	4.20	NA	NA	NA
	bDMARD	7	7557.27	0.93	0.37	1.91	NA	NA	NA
	nbDMARD	0	2197.44	0.00	0.00	1.68	NA	NA	NA
At least one VTE risk factor	Tofacitinib	2	1461.56	1.37	0.17	4.94	1.39	0.17	5.01
	bDMARD	11	9921.92	1.11	0.55	1.98	1.12	0.56	2.01
	nbDMARD	0	3195.63	0.00	0.00	1.15	0.00	0.00	1.10
Therapy start before 31-JAN-2020	Tofacitinib	2	1964.54	1.02	0.12	3.68	1.00	0.12	3.61
	bDMARD	6	9913.08	0.61	0.22	1.32	0.62	0.23	1.34
	nbDMARD	0	3448.60	0.00	0.00	1.07	0.00	0.00	1.03
Therapy start on or after 31-JAN-2020	Tofacitinib	0	376.31	0.00	0.00	9.80	0.00	0.00	9.63
	bDMARD	12	7566.12	1.59	0.82	2.77	1.59	0.82	2.77
	nbDMARD	0	1944.47	0.00	0.00	1.90	0.00	0.00	1.90
PE									
No previous b/tsDMARD	Tofacitinib	2	767.68	2.61	0.32	9.41	2.48	0.30	8.97
	bDMARD	17	9132.30	1.86	1.08	2.98	1.94	1.13	3.10
	nbDMARD	4	5385.48	0.74	0.20	1.90	0.70	0.19	1.79
One previous b/tsDMARD	Tofacitinib	1	678.52	1.47	0.04	8.21	1.66	0.04	9.23
	bDMARD	6	3892.22	1.54	0.57	3.36	1.51	0.56	3.29
At least 2 previous b/tsDMARD	Tofacitinib	3	892.70	3.36	0.69	9.82	3.50	0.72	10.23
	bDMARD	8	4439.14	1.80	0.78	3.55	1.79	0.77	3.52
No prior non-tofacitinib JAKi use	Tofacitinib	6	2230.63	2.69	0.99	5.85	2.71	1.00	5.91
	bDMARD	27	15743.10	1.72	1.13	2.50	1.74	1.15	2.54
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	31.97
	bDMARD	4	1720.56	2.32	0.63	5.95	2.33	0.64	5.98
Monotherapy	Tofacitinib	5	1246.33	4.01	1.30	9.36	4.01	1.30	9.37
	bDMARD	12	7605.38	1.58	0.82	2.76	1.58	0.81	2.76
Combination Therapy with a nbDMARD	Tofacitinib	1	1092.57	0.92	0.02	5.10	0.95	0.02	5.29
	bDMARD	19	9858.29	1.93	1.16	3.01	1.98	1.19	3.09

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with MTX	Tofacitinib	1	1037.76	0.96	0.02	5.37	1.01	0.03	5.63
	bDMARD	18	9244.90	1.95	1.15	3.08	1.97	1.16	3.11
Age <65 years	Tofacitinib	2	1589.95	1.26	0.15	4.54	NA	NA	NA
	bDMARD	9	11967.40	0.75	0.34	1.43	NA	NA	NA
	nbDMARD	1	3487.46	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	4	748.95	5.34	1.46	13.67	NA	NA	NA
	bDMARD	22	5496.27	4.00	2.51	6.06	NA	NA	NA
	nbDMARD	3	1898.01	1.58	0.33	4.62	NA	NA	NA
No VTE risk factor	Tofacitinib	1	879.23	1.14	0.03	6.34	NA	NA	NA
	bDMARD	5	7558.19	0.66	0.21	1.54	NA	NA	NA
	nbDMARD	1	2195.60	0.46	0.01	2.54	NA	NA	NA
At least one VTE risk factor	Tofacitinib	5	1459.67	3.43	1.11	7.99	3.56	1.16	8.31
	bDMARD	26	9905.47	2.62	1.71	3.85	2.65	1.73	3.89
	nbDMARD	3	3189.88	0.94	0.19	2.75	0.89	0.18	2.61
Therapy start before 31-JAN-2020	Tofacitinib	6	1962.59	3.06	1.12	6.65	2.95	1.08	6.43
	bDMARD	19	9908.72	1.92	1.15	2.99	2.00	1.20	3.13
	nbDMARD	3	3442.85	0.87	0.18	2.55	0.79	0.16	2.31
Therapy start on or after 31-JAN-2020	Tofacitinib	0	376.31	0.00	0.00	9.80	0.00	0.00	10.47
	bDMARD	12	7554.95	1.59	0.82	2.77	1.59	0.82	2.78
	nbDMARD	1	1942.62	0.51	0.01	2.87	0.51	0.01	2.82
14. Operations and hospitalizations									
No previous b/tsDMARD	Tofacitinib	10	751.39	13.31	6.38	24.48	12.98	6.21	23.87
	bDMARD	97	9000.47	10.78	8.74	13.15	10.88	8.83	13.28
	nbDMARD	31	5338.24	5.81	3.95	8.24	5.73	3.89	8.14
One previous b/tsDMARD	Tofacitinib	8	668.86	11.96	5.16	23.57	12.28	5.30	24.19
	bDMARD	67	3783.25	17.71	13.72	22.49	17.63	13.66	22.39
At least 2 previous b/tsDMARD	Tofacitinib	16	873.22	18.32	10.47	29.76	18.17	10.38	29.51
	bDMARD	71	4350.63	16.32	12.75	20.58	16.35	12.77	20.62
No prior non-tofacitinib JAKi use	Tofacitinib	31	2187.52	14.17	9.63	20.11	14.15	9.61	20.09
	bDMARD	203	15453.05	13.14	11.39	15.07	13.20	11.45	15.15

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	3	105.95	28.31	5.84	82.75	27.52	5.68	80.43
	bDMARD	32	1681.30	19.03	13.02	26.87	19.07	13.04	26.92
Monotherapy	Tofacitinib	18	1221.92	14.73	8.73	23.28	14.68	8.69	23.20
	bDMARD	108	7446.75	14.50	11.90	17.51	14.51	11.90	17.52
Combination Therapy with a nbDMARD	Tofacitinib	16	1071.55	14.93	8.53	24.25	14.98	8.56	24.34
	bDMARD	127	9687.60	13.11	10.93	15.60	13.26	11.05	15.78
Combination Therapy with MTX	Tofacitinib	16	1016.75	15.74	8.99	25.56	15.74	8.99	25.56
	bDMARD	115	9089.70	12.65	10.45	15.19	12.67	10.46	15.21
Age <65 years	Tofacitinib	18	1553.49	11.59	6.87	18.31	NA	NA	NA
	bDMARD	140	11754.89	11.91	10.02	14.05	NA	NA	NA
	nbDMARD	11	3464.72	3.17	1.58	5.68	NA	NA	NA
Age ≥65 years	Tofacitinib	16	739.99	21.62	12.36	35.11	NA	NA	NA
	bDMARD	95	5379.45	17.66	14.29	21.59	NA	NA	NA
	nbDMARD	20	1873.52	10.68	6.52	16.49	NA	NA	NA
Bone and joint surgery and other joint therapeutic procedures									
No previous b/tsDMARD	Tofacitinib	7	762.17	9.18	3.69	18.92	8.92	3.59	18.38
	bDMARD	80	9015.71	8.87	7.04	11.04	8.98	7.12	11.17
	nbDMARD	27	5346.52	5.05	3.33	7.35	4.97	3.28	7.24
One previous b/tsDMARD	Tofacitinib	6	669.48	8.96	3.29	19.51	9.05	3.32	19.71
	bDMARD	53	3799.63	13.95	10.45	18.25	13.92	10.43	18.21
At least 2 previous b/tsDMARD	Tofacitinib	12	880.64	13.63	7.04	23.80	13.54	6.99	23.65
	bDMARD	63	4365.04	14.43	11.09	18.47	14.45	11.10	18.49
No prior non-tofacitinib JAKi use	Tofacitinib	22	2206.35	9.97	6.25	15.10	9.97	6.24	15.09
	bDMARD	169	15493.28	10.91	9.33	12.68	10.95	9.36	12.73
At least one prior non-tofacitinib JAKi use	Tofacitinib	3	105.95	28.31	5.84	82.75	27.90	5.75	81.53
	bDMARD	27	1687.10	16.00	10.55	23.28	16.02	10.55	23.31
Monotherapy	Tofacitinib	11	1239.87	8.87	4.43	15.87	8.85	4.41	15.84
	bDMARD	94	7463.39	12.59	10.18	15.41	12.60	10.18	15.42

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with a nbDMARD	Tofacitinib	14	1072.43	13.05	7.14	21.90	13.13	7.17	22.04
	bDMARD	102	9716.99	10.50	8.56	12.74	10.61	8.65	12.88
Combination Therapy with MTX	Tofacitinib	14	1017.62	13.76	7.52	23.08	13.76	7.52	23.08
	bDMARD	93	9114.53	10.20	8.24	12.50	10.21	8.24	12.51
Age <65 years	Tofacitinib	14	1568.04	8.93	4.88	14.98	NA	NA	NA
	bDMARD	119	11784.95	10.10	8.37	12.08	NA	NA	NA
	nbDMARD	9	3468.80	2.59	1.19	4.93	NA	NA	NA
Age ≥65 years	Tofacitinib	11	744.25	14.78	7.38	26.45	NA	NA	NA
	bDMARD	77	5395.42	14.27	11.26	17.84	NA	NA	NA
	nbDMARD	18	1877.72	9.59	5.68	15.15	NA	NA	NA
Other operations and (major) therapeutic procedures that lead to hospitalization									
No previous b/tsDMARD	Tofacitinib	3	759.01	3.95	0.82	11.55	3.96	0.82	11.58
	bDMARD	18	9134.17	1.97	1.17	3.11	1.98	1.17	3.13
	nbDMARD	5	5384.27	0.93	0.30	2.17	0.92	0.30	2.15
One previous b/tsDMARD	Tofacitinib	2	677.96	2.95	0.36	10.66	3.20	0.39	11.55
	bDMARD	17	3871.80	4.39	2.56	7.03	4.33	2.52	6.94
At least 2 previous b/tsDMARD	Tofacitinib	4	885.55	4.52	1.23	11.57	4.43	1.21	11.35
	bDMARD	9	4442.39	2.03	0.93	3.85	2.03	0.93	3.86
No prior non-tofacitinib JAKi use	Tofacitinib	9	2214.25	4.06	1.86	7.72	4.05	1.85	7.69
	bDMARD	39	15717.48	2.48	1.76	3.39	2.51	1.78	3.43
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	30.51
	bDMARD	5	1730.88	2.89	0.94	6.74	2.91	0.94	6.79
Monotherapy	Tofacitinib	7	1230.76	5.69	2.29	11.72	5.67	2.28	11.69
	bDMARD	18	7593.65	2.37	1.40	3.75	2.37	1.40	3.75
Combination Therapy with a nbDMARD	Tofacitinib	2	1091.75	1.83	0.22	6.62	1.82	0.22	6.57
	bDMARD	26	9854.71	2.64	1.72	3.87	2.68	1.75	3.93
Combination Therapy with MTX	Tofacitinib	2	1036.94	1.93	0.23	6.97	1.94	0.23	6.99
	bDMARD	23	9242.83	2.49	1.58	3.73	2.51	1.59	3.76
Age <65 years	Tofacitinib	4	1575.45	2.54	0.69	6.50	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	24	11944.22	2.01	1.29	2.99	NA	NA	NA
	nbDMARD	2	3485.23	0.57	0.07	2.07	NA	NA	NA
Age ≥65 years	Tofacitinib	5	747.07	6.69	2.17	15.62	NA	NA	NA
	bDMARD	20	5504.14	3.63	2.22	5.61	NA	NA	NA
	nbDMARD	3	1899.05	1.58	0.33	4.62	NA	NA	NA
15. Other serious diagnoses, symptoms, and syndromes									
No previous b/tsDMARD	Tofacitinib	49	681.09	71.94	53.22	95.11	70.07	51.84	92.64
	bDMARD	533	8340.91	63.90	58.59	69.56	64.78	59.40	70.53
	nbDMARD	183	5103.26	35.86	30.85	41.45	35.20	30.28	40.68
One previous b/tsDMARD	Tofacitinib	39	609.46	63.99	45.50	87.48	65.70	46.71	89.82
	bDMARD	263	3429.40	76.69	67.70	86.54	76.34	67.39	86.14
At least 2 previous b/tsDMARD	Tofacitinib	78	813.62	95.87	75.78	119.65	95.87	75.78	119.65
	bDMARD	338	3893.97	86.80	77.79	96.57	86.74	77.58	96.67
No prior non-tofacitinib JAKi use	Tofacitinib	151	2010.04	75.12	63.62	88.11	75.12	63.62	88.11
	bDMARD	999	14191.78	70.39	66.09	74.90	70.62	66.30	75.14
At least one prior non-tofacitinib JAKi use	Tofacitinib	15	94.13	159.36	89.19	262.84	165.26	92.43	272.59
	bDMARD	135	1472.51	91.68	76.87	108.51	91.47	76.69	108.27
Monotherapy	Tofacitinib	89	1122.90	79.26	63.65	97.54	79.26	63.65	97.54
	bDMARD	526	6774.79	77.64	71.15	84.57	78.00	71.48	84.96
Combination Therapy with a nbDMARD	Tofacitinib	77	981.27	78.47	61.93	98.07	78.47	61.93	98.07
	bDMARD	608	8889.50	68.40	63.07	74.05	67.85	62.54	73.49
Combination Therapy with MTX	Tofacitinib	76	927.41	81.95	64.57	102.57	81.95	64.57	102.57
	bDMARD	569	8335.10	68.27	62.77	74.11	67.21	61.76	73.00
Age <65 years	Tofacitinib	89	1446.42	61.53	49.41	75.72	NA	NA	NA
	bDMARD	656	10868.85	60.36	55.83	65.16	NA	NA	NA
	nbDMARD	92	3340.45	27.54	22.20	33.78	NA	NA	NA
Age ≥65 years	Tofacitinib	77	657.75	117.06	92.39	146.31	NA	NA	NA
	bDMARD	478	4795.44	99.68	90.94	109.03	NA	NA	NA
	nbDMARD	91	1762.80	51.62	41.56	63.38	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
16. NMSC									
No previous b/tsDMARD	Tofacitinib	4	761.88	5.25	1.43	13.44	5.01	1.36	12.82
	bDMARD	18	9114.95	1.97	1.17	3.12	2.04	1.21	3.22
	nbDMARD	9	5371.24	1.68	0.77	3.18	1.60	0.73	3.04
One previous b/tsDMARD	Tofacitinib	2	676.08	2.96	0.36	10.69	3.17	0.38	11.45
	bDMARD	14	3883.30	3.61	1.97	6.05	3.56	1.95	5.98
At least 2 previous b/tsDMARD	Tofacitinib	6	886.83	6.77	2.48	14.73	6.43	2.36	14.00
	bDMARD	9	4439.97	2.03	0.93	3.85	2.05	0.94	3.89
No prior non-tofacitinib JAKi use	Tofacitinib	12	2216.53	5.41	2.80	9.46	5.44	2.81	9.51
	bDMARD	36	15709.28	2.29	1.61	3.17	2.33	1.63	3.22
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	35.55
	bDMARD	5	1728.94	2.89	0.94	6.75	2.88	0.94	6.73
Monotherapy	Tofacitinib	4	1244.22	3.21	0.88	8.23	3.21	0.88	8.23
	bDMARD	22	7583.85	2.90	1.82	4.39	2.90	1.82	4.39
Combination Therapy with a nbDMARD	Tofacitinib	8	1080.58	7.40	3.20	14.59	7.70	3.33	15.18
	bDMARD	19	9854.37	1.93	1.16	3.01	2.01	1.21	3.13
Combination Therapy with MTX	Tofacitinib	8	1025.77	7.80	3.37	15.37	8.06	3.48	15.89
	bDMARD	19	9237.93	2.06	1.24	3.21	2.09	1.26	3.26
Age <65 years	Tofacitinib	4	1586.45	2.52	0.69	6.46	NA	NA	NA
	bDMARD	16	11963.71	1.34	0.76	2.17	NA	NA	NA
	nbDMARD	1	3484.75	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	8	738.35	10.84	4.68	21.35	NA	NA	NA
	bDMARD	25	5474.51	4.57	2.96	6.74	NA	NA	NA
	nbDMARD	8	1886.49	4.24	1.83	8.36	NA	NA	NA
No malignancy risk factor	Tofacitinib	5	694.42	7.20	2.34	16.80	6.79	2.20	15.85
	bDMARD	13	5179.11	2.51	1.34	4.29	2.57	1.37	4.39
	nbDMARD	4	1493.49	2.68	0.73	6.86	2.55	0.70	6.54
At least one malignancy risk factor	Tofacitinib	7	1630.38	4.29	1.73	8.85	4.51	1.81	9.29
	bDMARD	28	12225.51	2.29	1.52	3.31	2.31	1.54	3.34
	nbDMARD	5	3872.41	1.29	0.42	3.01	1.23	0.40	2.87
No history of malignancy	Tofacitinib	10	2235.38	4.47	2.15	8.23	4.52	2.16	8.30

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	36	16661.12	2.16	1.51	2.99	2.20	1.54	3.04
	nbDMARD	7	5171.01	1.35	0.54	2.79	1.28	0.51	2.63
With history of malignancy	Tofacitinib	2	89.42	22.37	2.71	80.80	22.62	2.74	81.71
	bDMARD	5	777.09	6.43	2.09	15.02	6.42	2.09	14.99
	nbDMARD	2	200.23	9.99	1.21	36.08	10.00	1.21	36.11
Therapy start before 30-JUNE-2021	Tofacitinib	12	2269.21	5.29	2.73	9.24	5.20	2.68	9.08
	bDMARD	29	13298.67	2.18	1.46	3.13	2.25	1.51	3.23
	nbDMARD	7	4460.81	1.57	0.63	3.23	1.45	0.58	2.98
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	69.90
	bDMARD	12	4139.55	2.90	1.50	5.06	2.89	1.49	5.05
	nbDMARD	2	910.43	2.20	0.27	7.94	2.21	0.27	7.98
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	7	1587.59	4.41	1.77	9.08	4.49	1.81	9.25
	bDMARD	23	9231.19	2.49	1.58	3.74	2.55	1.62	3.83
	nbDMARD	4	3203.63	1.25	0.34	3.20	1.16	0.32	2.97
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	42.79	0.00	0.00	86.22	0.00	0.00	86.02
	bDMARD	5	2994.32	1.67	0.54	3.90	1.67	0.54	3.89
	nbDMARD	1	668.78	1.50	0.04	8.33	1.51	0.04	8.44
17. Malignancies (overall, excluding NMSC)									
No previous b/tsDMARD	Tofacitinib	8	763.46	10.48	4.52	20.65	10.40	4.49	20.50
	bDMARD	82	9080.28	9.03	7.18	11.21	9.12	7.26	11.32
	nbDMARD	30	5357.91	5.60	3.78	7.99	5.51	3.72	7.87
One previous b/tsDMARD	Tofacitinib	6	673.71	8.91	3.27	19.38	9.30	3.41	20.25
	bDMARD	38	3862.78	9.84	6.96	13.50	9.77	6.91	13.40
At least 2 previous b/tsDMARD	Tofacitinib	9	890.05	10.11	4.62	19.20	9.99	4.57	18.96
	bDMARD	40	4412.94	9.06	6.48	12.34	9.09	6.49	12.37
No prior non-tofacitinib JAKi use	Tofacitinib	20	2219.64	9.01	5.50	13.92	9.05	5.53	13.98
	bDMARD	140	15642.15	8.95	7.53	10.56	9.03	7.60	10.66

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	3	107.58	27.89	5.75	81.50	29.89	6.16	87.36
	bDMARD	20	1713.85	11.67	7.13	18.02	11.62	7.10	17.95
Monotherapy	Tofacitinib	13	1239.67	10.49	5.58	17.93	10.45	5.56	17.87
	bDMARD	69	7557.36	9.13	7.10	11.55	9.14	7.11	11.56
Combination Therapy with a nbDMARD	Tofacitinib	10	1087.55	9.19	4.41	16.91	9.30	4.45	17.10
	bDMARD	91	9798.63	9.29	7.48	11.40	9.40	7.57	11.54
Combination Therapy with MTX	Tofacitinib	9	1033.16	8.71	3.98	16.54	8.86	4.05	16.82
	bDMARD	86	9185.05	9.36	7.49	11.56	9.41	7.53	11.63
Age <65 years	Tofacitinib	10	1581.76	6.32	3.03	11.63	NA	NA	NA
	bDMARD	83	11890.04	6.98	5.56	8.65	NA	NA	NA
	nbDMARD	16	3468.07	4.61	2.64	7.49	NA	NA	NA
Age ≥65 years	Tofacitinib	13	745.46	17.44	9.29	29.82	NA	NA	NA
	bDMARD	77	5465.96	14.09	11.12	17.61	NA	NA	NA
	nbDMARD	14	1889.84	7.41	4.05	12.43	NA	NA	NA
No malignancy risk factor	Tofacitinib	6	694.55	8.64	3.17	18.80	8.41	3.09	18.30
	bDMARD	37	5160.06	7.17	5.05	9.88	7.27	5.12	10.02
	nbDMARD	6	1492.48	4.02	1.48	8.75	3.88	1.42	8.45
At least one malignancy risk factor	Tofacitinib	17	1632.67	10.41	6.07	16.67	10.64	6.20	17.04
	bDMARD	123	12162.34	10.11	8.41	12.07	10.19	8.46	12.15
	nbDMARD	24	3860.09	6.22	3.98	9.25	6.03	3.86	8.97
No history of malignancy	Tofacitinib	19	2239.31	8.48	5.11	13.25	8.55	5.14	13.35
	bDMARD	136	16597.34	8.19	6.87	9.69	8.26	6.93	9.77
	nbDMARD	25	5155.55	4.85	3.14	7.16	4.72	3.05	6.97
With history of malignancy	Tofacitinib	4	87.91	45.50	12.40	116.50	42.55	11.59	108.96
	bDMARD	24	758.66	31.63	20.27	47.07	31.79	20.36	47.30
	nbDMARD	5	202.36	24.71	8.02	57.66	25.01	8.12	58.35
Therapy start before 30-JUNE-2021	Tofacitinib	23	2271.64	10.12	6.42	15.19	10.10	6.40	15.16
	bDMARD	116	13238.70	8.76	7.24	10.51	8.88	7.34	10.65
	nbDMARD	21	4449.43	4.72	2.92	7.21	4.54	2.81	6.94
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	75.63

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	44	4117.30	10.69	7.76	14.35	10.65	7.73	14.29
	nbDMARD	9	908.48	9.91	4.53	18.81	10.01	4.58	18.99
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	17	1589.89	10.69	6.23	17.12	10.76	6.26	17.23
	bDMARD	89	9186.34	9.69	7.78	11.92	9.81	7.88	12.07
	nbDMARD	17	3193.46	5.32	3.10	8.52	5.12	2.98	8.20
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	42.79	0.00	0.00	86.22	0.00	0.00	99.67
	bDMARD	34	2976.00	11.42	7.91	15.96	11.39	7.88	15.91
	nbDMARD	7	666.62	10.50	4.22	21.64	10.57	4.25	21.77
18. Lymphoma (overall)									
No previous b/tsDMARD	Tofacitinib	1	769.78	1.30	0.03	7.24	1.30	0.03	7.25
	bDMARD	4	9144.79	0.44	0.12	1.12	0.43	0.12	1.11
	nbDMARD	1	5392.21	0.19	0.00	1.03	0.19	0.00	1.05
One previous b/tsDMARD	Tofacitinib	1	677.31	1.48	0.04	8.23	1.76	0.04	9.83
	bDMARD	0	3898.38	0.00	0.00	0.95	0.00	0.00	0.92
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.16
	bDMARD	2	4454.12	0.45	0.05	1.62	0.45	0.05	1.62
No prior non-tofacitinib JAKi use	Tofacitinib	2	2231.80	0.90	0.11	3.24	0.94	0.11	3.40
	bDMARD	6	15760.61	0.38	0.14	0.83	0.38	0.14	0.83
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	1	1248.71	0.80	0.02	4.46	0.80	0.02	4.48
	bDMARD	1	7618.46	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	1	1091.36	0.92	0.02	5.11	1.02	0.03	5.66
	bDMARD	5	9878.82	0.51	0.16	1.18	0.49	0.16	1.15
Combination Therapy with MTX	Tofacitinib	1	1036.55	0.96	0.02	5.38	1.11	0.03	6.19
	bDMARD	4	9263.34	0.43	0.12	1.11	0.43	0.12	1.09
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	4	11976.07	0.33	0.09	0.86	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	1	3488.45	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	2	750.06	2.67	0.32	9.63	NA	NA	NA
	bDMARD	2	5521.21	0.36	0.04	1.31	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	6.69
	bDMARD	2	5189.12	0.39	0.05	1.39	0.37	0.05	1.35
	nbDMARD	0	1505.20	0.00	0.00	2.45	0.00	0.00	2.48
At least one malignancy risk factor	Tofacitinib	2	1638.84	1.22	0.15	4.41	1.32	0.16	4.78
	bDMARD	4	12274.56	0.33	0.09	0.83	0.32	0.09	0.83
	nbDMARD	1	3881.67	0.26	0.01	1.44	0.25	0.01	1.41
No history of malignancy	Tofacitinib	2	2249.93	0.89	0.11	3.21	0.93	0.11	3.35
	bDMARD	5	16716.33	0.30	0.10	0.70	0.30	0.10	0.70
	nbDMARD	1	5187.83	0.19	0.00	1.07	0.19	0.00	1.04
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	123.65
	bDMARD	1	780.95	1.28	0.03	7.13	1.17	0.03	6.53
	nbDMARD	0	204.38	0.00	0.00	18.05	0.00	0.00	19.18
Therapy start before 30-JUNE-2021	Tofacitinib	2	2284.48	0.88	0.11	3.16	0.91	0.11	3.29
	bDMARD	6	13345.33	0.45	0.16	0.98	0.45	0.16	0.98
	nbDMARD	1	4476.62	0.22	0.01	1.24	0.22	0.01	1.22
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA
Non-Hodgkin lymphoma									
No previous b/tsDMARD	Tofacitinib	1	769.78	1.30	0.03	7.24	1.10	0.03	6.14
	bDMARD	0	9149.44	0.00	0.00	0.40	0.00	0.00	0.43
	nbDMARD	0	5393.07	0.00	0.00	0.68	0.00	0.00	0.63
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.38	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	NA	NA	NA
	bDMARD	0	4459.48	0.00	0.00	0.83	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
No prior non-tofacitinib JAKi use	Tofacitinib	1	2233.07	0.45	0.01	2.50	0.45	0.01	2.51
	bDMARD	0	15770.61	0.00	0.00	0.23	0.00	0.00	0.24
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	1	1248.71	0.80	0.02	4.46	0.80	0.02	4.45
	bDMARD	0	7622.87	0.00	0.00	0.48	0.00	0.00	0.48
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	NA	NA	NA
	bDMARD	0	9884.42	0.00	0.00	0.37	NA	NA	NA
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	NA	NA	NA
	bDMARD	0	9267.99	0.00	0.00	0.40	NA	NA	NA
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	0	11984.75	0.00	0.00	0.31	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	1	751.33	1.33	0.03	7.42	NA	NA	NA
	bDMARD	0	5522.55	0.00	0.00	0.67	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	NA	NA	NA
	bDMARD	0	5197.21	0.00	0.00	0.71	NA	NA	NA
	nbDMARD	0	1505.20	0.00	0.00	2.45	NA	NA	NA
At least one malignancy risk factor	Tofacitinib	1	1640.11	0.61	0.02	3.40	0.68	0.02	3.81
	bDMARD	0	12276.49	0.00	0.00	0.30	0.00	0.00	0.30
	nbDMARD	0	3882.53	0.00	0.00	0.95	0.00	0.00	0.91
No history of malignancy	Tofacitinib	1	2251.20	0.44	0.01	2.47	0.45	0.01	2.51
	bDMARD	0	16721.92	0.00	0.00	0.22	0.00	0.00	0.22
	nbDMARD	0	5188.69	0.00	0.00	0.71	0.00	0.00	0.67
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	NA	NA	NA
	bDMARD	0	785.38	0.00	0.00	4.70	NA	NA	NA
	nbDMARD	0	204.38	0.00	0.00	18.05	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	1	2285.75	0.44	0.01	2.44	0.42	0.01	2.36
	bDMARD	0	13355.34	0.00	0.00	0.28	0.00	0.00	0.29

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	0	4477.48	0.00	0.00	0.82	0.00	0.00	0.76
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA
Hodgkin lymphoma									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.99
	bDMARD	3	9145.11	0.33	0.07	0.96	0.32	0.07	0.94
	nbDMARD	1	5392.21	0.19	0.00	1.03	0.19	0.00	1.07
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.38	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	3.88
	bDMARD	1	4455.07	0.22	0.01	1.25	0.23	0.01	1.27
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.76
	bDMARD	4	15761.87	0.25	0.07	0.65	0.25	0.07	0.64
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.98
	bDMARD	1	7618.46	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.69
	bDMARD	3	9880.09	0.30	0.06	0.89	0.29	0.06	0.84
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	4.09
	bDMARD	3	9263.65	0.32	0.07	0.95	0.32	0.07	0.93
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	3	11976.39	0.25	0.05	0.73	NA	NA	NA
	nbDMARD	1	3488.45	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	1	5522.16	0.18	0.00	1.01	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	6.69
	bDMARD	2	5189.12	0.39	0.05	1.39	0.37	0.05	1.35

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	0	1505.20	0.00	0.00	2.45	0.00	0.00	2.48
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	0.00	0.00	2.38
	bDMARD	2	12275.83	0.16	0.02	0.59	0.16	0.02	0.59
	nbDMARD	1	3881.67	0.26	0.01	1.44	0.25	0.01	1.41
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	0.00	0.00	1.72
	bDMARD	3	16716.85	0.18	0.04	0.52	0.18	0.04	0.52
	nbDMARD	1	5187.83	0.19	0.00	1.07	0.19	0.00	1.05
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	123.57
	bDMARD	1	781.70	1.28	0.03	7.13	1.17	0.03	6.53
	nbDMARD	0	204.38	0.00	0.00	18.05	0.00	0.00	19.17
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	0.00	0.00	1.73
	bDMARD	4	13346.60	0.30	0.08	0.77	0.30	0.08	0.76
	nbDMARD	1	4476.62	0.22	0.01	1.24	0.22	0.01	1.25
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA
Chronic lymphatic leukemia									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.94
	bDMARD	1	9149.13	0.11	0.00	0.61	0.10	0.00	0.58
	nbDMARD	0	5393.07	0.00	0.00	0.68	0.00	0.00	0.74
One previous b/tsDMARD	Tofacitinib	1	677.31	1.48	0.04	8.23	1.76	0.04	9.83
	bDMARD	0	3898.38	0.00	0.00	0.95	0.00	0.00	0.92
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.47
	bDMARD	1	4458.52	0.22	0.01	1.25	0.22	0.01	1.23
No prior non-tofacitinib JAKi use	Tofacitinib	1	2231.80	0.45	0.01	2.50	0.47	0.01	2.60
	bDMARD	2	15769.35	0.13	0.02	0.46	0.13	0.02	0.46
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	NA	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	0	7622.87	0.00	0.00	0.48	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	1	1091.36	0.92	0.02	5.11	1.04	0.03	5.79
	bDMARD	2	9883.16	0.20	0.02	0.73	0.21	0.02	0.74
Combination Therapy with MTX	Tofacitinib	1	1036.55	0.96	0.02	5.38	1.11	0.03	6.20
	bDMARD	1	9267.67	0.11	0.00	0.60	0.11	0.00	0.59
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	1	11984.44	0.08	0.00	0.46	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	1	750.06	1.33	0.03	7.43	NA	NA	NA
	bDMARD	1	5521.59	0.18	0.00	1.01	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	NA	NA	NA
	bDMARD	0	5197.21	0.00	0.00	0.71	NA	NA	NA
	nbDMARD	0	1505.20	0.00	0.00	2.45	NA	NA	NA
At least one malignancy risk factor	Tofacitinib	1	1638.84	0.61	0.02	3.40	0.67	0.02	3.74
	bDMARD	2	12275.22	0.16	0.02	0.59	0.16	0.02	0.58
	nbDMARD	0	3882.53	0.00	0.00	0.95	0.00	0.00	0.94
No history of malignancy	Tofacitinib	1	2249.93	0.44	0.01	2.48	0.47	0.01	2.59
	bDMARD	2	16721.40	0.12	0.01	0.43	0.12	0.01	0.43
	nbDMARD	0	5188.69	0.00	0.00	0.71	0.00	0.00	0.69
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	NA	NA	NA
	bDMARD	0	784.63	0.00	0.00	4.70	NA	NA	NA
	nbDMARD	0	204.38	0.00	0.00	18.05	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	1	2284.48	0.44	0.01	2.44	0.45	0.01	2.50
	bDMARD	2	13354.07	0.15	0.02	0.54	0.15	0.02	0.54
	nbDMARD	0	4477.48	0.00	0.00	0.82	0.00	0.00	0.80
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
19. Lung Cancer									
No previous b/tsDMARD	Tofacitinib	1	769.48	1.30	0.03	7.24	1.32	0.03	7.38
	bDMARD	12	9147.27	1.31	0.68	2.29	1.34	0.69	2.33
	nbDMARD	5	5389.18	0.93	0.30	2.17	0.90	0.29	2.10
One previous b/tsDMARD	Tofacitinib	1	677.75	1.48	0.04	8.22	1.61	0.04	8.97
	bDMARD	7	3897.08	1.80	0.72	3.70	1.77	0.71	3.65
At least 2 previous b/tsDMARD	Tofacitinib	4	891.29	4.49	1.22	11.49	4.10	1.12	10.49
	bDMARD	4	4458.73	0.90	0.24	2.30	0.91	0.25	2.34
No prior non-tofacitinib JAKi use	Tofacitinib	6	2230.25	2.69	0.99	5.86	2.75	1.01	5.98
	bDMARD	21	15766.67	1.33	0.82	2.04	1.35	0.84	2.07
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	48.47
	bDMARD	2	1736.42	1.15	0.14	4.16	1.13	0.14	4.09
Monotherapy	Tofacitinib	2	1247.70	1.60	0.19	5.79	1.60	0.19	5.77
	bDMARD	4	7622.22	0.52	0.14	1.34	0.53	0.14	1.34
Combination Therapy with a nbDMARD	Tofacitinib	4	1090.81	3.67	1.00	9.39	3.78	1.03	9.68
	bDMARD	19	9880.87	1.92	1.16	3.00	1.98	1.19	3.09
Combination Therapy with MTX	Tofacitinib	3	1036.42	2.89	0.60	8.46	3.05	0.63	8.91
	bDMARD	19	9264.43	2.05	1.23	3.20	2.09	1.26	3.26
Age <65 years	Tofacitinib	3	1588.69	1.89	0.39	5.52	NA	NA	NA
	bDMARD	9	11982.60	0.75	0.34	1.43	NA	NA	NA
	nbDMARD	1	3488.98	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	3	749.82	4.00	0.83	11.69	NA	NA	NA
	bDMARD	14	5520.48	2.54	1.39	4.25	NA	NA	NA
	nbDMARD	4	1900.20	2.11	0.57	5.39	NA	NA	NA
No malignancy risk factor	Tofacitinib	1	700.39	1.43	0.04	7.96	1.27	0.03	7.06
	bDMARD	1	5197.07	0.19	0.00	1.07	0.20	0.01	1.13
	nbDMARD	0	1505.20	0.00	0.00	2.45	0.00	0.00	2.21
At least one malignancy risk factor	Tofacitinib	5	1638.12	3.05	0.99	7.12	3.19	1.04	7.45
	bDMARD	22	12272.42	1.79	1.12	2.71	1.82	1.14	2.75
	nbDMARD	5	3878.64	1.29	0.42	3.01	1.21	0.39	2.83
No history of malignancy	Tofacitinib	5	2249.21	2.22	0.72	5.19	2.29	0.74	5.33

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	20	16718.15	1.20	0.73	1.85	1.22	0.74	1.88
	nbDMARD	5	5184.80	0.96	0.31	2.25	0.90	0.29	2.10
With history of malignancy	Tofacitinib	1	89.30	11.20	0.28	62.39	10.05	0.25	56.02
	bDMARD	3	784.94	3.82	0.79	11.17	3.86	0.80	11.27
	nbDMARD	0	204.38	0.00	0.00	18.05	0.00	0.00	18.30
Therapy start before 30-JUNE-2021	Tofacitinib	6	2282.93	2.63	0.96	5.72	2.67	0.98	5.81
	bDMARD	16	13352.90	1.20	0.68	1.95	1.23	0.70	2.00
	nbDMARD	2	4476.20	0.45	0.05	1.61	0.41	0.05	1.49
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	84.37
	bDMARD	7	4150.19	1.69	0.68	3.48	1.67	0.67	3.44
	nbDMARD	3	912.98	3.29	0.68	9.60	3.41	0.70	9.95
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	5	1595.33	3.13	1.02	7.31	3.19	1.04	7.45
	bDMARD	15	9273.03	1.62	0.91	2.67	1.65	0.92	2.72
	nbDMARD	2	3209.74	0.62	0.08	2.25	0.58	0.07	2.11
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	42.79	0.00	0.00	86.22	0.00	0.00	124.39
	bDMARD	7	2999.40	2.33	0.94	4.81	2.32	0.93	4.77
	nbDMARD	3	668.90	4.48	0.92	13.11	4.54	0.94	13.28
20. All-cause Mortality									
No previous b/tsDMARD	Tofacitinib	5	769.78	6.50	2.11	15.16	6.18	2.01	14.42
	bDMARD	56	9149.29	6.12	4.62	7.95	6.38	4.82	8.28
	nbDMARD	15	5393.07	2.78	1.56	4.59	2.62	1.47	4.33
One previous b/tsDMARD	Tofacitinib	2	678.58	2.95	0.36	10.65	3.39	0.41	12.26
	bDMARD	23	3898.38	5.90	3.74	8.85	5.77	3.66	8.66
At least 2 previous b/tsDMARD	Tofacitinib	8	892.97	8.96	3.87	17.65	8.89	3.84	17.53
	bDMARD	23	4459.48	5.16	3.27	7.74	5.16	3.27	7.75
No prior non-tofacitinib JAKi use	Tofacitinib	14	2233.07	6.27	3.43	10.52	6.33	3.46	10.63
	bDMARD	95	15770.46	6.02	4.87	7.36	6.16	4.99	7.53

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	108.27	9.24	0.23	51.46	11.58	0.29	64.50
	bDMARD	7	1736.68	4.03	1.62	8.30	3.98	1.60	8.20
Monotherapy	Tofacitinib	8	1248.71	6.41	2.77	12.62	6.39	2.76	12.59
	bDMARD	52	7622.72	6.82	5.09	8.95	6.82	5.10	8.95
Combination Therapy with a nbDMARD	Tofacitinib	7	1092.62	6.41	2.58	13.20	6.74	2.71	13.88
	bDMARD	50	9884.42	5.06	3.75	6.67	5.32	3.95	7.01
Combination Therapy with MTX	Tofacitinib	7	1037.82	6.74	2.71	13.90	7.15	2.87	14.72
	bDMARD	48	9267.99	5.18	3.82	6.87	5.26	3.88	6.98
Age <65 years	Tofacitinib	3	1590.00	1.89	0.39	5.51	NA	NA	NA
	bDMARD	21	11984.60	1.75	1.08	2.68	NA	NA	NA
	nbDMARD	1	3489.31	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	12	751.33	15.97	8.25	27.90	NA	NA	NA
	bDMARD	81	5522.55	14.67	11.65	18.23	NA	NA	NA
	nbDMARD	14	1903.76	7.35	4.02	12.34	NA	NA	NA
21. Leukaemia (excl. B-CLL)									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	5.16
	bDMARD	1	9147.95	0.11	0.00	0.61	0.11	0.00	0.64
	nbDMARD	0	5393.07	0.00	0.00	0.68	0.00	0.00	0.63
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.46
	bDMARD	1	3898.25	0.26	0.01	1.43	0.25	0.01	1.39
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.47
	bDMARD	1	4459.35	0.22	0.01	1.25	0.22	0.01	1.23
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.66
	bDMARD	3	15768.86	0.19	0.04	0.56	0.20	0.04	0.57
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	NA	NA	NA
	bDMARD	0	7622.87	0.00	0.00	0.48	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.63

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	3	9882.67	0.30	0.06	0.89	0.33	0.07	0.95
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.82
	bDMARD	3	9266.24	0.32	0.07	0.95	0.33	0.07	0.96
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	0	11984.75	0.00	0.00	0.31	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	3	5520.79	0.54	0.11	1.59	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	4.67
	bDMARD	1	5195.72	0.19	0.00	1.07	0.20	0.01	1.13
	nbDMARD	0	1505.20	0.00	0.00	2.45	0.00	0.00	2.20
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	0.00	0.00	2.52
	bDMARD	2	12276.23	0.16	0.02	0.59	0.16	0.02	0.59
	nbDMARD	0	3882.53	0.00	0.00	0.95	0.00	0.00	0.91
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	0.00	0.00	1.67
	bDMARD	2	16720.30	0.12	0.01	0.43	0.12	0.02	0.45
	nbDMARD	0	5188.69	0.00	0.00	0.71	0.00	0.00	0.63
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	36.42
	bDMARD	1	785.25	1.27	0.03	7.10	1.30	0.03	7.25
	nbDMARD	0	204.38	0.00	0.00	18.05	0.00	0.00	17.55
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	0.00	0.00	1.56
	bDMARD	3	13353.59	0.22	0.05	0.66	0.24	0.05	0.69
	nbDMARD	0	4477.48	0.00	0.00	0.82	0.00	0.00	0.72
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA
22. Other haematopoietic neoplasms (malignant and benign)									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.25

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	3	9147.44	0.33	0.07	0.96	0.34	0.07	1.00
	nbDMARD	1	5393.07	0.19	0.00	1.03	0.18	0.00	0.99
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.38	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	NA	NA	NA
	bDMARD	0	4459.48	0.00	0.00	0.83	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.71
	bDMARD	3	15768.61	0.19	0.04	0.56	0.19	0.04	0.56
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.95
	bDMARD	2	7621.11	0.26	0.03	0.95	0.26	0.03	0.95
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.83
	bDMARD	1	9884.18	0.10	0.00	0.56	0.10	0.00	0.56
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.92
	bDMARD	1	9267.74	0.11	0.00	0.60	0.11	0.00	0.60
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	0	11984.75	0.00	0.00	0.31	NA	NA	NA
	nbDMARD	1	3489.31	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	3	5520.54	0.54	0.11	1.59	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	4.65
	bDMARD	2	5195.45	0.38	0.05	1.39	0.40	0.05	1.46
	nbDMARD	0	1505.20	0.00	0.00	2.45	0.00	0.00	2.22
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	0.00	0.00	2.44
	bDMARD	1	12276.24	0.08	0.00	0.45	0.08	0.00	0.45
	nbDMARD	1	3882.53	0.26	0.01	1.44	0.26	0.01	1.45
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	0.00	0.00	1.70
	bDMARD	3	16719.91	0.18	0.04	0.52	0.18	0.04	0.53
	nbDMARD	1	5188.69	0.19	0.00	1.07	0.19	0.00	1.03

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	NA	NA	NA
	bDMARD	0	785.38	0.00	0.00	4.70	NA	NA	NA
	nbDMARD	0	204.38	0.00	0.00	18.05	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	0.00	0.00	1.65
	bDMARD	2	13353.56	0.15	0.02	0.54	0.15	0.02	0.54
	nbDMARD	1	4477.48	0.22	0.01	1.24	0.22	0.01	1.21
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	81.57
	bDMARD	1	4151.73	0.24	0.01	1.34	0.24	0.01	1.34
	nbDMARD	0	915.59	0.00	0.00	4.03	0.00	0.00	4.02
23. Solid malignancies (overall)									
No previous b/tsDMARD	Tofacitinib	6	763.71	7.86	2.88	17.10	7.91	2.90	17.21
	bDMARD	66	9094.09	7.26	5.61	9.23	7.32	5.66	9.31
	nbDMARD	29	5358.82	5.41	3.62	7.77	5.33	3.57	7.66
One previous b/tsDMARD	Tofacitinib	5	674.98	7.41	2.41	17.29	7.68	2.49	17.92
	bDMARD	32	3865.08	8.28	5.66	11.69	8.23	5.63	11.62
At least 2 previous b/tsDMARD	Tofacitinib	9	890.05	10.11	4.62	19.20	9.94	4.55	18.87
	bDMARD	33	4424.79	7.46	5.13	10.47	7.48	5.15	10.51
No prior non-tofacitinib JAKi use	Tofacitinib	17	2221.16	7.65	4.46	12.25	7.67	4.47	12.28
	bDMARD	115	15665.90	7.34	6.06	8.81	7.41	6.12	8.90
At least one prior non-tofacitinib JAKi use	Tofacitinib	3	107.58	27.89	5.75	81.50	31.03	6.40	90.67
	bDMARD	16	1718.07	9.31	5.32	15.12	9.25	5.29	15.03
Monotherapy	Tofacitinib	12	1239.67	9.68	5.00	16.91	9.64	4.98	16.84
	bDMARD	55	7571.05	7.26	5.47	9.46	7.27	5.48	9.46
Combination Therapy with a nbDMARD	Tofacitinib	8	1089.07	7.35	3.17	14.47	7.38	3.18	14.54
	bDMARD	76	9812.91	7.74	6.10	9.69	7.83	6.17	9.80
Combination Therapy with MTX	Tofacitinib	7	1034.68	6.77	2.72	13.94	6.85	2.75	14.10
	bDMARD	72	9198.36	7.83	6.12	9.86	7.88	6.16	9.92
Age <65 years	Tofacitinib	10	1581.76	6.32	3.03	11.63	NA	NA	NA
	bDMARD	71	11909.68	5.96	4.66	7.52	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	15	3468.07	4.33	2.42	7.13	NA	NA	NA
Age ≥65 years	Tofacitinib	10	746.98	13.39	6.42	24.62	NA	NA	NA
	bDMARD	60	5474.28	10.96	8.36	14.11	NA	NA	NA
	nbDMARD	14	1890.75	7.40	4.05	12.42	NA	NA	NA
No malignancy risk factor	Tofacitinib	6	694.55	8.64	3.17	18.80	8.40	3.08	18.28
	bDMARD	31	5171.03	5.99	4.07	8.51	6.08	4.13	8.62
	nbDMARD	6	1493.40	4.02	1.47	8.74	3.89	1.43	8.47
At least one malignancy risk factor	Tofacitinib	14	1634.19	8.57	4.68	14.37	8.70	4.75	14.59
	bDMARD	100	12179.34	8.21	6.68	9.99	8.28	6.74	10.07
	nbDMARD	23	3860.09	5.96	3.78	8.94	5.76	3.65	8.65
No history of malignancy	Tofacitinib	17	2240.58	7.59	4.42	12.15	7.63	4.44	12.22
	bDMARD	115	16613.18	6.92	5.71	8.31	6.97	5.76	8.37
	nbDMARD	24	5155.82	4.65	2.98	6.93	4.53	2.90	6.75
With history of malignancy	Tofacitinib	3	88.16	34.03	7.02	99.45	30.97	6.39	90.51
	bDMARD	16	770.78	20.76	11.87	33.71	20.92	11.95	33.98
	nbDMARD	5	203.00	24.63	8.00	57.48	24.94	8.10	58.20
Therapy start before 30-JUNE-2021	Tofacitinib	20	2273.15	8.80	5.37	13.59	8.76	5.35	13.53
	bDMARD	95	13260.09	7.16	5.80	8.76	7.28	5.89	8.90
	nbDMARD	20	4450.35	4.49	2.75	6.94	4.31	2.63	6.65
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	74.14
	bDMARD	36	4123.87	8.73	6.11	12.09	8.70	6.09	12.04
	nbDMARD	9	908.48	9.91	4.53	18.81	10.01	4.58	19.01
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	14	1591.40	8.80	4.81	14.76	8.82	4.82	14.79
	bDMARD	72	9197.46	7.83	6.13	9.86	7.95	6.22	10.01
	nbDMARD	16	3193.46	5.01	2.86	8.14	4.79	2.74	7.79
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	42.79	0.00	0.00	86.22	0.00	0.00	97.54
	bDMARD	28	2981.88	9.39	6.24	13.57	9.36	6.22	13.52
	nbDMARD	7	666.62	10.50	4.22	21.64	10.59	4.26	21.81

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
24. Glioblastoma									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	NA	NA	NA
	bDMARD	0	9149.44	0.00	0.00	0.40	NA	NA	NA
	nbDMARD	0	5393.07	0.00	0.00	0.68	NA	NA	NA
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	NA	NA	NA
	bDMARD	0	3898.38	0.00	0.00	0.95	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	NA	NA	NA
	bDMARD	0	4459.48	0.00	0.00	0.83	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	NA	NA	NA
	bDMARD	0	15770.61	0.00	0.00	0.23	NA	NA	NA
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	NA	NA	NA
	bDMARD	0	1736.68	0.00	0.00	2.12	NA	NA	NA
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	NA	NA	NA
	bDMARD	0	7622.87	0.00	0.00	0.48	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	NA	NA	NA
	bDMARD	0	9884.42	0.00	0.00	0.37	NA	NA	NA
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	NA	NA	NA
	bDMARD	0	9267.99	0.00	0.00	0.40	NA	NA	NA
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	0	11984.75	0.00	0.00	0.31	NA	NA	NA
	nbDMARD	0	3489.31	0.00	0.00	1.06	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	0	5522.55	0.00	0.00	0.67	NA	NA	NA
	nbDMARD	0	1903.76	0.00	0.00	1.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	NA	NA	NA
	bDMARD	0	5197.21	0.00	0.00	0.71	NA	NA	NA
	nbDMARD	0	1505.20	0.00	0.00	2.45	NA	NA	NA
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	NA	NA	NA
	bDMARD	0	12276.49	0.00	0.00	0.30	NA	NA	NA
	nbDMARD	0	3882.53	0.00	0.00	0.95	NA	NA	NA

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	NA	NA	NA
	bDMARD	0	16721.92	0.00	0.00	0.22	NA	NA	NA
	nbDMARD	0	5188.69	0.00	0.00	0.71	NA	NA	NA
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	NA	NA	NA
	bDMARD	0	785.38	0.00	0.00	4.70	NA	NA	NA
	nbDMARD	0	204.38	0.00	0.00	18.05	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	NA	NA	NA
	bDMARD	0	13355.34	0.00	0.00	0.28	NA	NA	NA
	nbDMARD	0	4477.48	0.00	0.00	0.82	NA	NA	NA
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	NA	NA	NA
	bDMARD	0	4151.95	0.00	0.00	0.89	NA	NA	NA
	nbDMARD	0	915.59	0.00	0.00	4.03	NA	NA	NA
25. Benign neoplasms									
No previous b/tsDMARD	Tofacitinib	1	769.28	1.30	0.03	7.24	1.25	0.03	6.99
	bDMARD	28	9104.28	3.08	2.04	4.44	3.14	2.09	4.54
	nbDMARD	8	5376.18	1.49	0.64	2.93	1.45	0.62	2.85
One previous b/tsDMARD	Tofacitinib	2	677.72	2.95	0.36	10.66	2.96	0.36	10.69
	bDMARD	12	3873.37	3.10	1.60	5.41	3.10	1.60	5.41
At least 2 previous b/tsDMARD	Tofacitinib	7	883.16	7.93	3.19	16.33	7.53	3.03	15.51
	bDMARD	15	4439.59	3.38	1.89	5.57	3.41	1.91	5.63
No prior non-tofacitinib JAKi use	Tofacitinib	9	2221.97	4.05	1.85	7.69	4.00	1.83	7.59
	bDMARD	47	15694.42	2.99	2.20	3.98	3.03	2.22	4.02
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	108.19	9.24	0.23	51.50	11.42	0.29	63.63
	bDMARD	8	1722.82	4.64	2.00	9.15	4.59	1.98	9.04
Monotherapy	Tofacitinib	8	1239.96	6.45	2.79	12.71	6.48	2.80	12.76
	bDMARD	25	7578.41	3.30	2.13	4.87	3.30	2.13	4.87
Combination Therapy with a nbDMARD	Tofacitinib	2	1090.20	1.83	0.22	6.63	1.82	0.22	6.56
	bDMARD	30	9838.82	3.05	2.06	4.35	3.14	2.12	4.49
Combination Therapy with MTX	Tofacitinib	2	1035.39	1.93	0.23	6.98	1.90	0.23	6.86

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	29	9222.57	3.14	2.11	4.52	3.18	2.13	4.57
Age <65 years	Tofacitinib	3	1588.94	1.89	0.39	5.52	NA	NA	NA
	bDMARD	29	11928.79	2.43	1.63	3.49	NA	NA	NA
	nbDMARD	3	3481.81	0.86	0.18	2.52	NA	NA	NA
Age ≥65 years	Tofacitinib	7	741.21	9.44	3.80	19.46	NA	NA	NA
	bDMARD	26	5488.44	4.74	3.09	6.94	NA	NA	NA
	nbDMARD	5	1894.37	2.64	0.86	6.16	NA	NA	NA
No malignancy risk factor	Tofacitinib	2	696.11	2.87	0.35	10.38	2.75	0.33	9.93
	bDMARD	23	5160.44	4.46	2.83	6.69	4.51	2.86	6.77
	nbDMARD	2	1499.62	1.33	0.16	4.82	1.31	0.16	4.72
At least one malignancy risk factor	Tofacitinib	8	1634.05	4.90	2.11	9.65	4.97	2.14	9.79
	bDMARD	32	12223.19	2.62	1.79	3.70	2.64	1.80	3.72
	nbDMARD	6	3871.22	1.55	0.57	3.37	1.50	0.55	3.27
No history of malignancy	Tofacitinib	10	2240.02	4.46	2.14	8.21	4.42	2.12	8.14
	bDMARD	52	16637.33	3.13	2.33	4.10	3.16	2.36	4.14
	nbDMARD	7	5172.01	1.35	0.54	2.79	1.32	0.53	2.71
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	36.44
	bDMARD	3	779.90	3.85	0.79	11.24	3.91	0.81	11.43
	nbDMARD	1	204.16	4.90	0.12	27.29	4.85	0.12	27.04
Therapy start before 30-JUNE-2021	Tofacitinib	10	2274.57	4.40	2.11	8.09	4.30	2.06	7.92
	bDMARD	44	13275.45	3.31	2.41	4.45	3.36	2.44	4.51
	nbDMARD	6	4460.96	1.35	0.49	2.93	1.30	0.48	2.84
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	76.85
	bDMARD	11	4141.78	2.66	1.33	4.75	2.63	1.31	4.71
	nbDMARD	2	915.22	2.19	0.26	7.89	2.25	0.27	8.14
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	8	1591.26	5.03	2.17	9.91	5.03	2.17	9.91
	bDMARD	26	9229.51	2.82	1.84	4.13	2.86	1.86	4.18
	nbDMARD	4	3200.08	1.25	0.34	3.20	1.20	0.33	3.08

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	42.79	0.00	0.00	86.22	0.00	0.00	99.92
	bDMARD	6	2993.68	2.00	0.74	4.36	1.99	0.73	4.34
	nbDMARD	2	671.14	2.98	0.36	10.76	3.03	0.37	10.96
26. Unspecified neoplasms and precanceroses									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	4.37
	bDMARD	13	9140.38	1.42	0.76	2.43	1.48	0.79	2.54
	nbDMARD	4	5383.21	0.74	0.20	1.90	0.70	0.19	1.80
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.20
	bDMARD	4	3896.08	1.03	0.28	2.63	1.03	0.28	2.65
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.16
	bDMARD	2	4455.54	0.45	0.05	1.62	0.45	0.05	1.62
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.65
	bDMARD	17	15757.53	1.08	0.63	1.73	1.09	0.64	1.75
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	31.00
	bDMARD	2	1734.47	1.15	0.14	4.17	1.16	0.14	4.19
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.95
	bDMARD	9	7617.89	1.18	0.54	2.24	1.18	0.54	2.24
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.44
	bDMARD	10	9874.11	1.01	0.49	1.86	1.06	0.51	1.95
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.61
	bDMARD	9	9260.63	0.97	0.44	1.84	0.98	0.45	1.87
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	7	11973.22	0.58	0.24	1.20	NA	NA	NA
	nbDMARD	1	3488.12	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	12	5518.78	2.17	1.12	3.80	NA	NA	NA
	nbDMARD	3	1895.08	1.58	0.33	4.63	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	4.64
	bDMARD	2	5196.08	0.38	0.05	1.39	0.40	0.05	1.46

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
	nbDMARD	2	1497.06	1.34	0.16	4.83	1.22	0.15	4.40
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	0.00	0.00	2.32
	bDMARD	17	12262.32	1.39	0.81	2.22	1.40	0.81	2.24
	nbDMARD	2	3880.81	0.52	0.06	1.86	0.50	0.06	1.80
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	0.00	0.00	1.64
	bDMARD	16	16710.66	0.96	0.55	1.55	0.97	0.56	1.58
	nbDMARD	4	5178.83	0.77	0.21	1.98	0.73	0.20	1.88
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	39.22
	bDMARD	3	781.34	3.84	0.79	11.22	3.89	0.80	11.37
	nbDMARD	0	204.38	0.00	0.00	18.05	0.00	0.00	17.49
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	0.00	0.00	1.58
	bDMARD	16	13342.69	1.20	0.69	1.95	1.22	0.70	1.98
	nbDMARD	4	4468.73	0.90	0.24	2.29	0.86	0.23	2.20
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	92.93
	bDMARD	3	4149.31	0.72	0.15	2.11	0.72	0.15	2.10
	nbDMARD	0	914.48	0.00	0.00	4.03	0.00	0.00	4.11
27. Metastases, cancer related morbidities and associated syndroms									
No previous b/tsDMARD	Tofacitinib	0	769.78	0.00	0.00	4.79	0.00	0.00	5.10
	bDMARD	2	9149.18	0.22	0.03	0.79	0.22	0.03	0.79
	nbDMARD	3	5392.36	0.56	0.11	1.63	0.55	0.11	1.61
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	6.48
	bDMARD	1	3898.23	0.26	0.01	1.43	0.25	0.01	1.39
At least 2 previous b/tsDMARD	Tofacitinib	0	892.97	0.00	0.00	4.13	0.00	0.00	4.47
	bDMARD	3	4457.79	0.67	0.14	1.97	0.66	0.14	1.94
No prior non-tofacitinib JAKi use	Tofacitinib	0	2233.07	0.00	0.00	1.65	0.00	0.00	1.66
	bDMARD	5	15769.22	0.32	0.10	0.74	0.32	0.10	0.75
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	33.58
	bDMARD	1	1735.98	0.58	0.01	3.21	0.58	0.01	3.21

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
Monotherapy	Tofacitinib	0	1248.71	0.00	0.00	2.95	0.00	0.00	2.95
	bDMARD	1	7621.90	0.13	0.00	0.73	0.13	0.00	0.73
Combination Therapy with a nbDMARD	Tofacitinib	0	1092.62	0.00	0.00	3.38	0.00	0.00	3.41
	bDMARD	5	9883.30	0.51	0.16	1.18	0.52	0.17	1.21
Combination Therapy with MTX	Tofacitinib	0	1037.82	0.00	0.00	3.55	0.00	0.00	3.64
	bDMARD	5	9266.86	0.54	0.18	1.26	0.54	0.18	1.27
Age <65 years	Tofacitinib	0	1590.00	0.00	0.00	2.32	NA	NA	NA
	bDMARD	2	11984.03	0.17	0.02	0.60	NA	NA	NA
	nbDMARD	1	3489.27	0.29	0.01	1.60	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	4	5521.17	0.72	0.20	1.85	NA	NA	NA
	nbDMARD	2	1903.09	1.05	0.13	3.80	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	701.22	0.00	0.00	5.26	0.00	0.00	4.92
	bDMARD	3	5196.10	0.58	0.12	1.69	0.59	0.12	1.71
	nbDMARD	2	1504.53	1.33	0.16	4.80	1.30	0.16	4.69
At least one malignancy risk factor	Tofacitinib	0	1640.11	0.00	0.00	2.25	0.00	0.00	2.45
	bDMARD	3	12275.50	0.24	0.05	0.71	0.25	0.05	0.72
	nbDMARD	1	3882.49	0.26	0.01	1.44	0.24	0.01	1.36
No history of malignancy	Tofacitinib	0	2251.20	0.00	0.00	1.64	0.00	0.00	1.65
	bDMARD	3	16720.95	0.18	0.04	0.52	0.18	0.04	0.53
	nbDMARD	2	5188.62	0.39	0.05	1.39	0.38	0.05	1.36
With history of malignancy	Tofacitinib	0	90.13	0.00	0.00	40.93	0.00	0.00	36.67
	bDMARD	3	784.25	3.83	0.79	11.18	3.86	0.80	11.28
	nbDMARD	1	203.74	4.91	0.12	27.35	5.00	0.13	27.84
Therapy start before 30-JUNE-2021	Tofacitinib	0	2285.75	0.00	0.00	1.61	0.00	0.00	1.60
	bDMARD	3	13354.45	0.22	0.05	0.66	0.23	0.05	0.68
	nbDMARD	3	4476.77	0.67	0.14	1.96	0.60	0.12	1.76
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	55.58	0.00	0.00	66.37	0.00	0.00	68.66
	bDMARD	3	4150.75	0.72	0.15	2.11	0.72	0.15	2.11
	nbDMARD	0	915.59	0.00	0.00	4.03	0.00	0.00	4.07

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL
28. Interstitial lung disease									
No previous b/tsDMARD	Tofacitinib	1	768.09	1.30	0.03	7.25	1.27	0.03	7.06
	bDMARD	26	9126.28	2.85	1.86	4.17	2.90	1.90	4.25
	nbDMARD	7	5390.05	1.30	0.52	2.68	1.26	0.51	2.60
One previous b/tsDMARD	Tofacitinib	0	678.58	0.00	0.00	5.44	0.00	0.00	5.71
	bDMARD	9	3886.95	2.32	1.06	4.40	2.30	1.05	4.36
At least 2 previous b/tsDMARD	Tofacitinib	2	892.24	2.24	0.27	8.10	2.35	0.28	8.47
	bDMARD	10	4440.56	2.25	1.08	4.14	2.23	1.07	4.11
No prior non-tofacitinib JAKi use	Tofacitinib	3	2230.64	1.34	0.28	3.93	1.36	0.28	3.98
	bDMARD	40	15725.63	2.54	1.82	3.46	2.56	1.83	3.49
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	108.27	0.00	0.00	34.07	0.00	0.00	53.53
	bDMARD	5	1728.16	2.89	0.94	6.75	2.83	0.92	6.60
Monotherapy	Tofacitinib	1	1248.27	0.80	0.02	4.46	0.80	0.02	4.43
	bDMARD	13	7607.55	1.71	0.91	2.92	1.71	0.91	2.93
Combination Therapy with a nbDMARD	Tofacitinib	2	1090.63	1.83	0.22	6.62	1.90	0.23	6.86
	bDMARD	32	9846.24	3.25	2.22	4.59	3.27	2.24	4.62
Combination Therapy with MTX	Tofacitinib	2	1035.82	1.93	0.23	6.97	2.04	0.25	7.38
	bDMARD	29	9234.21	3.14	2.10	4.51	3.13	2.10	4.50
Age <65 years	Tofacitinib	3	1587.58	1.89	0.39	5.52	NA	NA	NA
	bDMARD	20	11960.14	1.67	1.02	2.58	NA	NA	NA
	nbDMARD	4	3488.13	1.15	0.31	2.94	NA	NA	NA
Age ≥65 years	Tofacitinib	0	751.33	0.00	0.00	4.91	NA	NA	NA
	bDMARD	25	5493.65	4.55	2.94	6.72	NA	NA	NA
	nbDMARD	3	1901.92	1.58	0.33	4.61	NA	NA	NA

Standardized IRs were calculated based on direct standardization if there were at least five events in each of the standardization groups (women <65 years, men <65 years, women ≥ 65 years, men ≥ 65 years), and based on indirect standardization otherwise. For the subgroups Age <65 years and Age ≥65 years no standardized IRs could be calculated by definition. If within a considered subgroup, any of the standardization groups did not contain patients, no standardized IRs could be calculated. If no standardized IR was available for one of these reasons or if there were no events across all cohorts, NA is given instead of a standardized IR.

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Table 14. On-drug approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total follow-up, years	Crude IR per 1000 PYs	Crude 95% CI		Std. IR per 1000 PYs	Std. 95% CI	
					LCL	UCL		LCL	UCL

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; CNS, central nervous system; CV, cardiovascular; DVT, deep vein thrombosis; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate; JAKi, Janus kinase inhibitor; LCL, lower confidence limit; MACE, major cardiovascular events; MTX, Methotrexate; NA, not applicable; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PML, progressive multifocal leukoencephalopathy; PY, patient year; std., standardized by age/sex; TB, tuberculosis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; UCL: upper confidence limit; VTE, venous thromboembolism

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IRs: Ever-exposed approach

The ever-exposed analysis was restricted to patients with at least one visit after initiation of the drug. For the ever-exposed approach plus latency period (outcomes 16 – 19 and 21 – 27 in section 9.4.1, i.e., malignancy outcomes), the possible maximum number of patients and the maximum mean total time at risk was 1130 and 4208.87 PYs for the tofacitinib cohort, and 6890 and 21124.99 PYs for the bDMARD cohort, respectively. The maximum mean time and maximum median time (Q1, Q3) in PYs were 3.72 and 3.92 (2.12, 5.39) for the tofacitinib cohort and 3.07 and 2.89 (1.33, 4.58) for the bDMARD cohort, respectively. The possible maximum number of patients and the maximum mean total time at risk for females and males were 863 (3219.61 PY) and 267 (989.26 PY) for the tofacitinib cohort, and 5037 (15552.07 PY) and 1853 (5572.92 PY) for the bDMARD cohort.

For the subgroup without prior b/tsDMARDs, the possible maximum number of patients, the maximum mean time and maximum median time (Q1, Q3) in PYs were 301, 4.14 and 4.40 (3.05, 5.57) for the tofacitinib cohort and 3581, 3.13 and 2.96 (1.39, 4.61) for the bDMARD cohort, respectively.

When restricting the analysis to patients with therapy start before 30-JUNE-2021, the maximum mean time and maximum median time (Q1, Q3) in PYs was 3.87 and 4.16 (2.27, 5.51) for the tofacitinib cohort and 3.92 and 4.17 (2.45, 5.44) for the bDMARD cohort. When restricting the analysis to patients with therapy start on or after 30-JUNE-2021, the maximum mean time and maximum median time (Q1, Q3) in PYs in the on-drug analysis was 2.25 and 2.66 (1.17, 3.34) for the tofacitinib cohort and 1.55 and 1.47 (0.73, 2.34) for the bDMARD cohort.

Since the ever-exposed plus latency period approach uses a latency period but the on-drug approach does not, it is possible that an event was counted in the on-drug approach but for the ever-exposed plus latency period approach falls into the latency period and was thus not counted for that approach. For this reason, the number of events could be higher in the on-drug approach than the ever-exposed approach plus latency period.

For the ever-exposed approach (outcome mortality), the possible maximum number of patients and the maximum mean total time at risk was 1200 and 4797.94 PYs for the tofacitinib cohort and 7514 and 24846.52 PYs for the bDMARD cohort. The respective numbers for females and males were 922 (3671.75 PY) and 278 (1126.19 PY) for the tofacitinib cohort, and 5495 (18267.80 PY) and 2019 (6578.72 PY) for the bDMARD cohort. For the whole cohort, the maximum mean time and maximum median time (Q1, Q3) in PY was 4.00 and 4.22 (2.18, 5.74) for the tofacitinib cohort and 3.31 and 3.02 (1.47, 4.99) for the bDMARD cohort.

For the subgroup without prior b/tsDMARDs, the possible maximum number of patients, the maximum mean time and the maximum median time (Q1, Q3) in PY in the on-drug approach was 314, 4.47 and 4.80 (3.33, 6.05) for the tofacitinib cohort and 3938, 3.33 and 3.03 (1.46, 5.02) for the bDMARD cohort. If restricting the analysis to patients with therapy start before 30-JUNE-2021, the maximum mean time and maximum median time (Q1, Q3) in PY was 4.08 and 4.36 (2.29, 5.82) for the tofacitinib cohort and 4.11 and 4.39 (2.47, 5.62) for the bDMARD cohort. If restricting the analysis to patients with therapy start on or after 30-JUNE-2021, the maximum mean time and maximum median time (Q1, Q3) in PY in the on-drug approach was 2.00 and 2.05 (0.93, 3.14) for the tofacitinib cohort and 1.66 and 1.58 (0.92, 2.42) for the bDMARD cohort.

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Results for the whole cohort are given in Table 15 for the ever-exposed approach plus latency period.

16. NMSC:

Overall: There were 19 events in the tofacitinib cohort and 54 events in the bDMARD cohort. The crude IR was 4.57 per 1000 PYs (95% CI: 2.75, 7.13) for the tofacitinib and 2.57 per 1000 PYs (95% CI: 1.93, 3.35) for the bDMARD cohort. For females, the crude IR was 4.71 per 1000 PYs (95% CI: 2.64, 7.77) (15 events) in the tofacitinib cohort and 2.52 per 1000 PYs (95% CI: 1.79, 3.44) (39 events) in the bDMARD cohort. For males, the crude IR was 4.09 per 1000 PYs (95% CI: 1.11, 10.47) (4 events) in the tofacitinib cohort and 2.70 per 1000 PYs (95% CI: 1.51, 4.46) (15 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 16.

- For the subgroup without prior b/tsDMARDs, there were 5 events in the tofacitinib cohort, and 27 events in the bDMARD cohort. The crude IR was 4.06 per 1000 PYs (95% CI: 1.32, 9.48) for the tofacitinib cohort and 2.43 per 1000 PYs (95% CI: 1.60, 3.54) for the bDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 2.51 per 1000 PYs (95% CI: 0.52, 7.32) (3 events) for the tofacitinib cohort and 3.09 per 1000 PYs (95% CI: 1.73, 5.10) (15 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 6.35 per 1000 PYs (95% CI: 3.17, 11.36) (11 events) for the tofacitinib cohort and 2.36 per 1000 PYs (95% CI: 1.22, 4.13) (12 events) for the bDMARD cohort.

- For the subgroup with no other prior JAKi, the crude IR was 4.91 per 1000 PYs (95% CI: 2.95, 7.66) (19 events) for the tofacitinib and 2.65 per 1000 PYs (95% CI: 1.98, 3.48) (52 events) for the bDMARD cohort.

- For the subgroup monotherapy, the crude IR was 3.78 per 1000 PYs (95% CI: 1.73, 7.17) (9 events) for the tofacitinib and 3.12 per 1000 PYs (95% CI: 2.07, 4.50) (28 events) for the bDMARD cohort.

- For the subgroup combination therapy with a nbDMARD, the crude IR was 5.62 per 1000 PYs (95% CI: 2.70, 10.34) (10 events) for the tofacitinib and 2.16 per 1000 PYs (95% CI: 1.41, 3.16) (26 events) for the bDMARD cohort.

- For the subgroup combination therapy with MTX, the crude IR was 6.03 per 1000 PYs (95% CI: 2.89, 11.09) (10 events) for the tofacitinib and 2.32 per 1000 PYs (95% CI: 1.52, 3.40) (26 events) for the bDMARD cohort.

- For the subgroup of patients with age below 65 years, the crude IR was 2.79 per 1000 PYs (95% CI: 1.20, 5.49) (8 events) for the tofacitinib and 1.46 per 1000 PYs (95% CI: 0.91, 2.24) (21 events) for the bDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 8.53 per 1000 PYs (95% CI: 4.26, 15.26) (11 events) for the tofacitinib and 4.94 per 1000 PYs (95% CI: 3.40, 6.94) (33 events) for the bDMARD cohort.

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- For the subgroup of patients without malignancy risk factors, the crude IR was 8.08 per 1000 PYs (95% CI: 3.87, 14.86) (10 events) for the tofacitinib cohort and 2.42 per 1000 PYs (95% CI: 1.36, 4.00) (15 events) for the bDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 3.08 per 1000 PYs (95% CI: 1.41, 5.84) (9 events) for the tofacitinib cohort and 2.64 per 1000 PYs (95% CI: 1.87, 3.60) (39 events) for the bDMARD cohort. For the subgroup of patients without history of malignancy, the crude IR was 3.75 per 1000 PYs (95% CI: 2.10, 6.18) (15 events) for the tofacitinib cohort and 2.25 per 1000 PYs (95% CI: 1.64, 3.01) (45 events) for the bDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 4.58 per 1000 PYs (95% CI: 2.71, 7.24) (18 events) for the tofacitinib cohort and 2.68 per 1000 PYs (95% CI: 1.96, 3.57) (46 events) for the bDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was one event in the tofacitinib cohort, based on only 103 patients (crude IR 4.33; 95% CI: 0.11, 24.10) and there were 8 events in the bDMARD cohort (crude IR 2.08; 95% CI: 0.90, 4.09).

17. Malignancies (overall, excluding NMSC):

Overall: There were 52 events in the tofacitinib and 216 events in the bDMARD cohort. The crude IR was 12.58 per 1000 PYs (95% CI: 9.40, 16.50) for the tofacitinib cohort and 10.39 per 1000 PYs (95% CI: 9.05, 11.87) for the bDMARD cohort. For females, the crude IR was 11.71 per 1000 PYs (95% CI: 8.24, 16.14) (37 events) in the tofacitinib cohort and 8.48 per 1000 PYs (95% CI: 7.09, 10.07) (130 events) in the bDMARD cohort. For males, the crude IR was 15.40 per 1000 PYs (95% CI: 8.62, 25.40) (15 events) in the tofacitinib cohort and 15.72 per 1000 PYs (95% CI: 12.57, 19.41) (86 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 16.

- For the subgroup without prior b/tsDMARDs, the crude IR was 13.90 per 1000 PYs (95% CI: 8.10, 22.25) (17 events) for the tofacitinib cohort and 9.64 per 1000 PYs (95% CI: 7.89, 11.66) (106 events) for the bDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 10.90 per 1000 PYs (95% CI: 5.81, 18.64) (13 events) for the tofacitinib cohort and 11.46 per 1000 PYs (95% CI: 8.63, 14.92) (55 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 12.80 per 1000 PYs (95% CI: 8.02, 19.39) (22 events) for the tofacitinib and 10.99 per 1000 PYs (95% CI: 8.28, 14.31) (55 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 11.92 per 1000 PYs (95% CI: 8.73, 15.90) (46 events) for the tofacitinib and 10.10 per 1000 PYs (95% CI: 8.73, 11.62) (196 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 11.47 per 1000 PYs (95% CI: 7.56, 16.69) (27 events) for the tofacitinib and 10.00 per 1000 PYs (95% CI: 8.03, 12.31) (89 events) for the bDMARD cohort.
- For the subgroup combination therapy with a nbDMARD, the crude IR was 14.05 per 1000 PYs (95% CI: 9.09, 20.74) (25 events) for the tofacitinib and 10.67 per 1000 PYs (95% CI: 8.90, 12.70) (127 events) for the bDMARD cohort.

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- For the subgroup combination therapy with MTX, the crude IR was 12.63 per 1000 PYs (95% CI: 7.82, 19.30) (21 events) for the tofacitinib and 10.48 per 1000 PYs (95% CI: 8.66, 12.57) (116 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 7.00 per 1000 PYs (95% CI: 4.28, 10.81) (20 events) for the tofacitinib and 7.61 per 1000 PYs (95% CI: 6.25, 9.19) (108 events) for the bDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 25.06 per 1000 PYs (95% CI: 17.14, 35.38) (32 events) for the tofacitinib and 16.33 per 1000 PYs (95% CI: 13.40, 19.72) (108 events) for the bDMARD cohort.
- For the subgroup of patients without malignancy risk factors, the crude IR was 10.53 per 1000 PYs (95% CI: 5.61, 18.00) (13 events) for the tofacitinib and 8.99 per 1000 PYs (95% CI: 6.77, 11.70) (55 events) for the bDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 13.45 per 1000 PYs (95% CI: 9.57, 18.39) (39 events) for the tofacitinib and 11.00 per 1000 PYs (95% CI: 9.36, 12.83) (161 events) for the bDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 11.31 per 1000 PYs (95% CI: 8.25, 15.13) (45 events) for the tofacitinib and 9.43 per 1000 PYs (95% CI: 8.13, 10.88) (187 events) for the bDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 12.04 per 1000 PYs (95% CI: 8.85, 16.01) (47 events) for the tofacitinib and 10.73 per 1000 PYs (95% CI: 9.23, 12.41) (182 events) for the bDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there were 5 events in the tofacitinib cohort, based on only 103 patients (crude IR 21.72; 95% CI: 7.05, 50.69), and 34 patients in the bDMARD cohort (crude IR 8.86; 95% CI: 6.14, 12.38)

18. Lymphoma (overall): There were 3 events in the tofacitinib cohort and 5 events in the bDMARD cohort. The crude IR was 0.71 per 1000 PYs (95% CI: 0.15, 2.08) for the tofacitinib cohort and 0.24 per 1000 PYs (95% CI: 0.08, 0.55) for the bDMARD cohort.

Non-Hodgkin lymphoma: There were 2 events in the tofacitinib cohort (crude IR 0.48; 95% CI: 0.06, 1.72) and no events in the bDMARD cohort. No stratified analyses were done.

Hodgkin lymphoma: There was no event in the tofacitinib cohort and there were 3 events in the bDMARD cohort (crude IR 0.14; 95% CI: 0.03, 0.42). No stratified analyses were done.

Chronic lymphatic leukemia: There was one event in the tofacitinib cohort and there were 2 events in the bDMARD cohort. The crude IR was 0.24 per 1000 PYs (95% CI: 0.01, 1.32) for the tofacitinib cohort and 0.09 per 1000 PYs (95% CI: 0.01, 0.34) for the bDMARD cohort. No stratified analyses were done.

19. Lung cancer:

Overall: There were 12 events in the tofacitinib cohort and 37 events in the bDMARD cohort. The crude IR was 2.86 per 1000 PYs (95% CI: 1.48, 4.99) for the tofacitinib cohort and 1.75 per 1000 PYs (95% CI: 1.23, 2.42) for the bDMARD cohort. For females, the crude IR was 1.87 per 1000 PYs (95% CI: 0.68, 4.06 (6 events) in the tofacitinib cohort and 0.97 per 1000 PYs (95% CI: 0.54, 1.59) (15 events) in the bDMARD cohort. For males,

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the crude IR was 6.11 per 1000 PYs (95% CI: 2.24, 13.30) (6 events) in the tofacitinib cohort and 3.96 per 1000 PYs (95% CI: 2.48, 5.99) (22 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 16.

- For the subgroup without prior b/tsDMARDs, the crude IR was 0.80 per 1000 PYs (95% CI: 0.02, 4.47) (one event) for the tofacitinib cohort and 2.16 per 1000 PYs (95% CI: 1.38, 3.21) (24 events) for the bDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 3.33 per 1000 PYs (95% CI: 0.91, 8.53) (4 events) for the tofacitinib cohort and 1.64 per 1000 PYs (95% CI: 0.71, 3.23) (8 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 4.00 per 1000 PYs (95% CI: 1.61, 8.24) (7 events) for the tofacitinib and 0.98 per 1000 PYs (95% CI: 0.32, 2.29) (5 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 2.81 per 1000 PYs (95% CI: 1.40, 5.03) (11 events) for the tofacitinib and 1.78 per 1000 PYs (95% CI: 1.24, 2.47) (35 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 1.25 per 1000 PYs (95% CI: 0.26, 3.65) (3 events) for the tofacitinib and 0.77 per 1000 PYs (95% CI: 0.31, 1.60) (7 events) for the bDMARD cohort.
- For the subgroup combination therapy with a nbDMARD, the crude IR was 5.00 per 1000 PYs (95% CI: 2.29, 9.50) (9 events) for the tofacitinib and 2.49 per 1000 PYs (95% CI: 1.68, 3.55) (30 events) for the bDMARD cohort.
- For the subgroup combination therapy with MTX, the crude IR was 4.17 per 1000 PYs (95% CI: 1.68, 8.59) (7 events) for the tofacitinib and 2.49 per 1000 PYs (95% CI: 1.66, 3.60) (28 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 1.38 per 1000 PYs (95% CI: 0.38, 3.54) (4 events) for the tofacitinib and 1.11 per 1000 PYs (95% CI: 0.64, 1.81) (16 events) for the bDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 6.11 per 1000 PYs (95% CI: 2.64, 12.05) (8 events) for the tofacitinib and 3.12 per 1000 PYs (95% CI: 1.93, 4.77) (21 events) for the bDMARD cohort.
- For the subgroup of patients without malignancy risk factors, the crude IR was 1.59 per 1000 PYs (95% CI: 0.19, 5.73) (2 events) for the tofacitinib and 0.16 per 1000 PYs (95% CI: 0.00, 0.90) (one event) for the bDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 3.40 per 1000 PYs (95% CI: 1.63, 6.26) (10 events) for the tofacitinib and 2.42 per 1000 PYs (95% CI: 1.70, 3.36) (36 events) for the bDMARD cohort.

- For the subgroup of patients without history of malignancy, the crude IR was 2.48 per 1000 PYs (95% CI: 1.19, 4.56) (10 events) for the tofacitinib and 1.74 per 1000 PYs (95% CI: 1.21, 2.42) (35 events) for the bDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 2.77 per 1000 PYs (95% CI: 1.38, 4.96) (11 events) for the tofacitinib and 1.97 per 1000 PYs (95% CI: 1.37, 2.76) (34 events) for the bDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there was one event in the tofacitinib cohort, based on only 103 patients (crude IR 4.31; 95% CI: 0.11, 24.03), and 3 patients in the bDMARD cohort (crude IR 0.78; 95% CI: 0.16, 2.27).

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20. All-cause Mortality (Table 15):

Overall: There were 66 events in the tofacitinib cohort and 302 events in the bDMARD cohort. The crude IR was 13.76 per 1000 PYs (95% CI: 10.64, 17.50) for the tofacitinib cohort and 12.15 per 1000 PYs (95% CI: 10.82, 13.61) for the bDMARD cohort. For females, the crude IR was 11.44 per 1000 PYs (95% CI: 8.24, 15.46) (42 events) in the tofacitinib cohort and 9.96 per 1000 PYs (95% CI: 8.57, 11.52) (182 events) in the bDMARD cohort. For males, the crude IR was 21.31 per 1000 PYs (95% CI: 13.65, 31.71) (24 events) in the tofacitinib cohort and 18.24 per 1000 PYs (95% CI: 15.12, 21.81) (120 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 16

- For the subgroup without prior b/tsDMARDs, the crude IR was 11.39 per 1000 PYs (95% CI: 6.51, 18.50) (16 events) for the tofacitinib cohort and 11.12 per 1000 PYs (95% CI: 9.39, 13.08) (146 events) for the bDMARD cohort.

- For the subgroup with one prior b/tsDMARDs, the crude IR was 13.95 per 1000 PYs (95% CI: 8.40, 21.78) (19 events) for the tofacitinib cohort and 13.50 per 1000 PYs (95% CI: 10.65, 16.87) (77 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 15.26 per 1000 PYs (95% CI: 10.37, 21.66) (31 events) for the tofacitinib cohort and 13.14 per 1000 PYs (95% CI: 10.40, 16.37) (79 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 13.89 per 1000 PYs (95% CI: 10.65, 17.81) (62 events) for the tofacitinib cohort and 12.33 per 1000 PYs (95% CI:10.94, 13.84) (285 events) for the bDMARD cohort.

- For the subgroup monotherapy, the crude IR was 13.15 per 1000 PYs (95% CI: 9.21, 18.20) (36 events) for the tofacitinib cohort and 13.95 per 1000 PYs (95% CI: 11.81, 16.37) (150 events) for the bDMARD cohort.
- For the subgroup combination therapy with a nbDMARD, the crude IR was 14.57 per 1000 PYs (95% CI: 9.83, 20.80) (30 events) for the tofacitinib cohort and 10.78 per 1000 PYs (95% CI: 9.14, 12.64) (152 events) for the bDMARD cohort.
- For the subgroup combination therapy with MTX, the crude IR was 14.57 per 1000 PYs (95% CI: 9.68, 21.06) (28 events) for the tofacitinib cohort and 10.52 per 1000 PYs (95% CI: 8.84, 12.43) (138 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 5.08 per 1000 PYs (95% CI: 2.96, 8.13) (17 events) for the tofacitinib cohort and 4.88 per 1000 PYs (95% CI: 3.89, 6.05) (83 events) for the bDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 33.82 per 1000 PYs (95% CI: 25.02, 44.72) (49 events) for the tofacitinib cohort and 27.92 per 1000 PYs (95% CI: 24.35, 31.88) (219 events) for the bDMARD cohort.

21. Leukaemia (excl. B-CLL): There was one event in the tofacitinib cohort and there were 9 events in the bDMARD cohort. crude IR was 0.24 per 1000 PYs (95% CI: 0.01, 1.32) for the tofacitinib and 0.43 per 1000 PYs (95% CI: 0.19, 0.81) for the bDMARD cohort. No stratified analyses were done.

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22. Other haematopoietic neoplasms (malignant and benign): There was no event in the tofacitinib cohort and one event in the bDMARD cohort No stratified analyses were done.

23. Solid malignancies:

Overall: There were 43 events in the tofacitinib and 193 events in the bDMARD cohort. The crude IR was 10.37 per 1000 PYs (95% CI: 7.50, 13.96) for the tofacitinib and 9.26 per 1000 PYs (95% CI: 8.00, 10.67) for the bDMARD cohort. For females, the crude IR was 9.14 per 1000 PYs (95% CI: 6.12, 13.13) (29 events) in the tofacitinib cohort and 7.36 per 1000 PYs (95% CI: 6.07, 8.85) (113 events) in the bDMARD cohort. For males, the crude IR was 14.34 per 1000 PYs (95% CI: 7.84, 24.05) (14 events) in the tofacitinib cohort and 14.59 per 1000 PYs (95% CI: 11.57, 18.16) (80 events) in the bDMARD cohort.

Stratified: Results for the stratified analyses are shown in Table 16

- For the subgroup without prior b/tsDMARDs, the crude IR was 10.59 per 1000 PYs (95% CI: 5.64, 18.12) (13 events) for the tofacitinib and 8.35 per 1000 PYs (95% CI: 6.73, 10.24) (92 events) for the bDMARD cohort.
- For the subgroup with one prior b/tsDMARDs, the crude IR was 10.05 per 1000 PYs (95% CI: 5.19, 17.56) (12 events) for the tofacitinib cohort and 10.40 per 1000 PYs (95% CI: 7.72, 13.71) (50 events) for the bDMARD cohort. For the subgroup with at least two prior b/tsDMARDs, the crude IR was 10.42 per 1000 PYs (95% CI: 6.18, 16.47) (18 events) for the tofacitinib and 10.17 per 1000 PYs (95% CI: 7.57, 13.38) (51 events) for the bDMARD cohort. For the subgroup with no other prior JAKi, the crude IR was 9.82 per 1000 PYs (95% CI: 6.95, 13.48) (38 events) for the tofacitinib and 8.95 per 1000 PYs (95% CI: 7.67, 10.38) (174 events) for the bDMARD cohort.
- For the subgroup monotherapy, the crude IR was 9.31 per 1000 PYs (95% CI: 5.84, 14.10) (22 events) for the tofacitinib and 9.20 per 1000 PYs (95% CI: 7.32, 11.42) (82 events) for the bDMARD cohort.
- For the subgroup combination therapy with a nbDMARD, the crude IR was 11.76 per 1000 PYs (95% CI: 7.28, 17.98) (21 events) for the tofacitinib and 9.31 per 1000 PYs (95% CI: 7.66, 11.21) (111 events) for the bDMARD cohort.
- For the subgroup combination therapy with MTX, the crude IR was 10.79 per 1000 PYs (95% CI: 6.39, 17.05) (18 events) for the tofacitinib and 9.10 per 1000 PYs (95% CI: 7.41, 11.06) (101 events) for the bDMARD cohort.
- For the subgroup of patients with age below 65 years, the crude IR was 5.93 per 1000 PYs (95% CI: 3.46, 9.50) (18 events) for the tofacitinib and 6.90 per 1000 PYs (95% CI: 5.60, 8.41) (98 events) for the bDMARD cohort. For the subgroup of patients with age at least 65 years, the crude IR was 20.28 per 1000 PYs (95% CI: 13.25, 29.72) (26 events) for the tofacitinib and 14.33 per 1000 PYs (95% CI: 11.59, 17.52) (95 events) for the bDMARD cohort.
- For the subgroup of patients without malignancy risk factors, the crude IR was 8.91 per 1000 PYs (95% CI: 4.45, 15.94) (11 events) for the tofacitinib and 7.66 per 1000 PYs (95% CI: 5.63, 10.19) (47 events) for the bDMARD cohort. For the subgroup of patients with malignancy risk factors, the crude IR was 10.99 per 1000 PYs (95% CI: 7.51, 15.51) (32 events) for the tofacitinib and 9.96 per 1000 PYs (95% CI: 8.41, 11.71) (146 events) for the bDMARD cohort.

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- For the subgroup of patients without history of malignancy, the crude IR was 9.27 per 1000 PYs (95% CI: 6.53, 12.78) (37 events) for the tofacitinib and 8.67 per 1000 PYs (95% CI: 7.42, 10.06) (172 events) for the bDMARD cohort.

- For the subgroup of patients with therapy start before 30-JUNE-2021, the crude IR was 10.21 per 1000 PYs (95% CI: 7.29, 13.90) (40 events) for the tofacitinib and 9.533 per 1000 PYs (95% CI: 8.12, 11.12) (162 events) for the bDMARD cohort. For the subgroup of patients with therapy start on or after 30-JUNE-2021, there were 3 events in the tofacitinib cohort, based on only 103 patients (crude IR 13.03; 95% CI: 2.69, 38.09), and 34 patients in the bDMARD cohort (crude IR 8.08; 95% CI: 5.49, 11.47).

24. Glioblastoma: There were no events in any cohort.

25. Benign neoplasms: There were 19 events in the tofacitinib cohort and 75 events in the bDMARD cohort. The crude IR was 4.56 per 1000 PYs (95% CI: 2.75, 7.12) for the tofacitinib cohort and 3.58 per 1000 PYs (95% CI: 2.81, 4.49) for the bDMARD cohort.

26. Unspecified neoplasms and precanceroses: There were 3 events in the tofacitinib cohort and 18 events in the bDMARD cohort. The crude IR was 0.71 per 1000 PYs (95% CI: 0.15, 2.08) for the tofacitinib cohort and 0.85 per 1000 PYs (95% CI:0.51, 1.35) for the bDMARD cohort.

27. Metastases, cancer related and morbidities and associated syndromes: There were 3 events in the tofacitinib cohort and 7 events in the bDMARD cohort. The crude IR was 0.71 per 1000 PYs (95% CI: 0.15, 2.08) for the tofacitinib cohort and 0.33 per 1000 PYs (95% CI: 0.13, 0.68) for the bDMARD cohort.

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Table 15. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
	Num-ber of events	Total fol-low-up, years	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years		LCL	UCL		LCL	UCL
16. NMSC												
Tofacitinib	19	4161.09	15	3182.85	4	978.24	4.57	2.75	7.13	4.62	2.78	7.22
bDMARD	54	21022.22	39	15476.13	15	5546.09	2.57	1.93	3.35	2.59	1.95	3.38
17. Malignancies (over-all, excluding NMSC)												
Tofacitinib	52	4133.69	37	3159.67	15	974.02	12.58	9.40	16.50	12.58	9.40	16.50
bDMARD	216	20796.67	130	15324.96	86	5471.71	10.39	9.05	11.87	10.17	8.85	11.62
18. Lymphoma (over-all)												
Tofacitinib	3	4207.21	3	3217.95	0	989.26	0.71	0.15	2.08	0.77	0.16	2.24
bDMARD	5	21113.05	1	15549.49	4	5563.56	0.24	0.08	0.55	0.24	0.08	0.55
Non-Hodgkin lym-phoma												
Tofacitinib	2	4208.56	2	3219.30	0	989.26	0.48	0.06	1.72	0.49	0.06	1.76
bDMARD	0	21124.99	0	15552.07	0	5572.92	0.00	0.00	0.17	0.00	0.00	0.18
Hodgkin lymphoma												
Tofacitinib	0	4208.87	0	3219.61	0	989.26	0.00	0.00	0.88	0.00	0.00	0.97
bDMARD	3	21115.94	0	15552.07	3	5563.87	0.14	0.03	0.42	0.14	0.03	0.41
Chronic lymphatic leu-kemia												
Tofacitinib	1	4207.52	1	3218.26	0	989.26	0.24	0.01	1.32	0.25	0.01	1.40
bDMARD	2	21122.10	1	15549.49	1	5572.61	0.09	0.01	0.34	0.09	0.01	0.34
19. Lung Cancer												
Tofacitinib	12	4197.52	6	3215.57	6	981.95	2.86	1.48	4.99	2.99	1.54	5.22
bDMARD	37	21102.58	15	15540.48	22	5562.10	1.75	1.23	2.42	1.77	1.24	2.43
20. All-cause Mortality												
Tofacitinib	66	4797.94	42	3671.75	24	1126.19	13.76	10.64	17.50	14.45	11.17	18.38
bDMARD	302	24846.52	182	18267.80	120	6578.72	12.15	10.82	13.61	12.25	10.91	13.72
21. Leukaemia (excl. B-CLL)												
Tofacitinib	1	4206.57	0	3219.61	1	986.96	0.24	0.01	1.32	0.25	0.01	1.41

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Table 15. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
	Number of events	Total follow-up, years	Number of events	Total follow-up, years	Number of events	Total follow-up, years		LCL	UCL		LCL	UCL
bDMARD	9	21115.99	4	15549.67	5	5566.33	0.43	0.19	0.81	0.43	0.20	0.82
22. Other haematopoietic neoplasms (malignant and benign)												
Tofacitinib	0	4208.87	0	3219.61	0	989.26	0.00	0.00	0.88	0.00	0.00	0.94
bDMARD	1	21123.46	1	15550.54	0	5572.92	0.05	0.00	0.26	0.05	0.00	0.26
23. Solid malignancies (overall)												
Tofacitinib	43	4147.82	29	3171.32	14	976.50	10.37	7.50	13.96	10.37	7.50	13.96
bDMARD	193	20834.96	113	15353.20	80	5481.76	9.26	8.00	10.67	9.08	7.84	10.46
24. Glioblastoma												
Tofacitinib	0	4208.87	0	3219.61	0	989.26	0.00	0.00	0.88	NA	NA	NA
bDMARD	0	21124.99	0	15552.07	0	5572.92	0.00	0.00	0.17	NA	NA	NA
25. Benign neoplasms												
Tofacitinib	19	4165.96	14	3187.51	5	978.45	4.56	2.75	7.12	4.53	2.72	7.07
bDMARD	75	20960.82	63	15412.90	12	5547.92	3.58	2.81	4.49	3.60	2.83	4.51
26. Unspecified neoplasms and precancerooses												
Tofacitinib	3	4208.13	2	3219.56	1	988.57	0.71	0.15	2.08	0.73	0.15	2.13
bDMARD	18	21092.29	12	15532.75	6	5559.54	0.85	0.51	1.35	0.86	0.51	1.35
27. Metastases, cancer related morbidities and associated syndroms												
Tofacitinib	3	4207.82	3	3218.56	0	989.26	0.71	0.15	2.08	0.74	0.15	2.16
bDMARD	7	21123.02	3	15551.38	4	5571.64	0.33	0.13	0.68	0.33	0.13	0.69

Standardized IRs were calculated based on direct standardization if there were at least five events in each of the standardization groups (women <65 years, men <65 years, women ≥ 65 years, men ≥ 65 years), and based on indirect standardization otherwise. For the subgroups Age <65 years and Age ≥65 years no standardized IRs could be calculated by definition. If within a considered subgroup, any of the standardization groups did not contain patients, no standardized IRs could be calculated. If no standardized IR was available for one of these reasons or if there were no events across all cohorts, NA is given instead of a standardized IR.

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Table 15. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs)

	Total		Females		Males		Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
	Num-ber of events	Total fol-low-up, years	Number of events	Total fol-low-up, years	Number of events	Total fol-low-up, years		LCL	UCL		LCL	UCL

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; IR, incidence rate; LCL, lower confidence limit; NA, not applicable; NMSC, non-melanoma skin cancer; PY, patient year; std., standardized by age/sex; TB, tuberculosis; UCL: upper confidence limit.

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
16. NMSC									
No previous b/tsDMARD	Tofacitinib	5	1230.50	4.06	1.32	9.48	3.86	1.25	9.00
	bDMARD	27	11097.28	2.43	1.60	3.54	2.50	1.64	3.63
One previous b/tsDMARD	Tofacitinib	3	1197.30	2.51	0.52	7.32	2.75	0.57	8.05
	bDMARD	15	4850.58	3.09	1.73	5.10	3.03	1.69	4.99
At least 2 previous b/tsDMARD	Tofacitinib	11	1733.28	6.35	3.17	11.36	6.33	3.16	11.33
	bDMARD	12	5074.37	2.36	1.22	4.13	2.37	1.22	4.13
No prior non-tofacitinib JAKi use	Tofacitinib	19	3873.22	4.91	2.95	7.66	4.95	2.98	7.73
	bDMARD	52	19600.72	2.65	1.98	3.48	2.68	2.00	3.51
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	0.00	0.00	15.84
	bDMARD	2	1421.50	1.41	0.17	5.08	1.35	0.16	4.89
Monotherapy	Tofacitinib	9	2383.17	3.78	1.73	7.17	3.80	1.74	7.21
	bDMARD	28	8985.09	3.12	2.07	4.50	3.11	2.07	4.50
Combination Therapy with a nbDMARD	Tofacitinib	10	1777.92	5.62	2.70	10.34	5.95	2.85	10.94
	bDMARD	26	12037.13	2.16	1.41	3.16	2.22	1.45	3.25
Combination therapy with MTX	Tofacitinib	10	1658.47	6.03	2.89	11.09	6.32	3.03	11.63
	bDMARD	26	11202.34	2.32	1.52	3.40	2.34	1.53	3.43
Age <65 years	Tofacitinib	8	2871.02	2.79	1.20	5.49	NA	NA	NA
	bDMARD	21	14342.25	1.46	0.91	2.24	NA	NA	NA
Age ≥65 years	Tofacitinib	11	1290.07	8.53	4.26	15.26	NA	NA	NA
	bDMARD	33	6679.97	4.94	3.40	6.94	NA	NA	NA
No malignancy risk factor	Tofacitinib	10	1237.73	8.08	3.87	14.86	7.75	3.71	14.26
	bDMARD	15	6192.06	2.42	1.36	4.00	2.46	1.38	4.06
At least one malignancy risk factor	Tofacitinib	9	2923.36	3.08	1.41	5.84	3.22	1.47	6.11
	bDMARD	39	14793.35	2.64	1.87	3.60	2.65	1.88	3.62
No history of malignancy	Tofacitinib	15	4002.14	3.75	2.10	6.18	3.80	2.13	6.27
	bDMARD	45	20019.16	2.25	1.64	3.01	2.27	1.66	3.04
With history of malignancy	Tofacitinib	4	158.95	25.17	6.86	64.43	23.53	6.41	60.26
	bDMARD	9	1003.07	8.97	4.10	17.03	9.08	4.15	17.23
Therapy start before 30-JUNE-2021	Tofacitinib	18	3929.90	4.58	2.71	7.24	4.56	2.70	7.21
	bDMARD	46	17171.97	2.68	1.96	3.57	2.72	1.99	3.62
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	231.19	4.33	0.11	24.10	5.31	0.13	29.57
	bDMARD	8	3850.25	2.08	0.90	4.09	2.07	0.89	4.08

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	8	2744.31	2.92	1.26	5.74	2.98	1.29	5.87
	bDMARD	33	12131.37	2.72	1.87	3.82	2.74	1.89	3.85
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	1	179.05	5.58	0.14	31.12	6.43	0.16	35.83
	bDMARD	6	2661.98	2.25	0.83	4.91	2.27	0.83	4.94
17. Malignancies (overall, excluding NMSC)									
No previous b/tsDMARD	Tofacitinib	17	1223.10	13.90	8.10	22.25	13.59	7.91	21.76
	bDMARD	106	10995.09	9.64	7.89	11.66	9.76	7.99	11.80
One previous b/tsDMARD	Tofacitinib	13	1192.38	10.90	5.81	18.64	11.71	6.23	20.03
	bDMARD	55	4798.66	11.46	8.63	14.92	11.27	8.49	14.67
At least 2 previous b/tsDMARD	Tofacitinib	22	1718.21	12.80	8.02	19.39	13.17	8.25	19.93
	bDMARD	55	5002.92	10.99	8.28	14.31	10.89	8.20	14.18
No prior non-tofacitinib JAKi use	Tofacitinib	46	3859.45	11.92	8.73	15.90	11.92	8.73	15.90
	bDMARD	196	19409.66	10.10	8.73	11.62	9.91	8.57	11.41
At least one prior non-tofacitinib JAKi use	Tofacitinib	6	274.24	21.88	8.03	47.62	22.95	8.42	49.96
	bDMARD	20	1387.01	14.42	8.81	22.27	14.29	8.72	22.07
Monotherapy	Tofacitinib	27	2353.86	11.47	7.56	16.69	11.63	7.66	16.92
	bDMARD	89	8898.16	10.00	8.03	12.31	9.97	8.00	12.26
Combination Therapy with a nbDMARD	Tofacitinib	25	1779.83	14.05	9.09	20.74	14.51	9.39	21.42
	bDMARD	127	11898.51	10.67	8.90	12.70	10.73	8.95	12.77
Combination therapy with MTX	Tofacitinib	21	1662.90	12.63	7.82	19.30	13.10	8.10	20.02
	bDMARD	116	11072.06	10.48	8.66	12.57	10.49	8.66	12.58
Age <65 years	Tofacitinib	20	2856.97	7.00	4.28	10.81	NA	NA	NA
	bDMARD	108	14183.12	7.61	6.25	9.19	NA	NA	NA
Age ≥65 years	Tofacitinib	32	1276.72	25.06	17.14	35.38	NA	NA	NA
	bDMARD	108	6613.56	16.33	13.40	19.72	NA	NA	NA
No malignancy risk factor	Tofacitinib	13	1234.72	10.53	5.61	18.00	10.43	5.55	17.84
	bDMARD	55	6120.68	8.99	6.77	11.70	9.09	6.85	11.83
At least one malignancy risk factor	Tofacitinib	39	2898.97	13.45	9.57	18.39	13.94	9.91	19.06
	bDMARD	161	14639.18	11.00	9.36	12.83	11.02	9.38	12.86
No history of malignancy	Tofacitinib	45	3980.16	11.31	8.25	15.13	11.56	8.43	15.47
	bDMARD	187	19830.38	9.43	8.13	10.88	9.47	8.16	10.93

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
With history of malignancy	Tofacitinib	7	153.53	45.59	18.33	93.94	46.30	18.61	95.39
	bDMARD	29	966.29	30.01	20.10	43.10	29.96	20.06	43.02
Therapy start before 30-JUNE-2021	Tofacitinib	47	3903.51	12.04	8.85	16.01	12.26	9.01	16.30
	bDMARD	182	16959.58	10.73	9.23	12.41	10.80	9.29	12.49
Therapy start on or after 30-JUNE-2021	Tofacitinib	5	230.18	21.72	7.05	50.69	23.62	7.67	55.11
	bDMARD	34	3837.09	8.86	6.14	12.38	8.85	6.13	12.36
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	34	2720.93	12.50	8.65	17.46	12.82	8.88	17.92
	bDMARD	138	11981.40	11.52	9.68	13.61	11.56	9.71	13.65
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	5	178.04	28.08	9.12	65.54	30.58	9.93	71.37
	bDMARD	23	2657.79	8.65	5.49	12.98	8.66	5.49	13.00
18. Lymphoma (overall)									
No previous b/tsDMARD	Tofacitinib	1	1248.17	0.80	0.02	4.46	0.79	0.02	4.38
	bDMARD	4	11141.80	0.36	0.10	0.92	0.36	0.10	0.92
One previous b/tsDMARD	Tofacitinib	1	1204.81	0.83	0.02	4.62	1.01	0.03	5.63
	bDMARD	0	4881.41	0.00	0.00	0.76	0.00	0.00	0.72
At least 2 previous b/tsDMARD	Tofacitinib	1	1754.22	0.57	0.01	3.18	0.64	0.02	3.54
	bDMARD	1	5089.85	0.20	0.00	1.09	0.19	0.00	1.06
No prior non-tofacitinib JAKi use	Tofacitinib	3	3919.33	0.77	0.16	2.24	0.81	0.17	2.37
	bDMARD	5	19689.36	0.25	0.08	0.59	0.25	0.08	0.59
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	2	2400.93	0.83	0.10	3.01	0.87	0.10	3.13
	bDMARD	0	9039.82	0.00	0.00	0.41	0.00	0.00	0.40
Combination Therapy with a nbDMARD	Tofacitinib	1	1806.28	0.55	0.01	3.08	0.59	0.02	3.31
	bDMARD	5	12073.23	0.41	0.13	0.97	0.41	0.13	0.95
Combination therapy with MTX	Tofacitinib	1	1686.84	0.59	0.02	3.30	0.65	0.02	3.61
	bDMARD	4	11241.01	0.36	0.10	0.91	0.35	0.10	0.90
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	3	14373.39	0.21	0.04	0.61	NA	NA	NA
Age ≥65 years	Tofacitinib	3	1313.92	2.28	0.47	6.67	NA	NA	NA
	bDMARD	2	6739.66	0.30	0.04	1.07	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
No malignancy risk factor	Tofacitinib	1	1262.65	0.79	0.02	4.41	0.84	0.02	4.70
	bDMARD	2	6210.02	0.32	0.04	1.16	0.32	0.04	1.17
At least one malignancy risk factor	Tofacitinib	2	2944.56	0.68	0.08	2.45	0.74	0.09	2.66
	bDMARD	3	14866.22	0.20	0.04	0.59	0.20	0.04	0.58
No history of malignancy	Tofacitinib	3	4043.18	0.74	0.15	2.17	0.79	0.16	2.32
	bDMARD	4	20101.42	0.20	0.05	0.51	0.20	0.05	0.51
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	0.00	0.00	36.94
	bDMARD	1	1011.63	0.99	0.03	5.51	0.91	0.02	5.09
Therapy start before 30-JUNE-2021	Tofacitinib	2	3975.05	0.50	0.06	1.82	0.54	0.07	1.96
	bDMARD	5	17251.05	0.29	0.09	0.68	0.29	0.09	0.67
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	232.15	4.31	0.11	24.00	7.00	0.18	38.99
	bDMARD	0	3862.00	0.00	0.00	0.96	0.00	0.00	0.95
Non-Hodgkin lymphoma									
No previous b/tsDMARD	Tofacitinib	1	1248.17	0.80	0.02	4.46	0.66	0.02	3.69
	bDMARD	0	11151.16	0.00	0.00	0.33	0.00	0.00	0.35
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	NA	NA	NA
	bDMARD	0	4881.41	0.00	0.00	0.76	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	1	1754.22	0.57	0.01	3.18	0.64	0.02	3.54
	bDMARD	0	5092.43	0.00	0.00	0.72	0.00	0.00	0.70
No prior non-tofacitinib JAKi use	Tofacitinib	2	3920.68	0.51	0.06	1.84	0.52	0.06	1.88
	bDMARD	0	19701.30	0.00	0.00	0.19	0.00	0.00	0.19
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	2	2400.93	0.83	0.10	3.01	0.87	0.10	3.13
	bDMARD	0	9039.82	0.00	0.00	0.41	0.00	0.00	0.40
Combination Therapy with a nbDMARD	Tofacitinib	0	1807.63	0.00	0.00	2.04	NA	NA	NA
	bDMARD	0	12085.17	0.00	0.00	0.31	NA	NA	NA
Combination therapy with MTX	Tofacitinib	0	1688.19	0.00	0.00	2.19	NA	NA	NA
	bDMARD	0	11250.38	0.00	0.00	0.33	NA	NA	NA
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	0	14377.60	0.00	0.00	0.26	NA	NA	NA
Age ≥65 years	Tofacitinib	2	1315.27	1.52	0.18	5.49	NA	NA	NA
	bDMARD	0	6747.39	0.00	0.00	0.55	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
No malignancy risk factor	Tofacitinib	1	1262.65	0.79	0.02	4.41	0.73	0.02	4.05
	bDMARD	0	6216.28	0.00	0.00	0.59	0.00	0.00	0.62
At least one malignancy risk factor	Tofacitinib	1	2945.91	0.34	0.01	1.89	0.38	0.01	2.14
	bDMARD	0	14871.91	0.00	0.00	0.25	0.00	0.00	0.25
No history of malignancy	Tofacitinib	2	4044.53	0.49	0.06	1.79	0.51	0.06	1.86
	bDMARD	0	20109.69	0.00	0.00	0.18	0.00	0.00	0.19
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	NA	NA	NA
	bDMARD	0	1015.31	0.00	0.00	3.63	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	1	3976.41	0.25	0.01	1.40	0.25	0.01	1.39
	bDMARD	0	17263.00	0.00	0.00	0.21	0.00	0.00	0.22
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	232.15	4.31	0.11	24.00	7.00	0.18	38.99
	bDMARD	0	3862.00	0.00	0.00	0.96	0.00	0.00	0.95
Hodgkin lymphoma									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	0.00	0.00	3.01
	bDMARD	3	11142.11	0.27	0.06	0.79	0.27	0.06	0.78
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	NA	NA	NA
	bDMARD	0	4881.41	0.00	0.00	0.76	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	1754.53	0.00	0.00	2.10	NA	NA	NA
	bDMARD	0	5092.43	0.00	0.00	0.72	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	3920.99	0.00	0.00	0.94	0.00	0.00	1.03
	bDMARD	3	19692.25	0.15	0.03	0.45	0.15	0.03	0.44
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	0	2401.24	0.00	0.00	1.54	NA	NA	NA
	bDMARD	0	9039.82	0.00	0.00	0.41	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	0	1807.63	0.00	0.00	2.04	0.00	0.00	2.16
	bDMARD	3	12076.12	0.25	0.05	0.73	0.24	0.05	0.70
Combination therapy with MTX	Tofacitinib	0	1688.19	0.00	0.00	2.19	0.00	0.00	2.39
	bDMARD	3	11241.33	0.27	0.06	0.78	0.26	0.05	0.77
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	2	14373.70	0.14	0.02	0.50	NA	NA	NA
Age ≥65 years	Tofacitinib	0	1315.58	0.00	0.00	2.80	NA	NA	NA
	bDMARD	1	6742.24	0.15	0.00	0.83	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
No malignancy risk factor	Tofacitinib	0	1262.96	0.00	0.00	2.92	0.00	0.00	4.57
	bDMARD	1	6212.60	0.16	0.00	0.90	0.15	0.00	0.85
At least one malignancy risk factor	Tofacitinib	0	2945.91	0.00	0.00	1.25	0.00	0.00	1.33
	bDMARD	2	14866.53	0.13	0.02	0.49	0.13	0.02	0.48
No history of malignancy	Tofacitinib	0	4044.84	0.00	0.00	0.91	0.00	0.00	1.00
	bDMARD	2	20104.31	0.10	0.01	0.36	0.10	0.01	0.36
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	0.00	0.00	36.94
	bDMARD	1	1011.63	0.99	0.03	5.51	0.91	0.02	5.09
Therapy start before 30-JUNE-2021	Tofacitinib	0	3976.72	0.00	0.00	0.93	0.00	0.00	1.05
	bDMARD	3	17253.95	0.17	0.04	0.51	0.17	0.04	0.50
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	NA	NA	NA
	bDMARD	0	3862.00	0.00	0.00	0.96	NA	NA	NA
Chronic lymphatic leukemia									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	0.00	0.00	3.00
	bDMARD	1	11150.85	0.09	0.00	0.50	0.09	0.00	0.49
One previous b/tsDMARD	Tofacitinib	1	1204.81	0.83	0.02	4.62	1.01	0.03	5.63
	bDMARD	0	4881.41	0.00	0.00	0.76	0.00	0.00	0.72
At least 2 previous b/tsDMARD	Tofacitinib	0	1754.53	0.00	0.00	2.10	0.00	0.00	2.34
	bDMARD	1	5089.85	0.20	0.00	1.09	0.19	0.00	1.06
No prior non-tofacitinib JAKi use	Tofacitinib	1	3919.64	0.26	0.01	1.42	0.27	0.01	1.49
	bDMARD	2	19698.41	0.10	0.01	0.37	0.10	0.01	0.37
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	0	2401.24	0.00	0.00	1.54	NA	NA	NA
	bDMARD	0	9039.82	0.00	0.00	0.41	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	1	1806.28	0.55	0.01	3.08	0.61	0.02	3.38
	bDMARD	2	12082.28	0.17	0.02	0.60	0.17	0.02	0.60
Combination therapy with MTX	Tofacitinib	1	1686.84	0.59	0.02	3.30	0.65	0.02	3.62
	bDMARD	1	11250.07	0.09	0.00	0.50	0.09	0.00	0.49
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	1	14377.29	0.07	0.00	0.39	NA	NA	NA
Age ≥65 years	Tofacitinib	1	1314.22	0.76	0.02	4.24	NA	NA	NA
	bDMARD	1	6744.82	0.15	0.00	0.83	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
No malignancy risk factor	Tofacitinib	0	1262.96	0.00	0.00	2.92	0.00	0.00	2.68
	bDMARD	1	6213.70	0.16	0.00	0.90	0.17	0.00	0.93
At least one malignancy risk factor	Tofacitinib	1	2944.56	0.34	0.01	1.89	0.37	0.01	2.07
	bDMARD	1	14871.59	0.07	0.00	0.37	0.07	0.00	0.37
No history of malignancy	Tofacitinib	1	4043.48	0.25	0.01	1.38	0.26	0.01	1.47
	bDMARD	2	20106.80	0.10	0.01	0.36	0.10	0.01	0.36
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	NA	NA	NA
	bDMARD	0	1015.31	0.00	0.00	3.63	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	1	3975.36	0.25	0.01	1.40	0.26	0.01	1.46
	bDMARD	2	17260.11	0.12	0.01	0.42	0.12	0.01	0.42
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89			
	bDMARD	0	3862.00	0.00	0.00	0.96			
19. Lung Cancer									
No previous b/tsDMARD	Tofacitinib	1	1246.45	0.80	0.02	4.47	0.80	0.02	4.45
	bDMARD	24	11134.95	2.16	1.38	3.21	2.20	1.41	3.28
One previous b/tsDMARD	Tofacitinib	4	1200.18	3.33	0.91	8.53	3.55	0.97	9.08
	bDMARD	8	4876.54	1.64	0.71	3.23	1.62	0.70	3.19
At least 2 previous b/tsDMARD	Tofacitinib	7	1750.88	4.00	1.61	8.24	4.13	1.66	8.50
	bDMARD	5	5091.09	0.98	0.32	2.29	0.97	0.32	2.27
No prior non-tofacitinib JAKi use	Tofacitinib	11	3910.11	2.81	1.40	5.03	2.93	1.46	5.25
	bDMARD	35	19679.15	1.78	1.24	2.47	1.79	1.25	2.49
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	287.41	3.48	0.09	19.39	3.48	0.09	19.40
	bDMARD	2	1423.43	1.41	0.17	5.08	1.40	0.17	5.07
Monotherapy	Tofacitinib	3	2399.08	1.25	0.26	3.65	1.27	0.26	3.71
	bDMARD	7	9036.79	0.77	0.31	1.60	0.77	0.31	1.59
Combination Therapy with a nbDMARD	Tofacitinib	9	1798.43	5.00	2.29	9.50	5.29	2.42	10.04
	bDMARD	30	12065.79	2.49	1.68	3.55	2.53	1.70	3.61
Combination therapy with MTX	Tofacitinib	7	1679.62	4.17	1.68	8.59	4.42	1.78	9.11
	bDMARD	28	11231.15	2.49	1.66	3.60	2.52	1.67	3.64
Age <65 years	Tofacitinib	4	2889.10	1.38	0.38	3.54	NA	NA	NA
	bDMARD	16	14368.05	1.11	0.64	1.81	NA	NA	NA
Age ≥65 years	Tofacitinib	8	1308.41	6.11	2.64	12.05	NA	NA	NA
	bDMARD	21	6734.53	3.12	1.93	4.77	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
No malignancy risk factor	Tofacitinib	2	1260.23	1.59	0.19	5.73	1.46	0.18	5.27
	bDMARD	1	6211.16	0.16	0.00	0.90	0.17	0.00	0.93
At least one malignancy risk factor	Tofacitinib	10	2937.29	3.40	1.63	6.26	3.58	1.71	6.58
	bDMARD	36	14854.61	2.42	1.70	3.36	2.44	1.71	3.38
No history of malignancy	Tofacitinib	10	4036.29	2.48	1.19	4.56	2.58	1.24	4.75
	bDMARD	35	20088.00	1.74	1.21	2.42	1.76	1.23	2.45
With history of malignancy	Tofacitinib	2	161.23	12.40	1.50	44.81	12.39	1.50	44.76
	bDMARD	2	1014.58	1.97	0.24	7.12	1.97	0.24	7.13
Therapy start before 30-JUNE-2021	Tofacitinib	11	3965.62	2.77	1.38	4.96	2.87	1.43	5.13
	bDMARD	34	17241.38	1.97	1.37	2.76	1.99	1.38	2.79
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	231.89	4.31	0.11	24.03	4.09	0.10	22.79
	bDMARD	3	3861.20	0.78	0.16	2.27	0.77	0.16	2.26
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	9	2757.53	3.26	1.49	6.20	3.38	1.55	6.42
	bDMARD	33	12183.48	2.71	1.86	3.80	2.73	1.88	3.84
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	1	179.75	5.56	0.14	31.00	6.50	0.16	36.21
	bDMARD	3	2671.13	1.12	0.23	3.28	1.11	0.23	3.25
20. All-cause Mortality									
No previous b/tsDMARD	Tofacitinib	16	1404.24	11.39	6.51	18.50	10.84	6.19	17.60
	bDMARD	146	13130.33	11.12	9.39	13.08	11.49	9.70	13.51
One previous b/tsDMARD	Tofacitinib	19	1362.23	13.95	8.40	21.78	16.03	9.65	25.04
	bDMARD	77	5703.22	13.50	10.65	16.87	13.09	10.33	16.37
At least 2 previous b/tsDMARD	Tofacitinib	31	2031.47	15.26	10.37	21.66	15.26	10.37	21.66
	bDMARD	79	6012.97	13.14	10.40	16.37	12.47	9.85	15.57
No prior non-tofacitinib JAKi use	Tofacitinib	62	4462.22	13.89	10.65	17.81	14.48	11.10	18.56
	bDMARD	285	23120.79	12.33	10.94	13.84	12.43	11.03	13.97
At least one prior non-tofacitinib JAKi use	Tofacitinib	4	335.72	11.91	3.25	30.51	14.26	3.89	36.52
	bDMARD	17	1725.73	9.85	5.74	15.77	9.54	5.56	15.28
Monotherapy	Tofacitinib	36	2738.52	13.15	9.21	18.20	13.82	9.68	19.14
	bDMARD	150	10750.03	13.95	11.81	16.37	13.78	11.66	16.17
Combination Therapy with a nbDMARD	Tofacitinib	30	2059.42	14.57	9.83	20.80	15.36	10.36	21.92
	bDMARD	152	14096.49	10.78	9.14	12.64	11.04	9.36	12.95

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with MTX	Tofacitinib	28	1921.76	14.57	9.68	21.06	15.32	10.18	22.14
	bDMARD	138	13120.34	10.52	8.84	12.43	10.59	8.90	12.52
Age <65 years	Tofacitinib	17	3349.23	5.08	2.96	8.13	NA	NA	NA
	bDMARD	83	17003.66	4.88	3.89	6.05	NA	NA	NA
Age ≥65 years	Tofacitinib	49	1448.71	33.82	25.02	44.72	NA	NA	NA
	bDMARD	219	7842.86	27.92	24.35	31.88	NA	NA	NA
21. Leukaemia (excl. B-CLL)									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	0.00	0.00	2.89
	bDMARD	5	11146.86	0.45	0.15	1.05	0.47	0.15	1.09
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	0.00	0.00	3.71
	bDMARD	1	4880.24	0.20	0.01	1.14	0.20	0.00	1.09
At least 2 previous b/tsDMARD	Tofacitinib	1	1752.24	0.57	0.01	3.18	0.58	0.01	3.21
	bDMARD	3	5088.90	0.59	0.12	1.72	0.59	0.12	1.72
No prior non-tofacitinib JAKi use	Tofacitinib	1	3918.70	0.26	0.01	1.42	0.27	0.01	1.50
	bDMARD	8	19694.60	0.41	0.18	0.80	0.41	0.18	0.81
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	0.00	0.00	13.07
	bDMARD	1	1421.40	0.70	0.02	3.92	0.70	0.02	3.90
Monotherapy	Tofacitinib	0	2401.24	0.00	0.00	1.54	0.00	0.00	1.55
	bDMARD	1	9037.50	0.11	0.00	0.62	0.11	0.00	0.61
Combination Therapy with a nbDMARD	Tofacitinib	1	1805.34	0.55	0.01	3.09	0.61	0.02	3.37
	bDMARD	8	12078.49	0.66	0.29	1.31	0.68	0.30	1.35
Combination therapy with MTX	Tofacitinib	1	1685.89	0.59	0.02	3.30	0.65	0.02	3.61
	bDMARD	7	11244.80	0.62	0.25	1.28	0.63	0.25	1.30
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	1	14377.60	0.07	0.00	0.39	NA	NA	NA
Age ≥65 years	Tofacitinib	1	1313.28	0.76	0.02	4.24	NA	NA	NA
	bDMARD	8	6738.39	1.19	0.51	2.34	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	1262.96	0.00	0.00	2.92	0.00	0.00	3.28
	bDMARD	3	6214.79	0.48	0.10	1.41	0.48	0.10	1.41
At least one malignancy risk factor	Tofacitinib	1	2943.61	0.34	0.01	1.89	0.38	0.01	2.09
	bDMARD	6	14864.40	0.40	0.15	0.88	0.41	0.15	0.89
No history of malignancy	Tofacitinib	1	4042.54	0.25	0.01	1.38	0.26	0.01	1.45
	bDMARD	8	20100.82	0.40	0.17	0.78	0.41	0.18	0.80

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	0.00	0.00	18.90
	bDMARD	1	1015.18	0.99	0.02	5.49	1.02	0.03	5.69
Therapy start before 30-JUNE-2021	Tofacitinib	1	3974.42	0.25	0.01	1.40	0.26	0.01	1.45
	bDMARD	8	17254.49	0.46	0.20	0.91	0.48	0.21	0.94
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	0.00	0.00	16.06
	bDMARD	1	3861.51	0.26	0.01	1.44	0.26	0.01	1.43
22. Other haematopoietic neoplasms (malig-nant and benign)									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	0.00	0.00	2.69
	bDMARD	1	11149.63	0.09	0.00	0.50	0.09	0.00	0.51
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	NA	NA	NA
	bDMARD	0	4881.41	0.00	0.00	0.76	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	1754.53	0.00	0.00	2.10	NA	NA	NA
	bDMARD	0	5092.43	0.00	0.00	0.72	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	3920.99	0.00	0.00	0.94	0.00	0.00	1.00
	bDMARD	1	19699.77	0.05	0.00	0.28	0.05	0.00	0.28
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	0	2401.24	0.00	0.00	1.54	0.00	0.00	1.60
	bDMARD	1	9038.29	0.11	0.00	0.62	0.11	0.00	0.61
Combination Therapy with a nbDMARD	Tofacitinib	0	1807.63	0.00	0.00	2.04	0.00	0.00	2.15
	bDMARD	0	12085.17	0.00	0.00	0.31	0.00	0.00	0.29
Combination therapy with MTX	Tofacitinib	0	1688.19	0.00	0.00	2.19	NA	NA	NA
	bDMARD	0	11250.38	0.00	0.00	0.33	NA	NA	NA
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	0	14377.60	0.00	0.00	0.26	NA	NA	NA
Age ≥65 years	Tofacitinib	0	1315.58	0.00	0.00	2.80	NA	NA	NA
	bDMARD	1	6745.86	0.15	0.00	0.83	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	1262.96	0.00	0.00	2.92	0.00	0.00	2.68
	bDMARD	1	6214.75	0.16	0.00	0.90	0.17	0.00	0.93
At least one malignancy risk factor	Tofacitinib	0	2945.91	0.00	0.00	1.25	0.00	0.00	1.32
	bDMARD	0	14871.91	0.00	0.00	0.25	0.00	0.00	0.24
No history of malignancy	Tofacitinib	0	4044.84	0.00	0.00	0.91	0.00	0.00	0.98

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	1	20108.16	0.05	0.00	0.28	0.05	0.00	0.27
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	NA	NA	NA
	bDMARD	0	1015.31	0.00	0.00	3.63	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	0	3976.72	0.00	0.00	0.93	0.00	0.00	1.08
	bDMARD	0	17263.00	0.00	0.00	0.21	0.00	0.00	0.21
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	0.00	0.00	25.79
	bDMARD	1	3860.47	0.26	0.01	1.44	0.26	0.01	1.44
23. Solid malignancies (overall)									
No previous b/tsDMARD	Tofacitinib	13	1227.18	10.59	5.64	18.12	10.48	5.57	17.91
	bDMARD	92	11013.78	8.35	6.73	10.24	8.45	6.81	10.36
One previous b/tsDMARD	Tofacitinib	12	1193.73	10.05	5.19	17.56	10.73	5.54	18.75
	bDMARD	50	4807.89	10.40	7.72	13.71	10.24	7.60	13.50
At least 2 previous b/tsDMARD	Tofacitinib	18	1726.91	10.42	6.18	16.47	10.79	6.39	17.05
	bDMARD	51	5013.29	10.17	7.57	13.38	10.06	7.49	13.22
No prior non-tofacitinib JAKi use	Tofacitinib	38	3868.78	9.82	6.95	13.48	9.82	6.95	13.48
	bDMARD	174	19443.16	8.95	7.67	10.38	8.80	7.54	10.21
At least one prior non-tofacitinib JAKi use	Tofacitinib	5	279.03	17.92	5.82	41.82	19.26	6.25	44.94
	bDMARD	19	1391.80	13.65	8.22	21.32	13.46	8.10	21.03
Monotherapy	Tofacitinib	22	2362.51	9.31	5.84	14.10	9.44	5.92	14.30
	bDMARD	82	8910.95	9.20	7.32	11.42	9.17	7.29	11.38
Combination Therapy with a nbDMARD	Tofacitinib	21	1785.31	11.76	7.28	17.98	12.10	7.49	18.50
	bDMARD	111	11924.01	9.31	7.66	11.21	9.36	7.70	11.28
Combination therapy with MTX	Tofacitinib	18	1668.33	10.79	6.39	17.05	11.16	6.61	17.63
	bDMARD	101	11094.97	9.10	7.41	11.06	9.12	7.43	11.09
Age <65 years	Tofacitinib	17	2865.99	5.93	3.46	9.50	NA	NA	NA
	bDMARD	98	14205.31	6.90	5.60	8.41	NA	NA	NA
Age ≥65 years	Tofacitinib	26	1281.83	20.28	13.25	29.72	NA	NA	NA
	bDMARD	95	6629.65	14.33	11.59	17.52	NA	NA	NA
No malignancy risk factor	Tofacitinib	11	1235.08	8.91	4.45	15.94	8.81	4.39	15.76
	bDMARD	47	6132.80	7.66	5.63	10.19	7.75	5.69	10.30
At least one malignancy risk factor	Tofacitinib	32	2912.74	10.99	7.51	15.51	11.37	7.78	16.06
	bDMARD	146	14665.35	9.96	8.41	11.71	9.98	8.43	11.74
No history of malignancy	Tofacitinib	37	3990.89	9.27	6.53	12.78	9.47	6.67	13.06

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	172	19848.16	8.67	7.42	10.06	8.71	7.45	10.11
With history of malignancy	Tofacitinib	6	156.92	38.24	14.03	83.22	39.33	14.43	85.61
	bDMARD	21	986.80	21.28	13.17	32.53	21.22	13.13	32.44
Therapy start before 30-JUNE-2021	Tofacitinib	40	3917.64	10.21	7.29	13.90	10.39	7.42	14.15
	bDMARD	162	16997.89	9.53	8.12	11.12	9.60	8.18	11.20
Therapy start on or after 30-JUNE-2021	Tofacitinib	3	230.18	13.03	2.69	38.09	13.45	2.77	39.32
	bDMARD	31	3837.07	8.08	5.49	11.47	8.07	5.48	11.45
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	29	2734.70	10.60	7.10	15.23	10.89	7.29	15.64
	bDMARD	124	12009.59	10.33	8.59	12.31	10.37	8.62	12.36
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	3	178.04	16.85	3.47	49.24	17.85	3.68	52.18
	bDMARD	22	2655.76	8.28	5.19	12.54	8.27	5.18	12.52
24. Glioblastoma									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	NA	NA	NA
	bDMARD	0	11151.16	0.00	0.00	0.33	NA	NA	NA
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	NA	NA	NA
	bDMARD	0	4881.41	0.00	0.00	0.76	NA	NA	NA
At least 2 previous b/tsDMARD	Tofacitinib	0	1754.53	0.00	0.00	2.10	NA	NA	NA
	bDMARD	0	5092.43	0.00	0.00	0.72	NA	NA	NA
No prior non-tofacitinib JAKi use	Tofacitinib	0	3920.99	0.00	0.00	0.94	NA	NA	NA
	bDMARD	0	19701.30	0.00	0.00	0.19	NA	NA	NA
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	NA	NA	NA
	bDMARD	0	1423.69	0.00	0.00	2.59	NA	NA	NA
Monotherapy	Tofacitinib	0	2401.24	0.00	0.00	1.54	NA	NA	NA
	bDMARD	0	9039.82	0.00	0.00	0.41	NA	NA	NA
Combination Therapy with a nbDMARD	Tofacitinib	0	1807.63	0.00	0.00	2.04	NA	NA	NA
	bDMARD	0	12085.17	0.00	0.00	0.31	NA	NA	NA
Combination therapy with MTX	Tofacitinib	0	1688.19	0.00	0.00	2.19	NA	NA	NA
	bDMARD	0	11250.38	0.00	0.00	0.33	NA	NA	NA
Age <65 years	Tofacitinib	0	2893.29	0.00	0.00	1.27	NA	NA	NA
	bDMARD	0	14377.60	0.00	0.00	0.26	NA	NA	NA
Age ≥65 years	Tofacitinib	0	1315.58	0.00	0.00	2.80	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	0	6747.39	0.00	0.00	0.55	NA	NA	NA
No malignancy risk factor	Tofacitinib	0	1262.96	0.00	0.00	2.92	NA	NA	NA
	bDMARD	0	6216.28	0.00	0.00	0.59	NA	NA	NA
At least one malignancy risk factor	Tofacitinib	0	2945.91	0.00	0.00	1.25	NA	NA	NA
	bDMARD	0	14871.91	0.00	0.00	0.25	NA	NA	NA
No history of malignancy	Tofacitinib	0	4044.84	0.00	0.00	0.91	NA	NA	NA
	bDMARD	0	20109.69	0.00	0.00	0.18	NA	NA	NA
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	NA	NA	NA
	bDMARD	0	1015.31	0.00	0.00	3.63	NA	NA	NA
Therapy start before 30-JUNE-2021	Tofacitinib	0	3976.72	0.00	0.00	0.93	NA	NA	NA
	bDMARD	0	17263.00	0.00	0.00	0.21	NA	NA	NA
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	NA	NA	NA
	bDMARD	0	3862.00	0.00	0.00	0.96	NA	NA	NA
25. Benign neoplasms									
No previous b/tsDMARD	Tofacitinib	6	1241.58	4.83	1.77	10.52	4.64	1.70	10.10
	bDMARD	30	11086.60	2.71	1.83	3.86	2.75	1.86	3.93
One previous b/tsDMARD	Tofacitinib	4	1193.15	3.35	0.91	8.58	3.40	0.93	8.72
	bDMARD	16	4850.92	3.30	1.89	5.36	3.29	1.88	5.34
At least 2 previous b/tsDMARD	Tofacitinib	9	1731.23	5.20	2.38	9.87	5.15	2.36	9.78
	bDMARD	29	5023.31	5.77	3.87	8.29	5.79	3.88	8.32
No prior non-tofacitinib JAKi use	Tofacitinib	18	3879.13	4.64	2.75	7.33	4.61	2.73	7.29
	bDMARD	67	19555.79	3.43	2.66	4.35	3.44	2.67	4.37
At least one prior non-tofacitinib JAKi use	Tofacitinib	1	286.83	3.49	0.09	19.43	3.43	0.09	19.11
	bDMARD	8	1405.03	5.69	2.46	11.22	5.71	2.47	11.26
Monotherapy	Tofacitinib	13	2370.07	5.49	2.92	9.38	5.51	2.93	9.41
	bDMARD	33	8969.10	3.68	2.53	5.17	3.68	2.53	5.16
Combination Therapy with a nbDMARD	Tofacitinib	6	1795.88	3.34	1.23	7.27	3.34	1.23	7.27
	bDMARD	42	11991.72	3.50	2.52	4.73	3.54	2.55	4.79
Combination therapy with MTX	Tofacitinib	6	1676.44	3.58	1.31	7.79	3.56	1.31	7.76
	bDMARD	37	11167.52	3.31	2.33	4.57	3.32	2.34	4.58
Age <65 years	Tofacitinib	10	2871.82	3.48	1.67	6.40	NA	NA	NA
	bDMARD	43	14275.28	3.01	2.18	4.06	NA	NA	NA
Age ≥65 years	Tofacitinib	9	1294.14	6.95	3.18	13.20	NA	NA	NA

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	32	6685.54	4.79	3.27	6.76	NA	NA	NA
No malignancy risk factor	Tofacitinib	9	1240.87	7.25	3.32	13.77	7.03	3.21	13.34
	bDMARD	29	6147.63	4.72	3.16	6.77	4.75	3.18	6.83
At least one malignancy risk factor	Tofacitinib	10	2925.09	3.42	1.64	6.29	3.45	1.65	6.34
	bDMARD	46	14776.39	3.11	2.28	4.15	3.12	2.28	4.16
No history of malignancy	Tofacitinib	19	4001.93	4.75	2.86	7.41	4.71	2.83	7.35
	bDMARD	70	19956.71	3.51	2.73	4.43	3.53	2.75	4.45
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	0.00	0.00	19.98
	bDMARD	5	1004.12	4.98	1.62	11.62	5.11	1.66	11.92
Therapy start before 30-JUNE-2021	Tofacitinib	19	3933.81	4.83	2.91	7.54	4.76	2.87	7.44
	bDMARD	62	17109.63	3.62	2.78	4.65	3.65	2.80	4.67
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	0.00	0.00	19.54
	bDMARD	13	3851.19	3.38	1.80	5.77	3.36	1.79	5.75
At least one malignancy risk factor and therapy start before 30-JUNE-2021	Tofacitinib	10	2745.08	3.64	1.75	6.70	3.64	1.74	6.69
	bDMARD	38	12113.01	3.14	2.22	4.31	3.15	2.23	4.33
At least one malignancy risk factor and therapy start on or after 30-JUNE-2021	Tofacitinib	0	180.01	0.00	0.00	20.49	0.00	0.00	23.79
	bDMARD	8	2663.38	3.00	1.30	5.92	3.03	1.31	5.96
26. Unspecified neoplasms and precanceroses									
No previous b/tsDMARD	Tofacitinib	2	1247.48	1.60	0.19	5.79	1.48	0.18	5.35
	bDMARD	12	11126.94	1.08	0.56	1.88	1.10	0.57	1.92
One previous b/tsDMARD	Tofacitinib	0	1206.16	0.00	0.00	3.06	0.00	0.00	3.37
	bDMARD	4	4876.47	0.82	0.22	2.10	0.80	0.22	2.05
At least 2 previous b/tsDMARD	Tofacitinib	1	1754.48	0.57	0.01	3.18	0.55	0.01	3.09
	bDMARD	2	5088.89	0.39	0.05	1.42	0.40	0.05	1.43
No prior non-tofacitinib JAKi use	Tofacitinib	3	3920.25	0.77	0.16	2.24	0.78	0.16	2.29
	bDMARD	17	19670.17	0.86	0.50	1.38	0.87	0.51	1.39
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	0.00	0.00	11.10
	bDMARD	1	1422.12	0.70	0.02	3.92	0.73	0.02	4.04
Monotherapy	Tofacitinib	1	2401.24	0.42	0.01	2.32	0.42	0.01	2.34
	bDMARD	5	9030.01	0.55	0.18	1.29	0.55	0.18	1.29
Combination Therapy with a nbDMARD	Tofacitinib	2	1806.89	1.11	0.13	4.00	1.16	0.14	4.18

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
	bDMARD	13	12062.28	1.08	0.57	1.84	1.09	0.58	1.86
Combination therapy with MTX	Tofacitinib	1	1687.50	0.59	0.02	3.30	0.62	0.02	3.46
	bDMARD	12	11230.44	1.07	0.55	1.87	1.07	0.55	1.86
Age <65 years	Tofacitinib	1	2892.60	0.35	0.01	1.93	NA	NA	NA
	bDMARD	9	14354.34	0.63	0.29	1.19	NA	NA	NA
Age ≥65 years	Tofacitinib	2	1315.52	1.52	0.18	5.49	NA	NA	NA
	bDMARD	9	6737.95	1.34	0.61	2.54	NA	NA	NA
No malignancy risk factor	Tofacitinib	1	1262.91	0.79	0.02	4.41	0.74	0.02	4.10
	bDMARD	3	6211.42	0.48	0.10	1.41	0.50	0.10	1.45
At least one malignancy risk factor	Tofacitinib	2	2945.22	0.68	0.08	2.45	0.71	0.09	2.56
	bDMARD	15	14844.06	1.01	0.57	1.67	1.01	0.57	1.67
No history of malignancy	Tofacitinib	3	4044.09	0.74	0.15	2.17	0.76	0.16	2.22
	bDMARD	14	20088.95	0.70	0.38	1.17	0.70	0.38	1.18
With history of malignancy	Tofacitinib	0	164.03	0.00	0.00	22.49	0.00	0.00	22.45
	bDMARD	4	1003.35	3.99	1.09	10.21	3.98	1.08	10.19
Therapy start before 30-JUNE-2021	Tofacitinib	2	3975.97	0.50	0.06	1.82	0.51	0.06	1.84
	bDMARD	17	17230.57	0.99	0.57	1.58	0.99	0.58	1.59
Therapy start on or after 30-JUNE-2021	Tofacitinib	1	232.15	4.31	0.11	24.00	7.00	0.18	38.98
	bDMARD	1	3861.73	0.26	0.01	1.44	0.26	0.01	1.44
27. Metastases and cancer related morbidities and associated syndroms									
No previous b/tsDMARD	Tofacitinib	0	1248.17	0.00	0.00	2.96	0.00	0.00	3.11
	bDMARD	3	11150.72	0.27	0.06	0.79	0.27	0.06	0.80
One previous b/tsDMARD	Tofacitinib	2	1205.57	1.66	0.20	5.99	1.77	0.21	6.38
	bDMARD	2	4881.39	0.41	0.05	1.48	0.40	0.05	1.46
At least 2 previous b/tsDMARD	Tofacitinib	1	1754.08	0.57	0.01	3.18	0.66	0.02	3.69
	bDMARD	2	5090.92	0.39	0.05	1.42	0.38	0.05	1.35
No prior non-tofacitinib JAKi use	Tofacitinib	3	3919.95	0.77	0.16	2.24	0.78	0.16	2.29
	bDMARD	6	19700.37	0.30	0.11	0.66	0.31	0.11	0.67
At least one prior non-tofacitinib JAKi use	Tofacitinib	0	287.87	0.00	0.00	12.81	0.00	0.00	19.57
	bDMARD	1	1422.65	0.70	0.02	3.92	0.66	0.02	3.66
Monotherapy	Tofacitinib	2	2400.66	0.83	0.10	3.01	0.85	0.10	3.08
	bDMARD	2	9038.78	0.22	0.03	0.80	0.22	0.03	0.79

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Table 16. Ever-exposed approach: Total number of events, crude and standardized IRs (per 1000 PYs) for subgroups

		Number of events	Total fol-low-up, years	Crude IR per 1000 PY	Crude 95% CI		Std. IR per 1000 PY	Std. 95% CI	
					LCL	UCL		LCL	UCL
Combination Therapy with a nbDMARD	Tofacitinib	1	1807.16	0.55	0.01	3.08	0.58	0.01	3.21
	bDMARD	5	12084.24	0.41	0.13	0.97	0.42	0.14	0.98
Combination therapy with MTX	Tofacitinib	1	1687.72	0.59	0.02	3.30	0.61	0.02	3.42
	bDMARD	5	11249.45	0.44	0.14	1.04	0.44	0.14	1.04
Age <65 years	Tofacitinib	1	2893.17	0.35	0.01	1.93	NA	NA	NA
	bDMARD	4	14376.10	0.28	0.08	0.71	NA	NA	NA
Age ≥65 years	Tofacitinib	2	1314.65	1.52	0.18	5.50	NA	NA	NA
	bDMARD	3	6746.92	0.44	0.09	1.30	NA	NA	NA
No malignancy risk factor	Tofacitinib	1	1262.49	0.79	0.02	4.41	0.76	0.02	4.23
	bDMARD	3	6215.59	0.48	0.10	1.41	0.49	0.10	1.43
At least one malignancy risk factor	Tofacitinib	2	2945.33	0.68	0.08	2.45	0.71	0.09	2.58
	bDMARD	4	14870.62	0.27	0.07	0.69	0.27	0.07	0.69
No history of malignancy	Tofacitinib	1	4044.38	0.25	0.01	1.38	0.26	0.01	1.43
	bDMARD	6	20108.19	0.30	0.11	0.65	0.30	0.11	0.65
With history of malignancy	Tofacitinib	2	163.44	12.24	1.48	44.21	11.79	1.43	42.58
	bDMARD	1	1014.84	0.99	0.02	5.49	0.99	0.03	5.54
Therapy start before 30-JUNE-2021	Tofacitinib	3	3975.67	0.75	0.16	2.21	0.79	0.16	2.31
	bDMARD	5	17261.72	0.29	0.09	0.68	0.29	0.09	0.68
Therapy start on or after 30-JUNE-2021	Tofacitinib	0	232.15	0.00	0.00	15.89	0.00	0.00	16.73
	bDMARD	2	3861.31	0.52	0.06	1.87	0.52	0.06	1.87

Standardized IRs were calculated based on direct standardization if there were at least five events in each of the standardization groups (women <65 years, men <65 years, women ≥ 65 years, men ≥ 65 years), and based on indirect standardization otherwise. For the subgroups Age <65 years and Age ≥65 years no standardized IRs could be calculated by definition. If within a considered subgroup, any of the standardization groups did not contain patients, no standardized IRs could be calculated. If no standardized IR was available for one of these reasons or if there were no events across all cohorts, NA is given instead of a standardized IR.
Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval IR, incidence rate; JAKi, Janus kinase inhibitor; LCL, lower confidence limit; MTX, Methotrexate; NA, not applicable; NMSC, non-melanoma skin cancer; PY, patient year; std., standardized by age/sex; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; UCL: upper confidence limit.

10.4. Main Results

The results of the Cox regression models for the on-drug approach are presented in Table 17. Since there were fewer than five events occurring in the tofacitinib cohort for analyses restricted to the first event per patient, Cox regression was not performed for the following outcomes: other infections of the respiratory system, infections of CNS, bone / joint infections, opportunistic infections, TB, hepatic failure, DVT, bone marrow depression and hypoplastic anaemia, decreased white blood cells, platelet disorders, central demyelination, psychiatric disorders, allergic conditions and hypersensitivity, PML, GI perforations (overall, and subtypes), ILD, leukaemia, other haematopoietic neoplasms, glioblastoma, unspecified neoplasms and precanceroses, metastases and lymphoma (overall and subtypes).

For model C, imbalances between the tofacitinib and bDMARD groups in the original (i.e., unweighted) sample were found for DAS28-ESR, FFbH, number of previously used b/tsDMARDs, year of therapy start, and RA disease duration. After weighting, values above the cut-off (i.e., ±0.1) remained for the variable year of therapy start, which was therefore added to the outcome models (see Table 23).

Due to the even smaller number of events in the b/tsDMARD naive tofacitinib cohort, no Cox regression to compare the tofacitinib and nbDMARD groups among b/tsDMARD naive patients was moreover performed for the following outcomes: sepsis, myocardial infarction, heart failure, coronary artery disease, embolic and thrombotic events, hematologic disorders, stroke, other disorders of the CNS, disorders of the peripheral nervous system, other operations and (major) therapeutic procedures that lead to hospitalization, NMSC, lung cancer, and benign neoplasms.

For model C applied to the b/tsDMARD naive tofacitinib cohort, imbalances between the tofacitinib and nbDMARD groups in the original (i.e., unweighted) sample were found for age, DAS28-ESR, FFbH, glucocorticoid dosage, smoking, year of therapy start, RA disease duration and the outcome-specific variables chronic renal disease and CV risk factors. After weighting, values above the cut-off (i.e., ±0.1) remained for the variables year of therapy start and additionally (except for the outcomes serious infections and subtypes, HZ and mortality) for RA disease duration, which were therefore added to the outcome models (see Table 23).

The histograms of the PS distributions (both for therapy and for informative dropout) generally show similar patterns across outcomes (see Table 22), which is expected as most of the covariates considered in the PS models were the same across outcomes. The overlap in the dropout PS distributions was generally good between tofacitinib and both comparator cohorts. The overlap in the therapy PS distributions was reasonably good for propensity scores > 0.05 but limited for smaller propensity scores.

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On-drug approach

1. Serious infections (excluding TB, overall)

The hazard of serious infections was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.07; 95% CI: 0.77 – 1.47). In comparison to the nbDMARD cohort, the hazard among the tofacitinib cohort was higher using the fully adjusted model C, but the difference was not statistically significant (model C: HR 1.55; 95% CI: 0.83 – 2.88).

- Pneumonia: The hazard of pneumonia was higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.46; 95% CI: 0.83 – 2.56) and the nbDMARD (model C: HR 2.55; 95% CI: 0.98 – 6.61), but neither result was statistically significant.

- Sepsis: Regardless of the model used, the hazard of sepsis was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.04; 95% CI: 0.49 – 2.20).

- Other infections: Regardless of the model used, the hazard of other infections was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.09; 95% CI: 0.68 – 1.75) or the tofacitinib and nbDMARD cohorts (model C: HR 1.29; 95% CI: 0.45 – 3.69).

3. HZ: Regardless of the model used, the hazard of HZ statistically was significantly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 2.38; 95% CI: 1.65 – 3.43) and compared to the nbDMARD cohort (model C: HR 5.79; 95% CI: 2.75 – 12.18).

4. Fractures: Regardless of the model used, the hazard of fractures was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.18; 95% CI: 0.84 – 1.66). In contrast, regardless of the model used, the hazard of fractures statistically was significantly higher in the tofacitinib cohort compared to the nbDMARD cohort (model C: HR 2.19; 95% CI: 1.27 – 3.77).

5. Cardiac disorders (overall): The hazard of cardiac disorders was higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.45, 95% CI: 0.99 – 2.12), however, the difference was not statistically significant (model C: p=0.059). In contrast, regardless of the model used, the hazard of cardiac disorders statistically was significantly higher in the tofacitinib cohort compared to the nbDMARD cohort (model C: HR 2.53; 95% CI: 1.29 – 4.96).

- Heart failure: The hazard of heart failure was higher in the tofacitinib cohort compared to the bDMARD cohort, however, the difference was not statistically significant (model C: HR 1.74; 95% CI: 0.75 – 4.07).
- Coronary artery disease: Regardless of the model used, the hazard of coronary artery disease was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 0.97; 95% CI: 0.42 – 2.25).

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- Myocardial infarction: The hazard of myocardial infarction was higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.97; 95% CI: 0.98 – 3.96), however, the difference was not statistically significant (model C: p=0.058).
- Cardiovascular risk (MACE): Regardless of the model used, the hazard of MACE statistically was significantly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.78; 95% CI: 1.04 – 3.06). In contrast, the hazard of MACE statistically was significantly higher in the tofacitinib cohort compared to the nbDMARD cohort only for the unadjusted model and elevated (but without statistical significance) for model C (HR 2.26; 95% CI: 0.92 – 5.54).
- Other cardiac disorders: Regardless of the model used, the hazard of other cardiac disorders was slightly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.32; 95% CI: 0.78 – 2.25), however, the difference was not statistically significant. In contrast, the hazard of other cardiac disorders statistically was significantly higher in the tofacitinib cohort compared to the nbDMARD cohort for the unadjusted model and elevated (without statistical significance) for model C (HR 2.64; 95% CI: 0.95 – 7.34).

6. Hematologic disorders (overall): Regardless of the model used, the hazard of hematologic disorders overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.06; 95% CI: 0.45 – 2.52).

Other blood dyscrasia: Regardless of the model used, the hazard of other blood dyscrasia was slightly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.33; 95% CI: 0.51 – 3.48), however, the difference was not statistically significant.

7. Disorders of the nervous system (excluding infections) (overall): Regardless of the model used, the hazard of disorders of the nervous system (excluding infections) overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.07; 95% CI: 0.71 – 1.63) or the tofacitinib and nbDMARD cohorts (model C: HR 1.20; 95% CI: 0.45 – 3.17).

- Stroke: The hazard of stroke was higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.93; 95% CI: 0.98 – 3.81), however, the difference was not statistically significant (model C: p=0.056).
- Other disorders of the CNS: Regardless of the model used, the hazard of other disorders of the CNS was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.16; 95% CI: 0.61 – 2.19).
- Disorders of the peripheral nervous system: Regardless of the model used, the hazard of disorders of the peripheral nervous system was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.08; 95% CI: 0.36 – 3.23).

13. Embolic and thrombotic events, venous or vessel type unspecified (overall): Regardless of the model used, the hazard of embolic and thrombotic events, venous or vessel type unspecified overall was slightly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 1.25; 95% CI: 0.51 – 3.07), however, the difference was not statistically significant.

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VTE: Regardless of the model used, the hazard of VTE was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.14; 95% CI: 0.44 – 2.96).

PE: The hazard of PE was higher in the tofacitinib cohort compared to the bDMARD cohort using the fully adjusted model C, however, the difference was not statistically significant (model C: HR 1.55; 95% CI: 0.85 – 4.11).

14. Operations and hospitalizations (overall): Regardless of the model used, the hazard of operations and hospitalizations overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.00; 95% CI: 0.66 – 1.51). In contrast, the hazard of operations and hospitalizations overall was higher in the tofacitinib cohort compared to the nbDMARD cohort for model C, but without statistical significance (HR 1.77; 95% CI: 0.85 – 3.70).

- Bone and joint surgery and other joint therapeutic procedures: Regardless of the model used, the hazard of bone and joint surgery and other joint therapeutic procedures was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 0.94; 95% CI: 0.59 – 1.51). However, the hazard of bone and joint surgery and other joint therapeutic procedures was higher in the tofacitinib cohort compared to the nbDMARD cohort, but without statistical significance (model C: HR 1.45; 95% CI: 0.62 – 3.40).
- Other operations and (major) therapeutic procedures that lead to hospitalization: Regardless of the model used, the hazard of other operations and (major) therapeutic procedures that lead to hospitalization was slightly higher in the tofacitinib cohort compared to the bDMARD cohort, but without statistical significance (model C: HR 1.28; 95% CI: 0.60 – 2.74). The hazard of other operations and (major) therapeutic procedures that lead to hospitalization was higher in the tofacitinib cohort compared to the nbDMARD cohort, but without statistical significance (model C: HR 2.87; 95% CI: 0.65 – 12.73).

15. Other serious diagnoses, symptoms, and syndromes (overall): Regardless of the model used, the hazard of other serious diagnoses, symptoms, and syndromes overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 0.98; 95% CI: 0.82 – 1.19). In contrast, regardless of the model used, the hazard of other serious diagnoses, symptoms, and syndromes overall statistically was significantly higher in the tofacitinib cohort compared to the nbDMARD cohort (model C: HR 1.91; 95% CI: 1.36 – 2.69).

16. NMSC: Regardless of the model used, the hazard of NMSC statistically was significantly higher in the tofacitinib cohort compared to the bDMARD cohort (model C: HR 2.40; 95% CI: 1.21 – 4.80).

17. Malignancies (overall, excluding NMSC): Regardless of the model used, the hazard of malignancies (overall, excluding NMSC) was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.06; 95% CI: 0.66 – 1.69. However, the hazard of malignancies (overall, excluding NMSC) was higher in the tofacitinib cohort compared to the nbDMARD cohort, but without statistical significance (model C: HR 2.04; 95% CI: 0.87 – 4.75).

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19. Lung cancer: Regardless of the model used, the hazard of lung cancer was higher in the tofacitinib cohort compared to the bDMARD cohort, but without statistical significance (model C: HR 1.86; 95% CI: 0.72 – 4.82).

20. All-cause Mortality: Regardless of the model used, the hazard of all-cause mortality was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 0.94; 95% CI: 0.52 – 1.71). In contrast, the hazard of all-cause mortality was higher in the tofacitinib cohort compared to the nbDMARD cohort, but without statistical significance (model C: HR 1.88; 95% CI: 0.66 – 5.35).

23. Solid malignancies (overall): Regardless of the model used, the hazard of solid malignancies overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.07; 95% CI: 0.65 – 1.77). However, the hazard of solid malignancies was higher in the tofacitinib cohort compared to the nbDMARD cohort, but without statistical significance (model C: HR 1.45; 95% CI: 0.56 – 3.77).

25. Benign neoplasms: Regardless of the model used the hazard of benign neoplasms was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.06; 95% CI: 0.51 – 2.21).

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Table 17. Cox regression models for the on-drug approach

Outcome	Tofacitinib versus	Model A			Model B			Model C		
			95% CI			95% CI			95% CI	
		HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
1. Serious infection	bDMARD	1.12	0.84	1.49	1.16	0.87	1.56	1.07	0.77	1.47
	nbDMARD	1.69	0.93	3.06	1.55	0.85	2.81	1.55	0.83	2.88
Pneumonia	bDMARD	1.46	0.87	2.46	1.53	0.91	2.58	1.46	0.83	2.56
	nbDMARD	2.33	0.94	5.77	2.14	0.86	5.30	2.55	0.98	6.61
Sepsis	bDMARD	1.35	0.66	2.74	1.45	0.71	2.96	1.04	0.49	2.20
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other infections	bDMARD	1.06	0.70	1.60	1.09	0.72	1.64	1.09	0.68	1.75
	nbDMARD	1.43	0.53	3.86	1.26	0.47	3.40	1.29	0.45	3.69
3. HZ	bDMARD	**2.63**	**1.90**	**3.63**	**2.57**	**1.85**	**3.55**	**2.38**	**1.65**	**3.43**
	nbDMARD	**5.32**	**2.72**	**10.39**	**5.16**	**2.64**	**10.09**	**5.79**	**2.75**	**12.18**
4. Fractures	bDMARD	1.18	0.87	1.60	1.16	0.85	1.57	1.18	0.84	1.66
	nbDMARD	**2.58**	**1.53**	**4.37**	**2.37**	**1.40**	**4.02**	**2.19**	**1.27**	**3.77**
5. Cardiac disorders	bDMARD	1.30	0.92	1.82	1.35	0.96	1.90	1.45	0.99	2.12
	nbDMARD	**2.68**	**1.40**	**5.12**	**2.55**	**1.33**	**4.91**	**2.53**	**1.29**	**4.96**
Heart failure	bDMARD	1.25	0.64	2.46	1.30	0.66	2.55	1.74	0.75	4.07
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Coronary artery disease	bDMARD	0.84	0.39	1.83	.85	0.39	1.87	0.97	0.42	2.25
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA

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Table 17. Cox regression models for the on-drug approach

Outcome	Tofacitinib versus	Model A			Model B			Model C		
			95% CI			95% CI			95% CI	
		HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
Myocardial infarction	bDMARD	1.78	0.93	3.44	1.84	0.95	3.55	1.97	0.98	3.96
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
MACE	bDMARD	**1.66**	**1.02**	**2.70**	**1.77**	**1.08**	**2.88**	**1.78**	**1.04**	**3.06**
	nbDMARD	**2.45**	**1.01**	**5.94**	2.40	0.99	5.87	2.26	0.92	5.54
Other cardiac disorders	bDMARD	1.33	0.83	2.14	1.39	0.86	2.24	1.32	0.78	2.25
	nbDMARD	**2.71**	**1.03**	**7.10**	2.48	0.94	6.55	2.64	0.95	7.34
6. Hematologic disorders	bDMARD	1.10	0.50	2.42	1.12	0.51	2.49	1.06	0.45	2.52
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other blood dyscrasia	bDMARD	1.45	0.61	3.46	1.49	0.62	3.58	1.33	0.51	3.48
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
7. Disorders of the nervous system	bDMARD	1.12	0.79	1.60	1.17	0.82	1.67	1.07	0.71	1.63
	nbDMARD	1.19	0.50	2.82	1.12	0.47	2.67	1.20	0.45	3.17
Stroke	bDMARD	1.64	0.92	2.93	1.75	0.97	3.13	1.93	0.98	3.81
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other disorders of the CNS	bDMARD	1.15	0.68	1.95	1.16	0.69	1.97	1.16	0.61	2.19
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Disorders of the peripheral nervous system	bDMARD	0.82	0.33	2.08	0.88	.035	2.24	1.08	0.36	3.23
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
13. Embolic and thrombotic events	bDMARD	1.26	0.57	2.82	1.34	0.60	3.00	1.25	0.51	3.07

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Table 17. Cox regression models for the on-drug approach

Outcome	Tofacitinib versus	Model A			Model B			Model C		
			95% CI			95% CI			95% CI	
		HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
VTE	bDMARD	1.08	0.46	2.55	1.14	0.48	2.71	1.14	0.44	2.96
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
PE	bDMARD	1.43	0.60	3.44	1.52	0.63	3.66	1.55	0.58	4.11
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Operations and hospitalizations	bDMARD	1.05	0.73	1.51	1.07	0.74	1.54	1.00	0.66	1.51
	nbDMARD	**2.22**	**1.07**	**4.61**	2.02	0.97	4.21	1.77	0.85	3.70
Bone and joint surgery and other joint therapeutic procedures	bDMARD	0.95	0.63	1.43	0.95	0.63	1.45	0.94	0.59	1.51
	nbDMARD	1.73	0.75	4.01	1.56	0.67	3.61	1.45	0.62	3.40
Other operations and (major) therapeutic procedures that lead to hospitalization	bDMARD	1.54	0.75	3.15	1.61	0.78	3.31	1.28	0.60	2.74
	nbDMARD	4.33	0.95	19.73	4.04	0.89	18.33	2.87	0.65	12.73
15. Other serious diagnoses, symptoms, and syndromes	bDMARD	1.05	0.88	1.24	1.04	0.88	1.23	0.98	0.82	1.19
	nbDMARD	**2.09**	**1.52**	**2.88**	**1.98**	**1.43**	**2.74**	**1.91**	**1.36**	**2.69**
16. NMSC	bDMARD	**2.22**	**1.17**	**4.22**	**2.32**	**1.22**	**4.42**	**2.40**	**1.21**	**4.80**
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
17. Malignancies (excl. NMSC)	bDMARD	1.08	0.70	1.67	1.10	0.71	1.71	1.06	0.66	1.69
	nbDMARD	1.77	0.78	3.99	1.63	0.72	3.69	2.04	0.87	4.75
19. Lung Cancer	bDMARD	1.96	0.80	4.80	2.02	0.83	4.95	1.86	0.72	4.82

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Table 17. Cox regression models for the on-drug approach

Outcome	Tofacitinib versus	Model A			Model B			Model C		
			95% CI			95% CI			95% CI	
		HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA
20. All-cause Mortality	bDMARD	1.10	0.64	1.89	1.14	0.66	1.97	0.94	0.52	1.71
	nbDMARD	2.20	0.81	5.98	1.89	0.69	5.20	1.88	0.66	5.35
23. Solid malignancies (overall)	bDMARD	1.14	0.71	1.82	1.17	0.73	1.87	1.07	0.65	1.77
	nbDMARD	1.35	0.54	3.37	1.25	0.50	3.12	1.45	0.56	3.77
25. Benign neoplasms	bDMARD	1.36	0.70	2.66	1.42	0.73	2.79	1.06	0.51	2.21
	nbDMARD	NA	NA	NA	NA	NA	NA	NA	NA	NA

Model A is unadjusted, Model B is adjusted for age and sex, and Model C is adjusted for age, sex, RA disease duration, RF/ ACPA positivity, year of therapy start, DAS28-ESR, FFbH, previous b/tsDMARDs, glucocorticoid dosage, and smoking, plus potentially outcome specific covariates. For a detailed description of model covariates, see Table 4.
Cox regression models for comparing tofacitinib to bDMARDs (nbDMARDs) were only calculated for outcomes of interest with at least five events in the tofacitinib cohort (among bionaive patients in the tofacitinib cohort). If no model was calculated, NA is given instead of estimates. Statistically significant results are marked in bold.
Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; HZ, herpes zoster; LCL, lower confidence limit; MACE, major cardiovascular events; NA, not applicable; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; UCL: upper confidence limit; VTE, venous thromboembolism.

Table 18. Cox regression models for Tofacitinib vs. bDMARDs in the on-drug approach, sensitivity analysis (Model C)

Outcome	Model C		
	HR	95% CI	
		LCL	UCL
1. Serious infection	1.13	0.82	1.55
Pneumonia	1.45	0.83	2.55
Sepsis	0.88	0.40	1.95
Other infections	1.19	0.76	1.88
3. HZ	**2.42**	**1.68**	**3.48**
4. Fractures	1.21	0.87	1.69
5. Cardiac disorders	1.40	0.95	2.05
Heart failure	1.73	0.74	4.05
Coronary artery disease	0.97	0.42	2.25
Myocardial infarction	1.98	0.98	3.99
MACE	**1.78**	**1.04**	**3.04**
Other cardiac disorders	1.25	0.72	2.14
6. Hematologic disorders	1.19	0.53	2.70
Other blood dyscrasia	1.33	0.51	3.48
7. Disorders of the nervous system	1.13	0.75	1.71
Stroke	1.93	0.98	3.80
Other disorders of the CNS	1.33	0.71	2.46
Disorders of the peripheral nervous system	1.05	0.35	3.17
13. Embolic and thrombotic events	1.25	0.51	3.07
VTE	1.14	0.44	2.96
PE	1.55	0.58	4.11
14. Operations and hospitalizations	0.99	0.66	1.50
Bone and joint surgery and other joint therapeutic procedures	0.95	0.59	1.52
Other operations and (major) therapeutic procedures that lead to hospitalization	1.29	0.60	2.75
15. Other serious diagnoses, symptoms, and syndromes	1.02	0.85	1.22
16. NMSC	2.68	1.37	5.23
17. Malignancies (excl. NMSC)	1.12	0.71	1.76
19. Lung Cancer	2.50	1.07	5.84
20. All-cause Mortality	0.94	0.52	1.69
23. Solid malignancies (overall)	1.14	0.69	1.88
25. Benign neoplasms	1.06	0.51	2.19

Model C is adjusted for age, sex, RA disease duration,ʳRF/ ACPA positivity, year of therapy start, DAS28-ESR,ʳFFbH,ʳprevious b/tsDMARDs, glucocorticoid dosage, and smoking, plus potentially outcome specific covariates. For a detailed description of model covariates, see Table 4. Statistically significant results are marked in bold.
Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; HZ, herpes zoster; LCL,

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Table 18. Cox regression models for Tofacitinib vs. bDMARDs in the on-drug approach, sensitivity analysis (Model C)

Outcome	Model C		
	HR	95% CI	
		LCL	UCL

lower confidence limit; MACE, major cardiovascular events; NA, not applicable; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; UCL: upper confidence limit; VTE, venous thromboembolism.

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Ever-exposed approach

The results of the Cox regression models for the ever-exposed approach are presented in Table 19.

16. NMSC:
Regardless of the model used, the hazard of NMSC was higher in the tofacitinib cohort compared to the bDMARD cohort, but without statistical significance (model C: HR 1.57; 95% CI: 0.84 – 2.93).

17. Malignancies (overall, excluding NMSC):
Regardless of the model used, the hazard of malignancies (overall, excluding NMSC) was slightly higher in the tofacitinib cohort compared to the bDMARD cohort, but without statistical significance (model C: HR 1.31; 95% CI: 0.89 – 1.93).

19. Lung cancer:
The hazard of lung cancer was higher in the tofacitinib cohort compared to the bDMARD cohort, however, the difference was not statistically significant (model C: HR 1.70; 95% CI: 0.75 – 3.87).

20. All-cause Mortality:
Regardless of the model used, the hazard of all-cause mortality was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 0.93; 95% CI: 0.66 – 1.31).

23. Solid malignancies (overall):
Regardless of the model used, the hazard of solid malignancies overall was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.04; 95% CI: 0.70 – 1.56).

25. Benign neoplasms:
Regardless of the model used, the hazard of benign neoplasms was similar and statistically not significantly different when comparing the tofacitinib and bDMARD cohorts (model C: HR 1.01; 95% CI: 0.55 – 1.83).

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Table 19. Cox regression models for Tofacitinib vs. bDMARDs in the ever-exposed / ever-exposed with latency period approach

Outcome	Model A			Model B			Model C		
		95% CI			95% CI		HR	95% CI	
	HR	LCL	UCL	HR	LCL	UCL		LCL	UCL
16. NMSC	1.72	0.94	3.13	1.71	0.93	3.13	1.57	0.84	2.93
17. Malignancies (overall, excluding NMSC)	1.29	0.91	1.83	1.33	0.93	1.89	1.31	0.89	1.93
19. Lung Cancer	1.68	0.76	3.68	1.72	0.78	3.80	1.70	0.75	3.87
20. All-cause Mortality	1.03	0.74	1.42	1.08	0.78	1.49	0.93	0.66	1.31
23. Solid malignancies (overall)	1.12	0.76	1.65	1.16	0.79	1.71	1.04	0.70	1.56
25. Benign neoplasms	1.30	0.73	2.32	1.36	0.76	2.44	1.01	0.55	1.83

Model A is unadjusted, Model B is adjusted for age and sex, and Model C is adjusted for age, sex, RA disease duration, RF/ ACPA positivity, year of therapy start, DAS28-ESR, FFbH, previous b/tsDMARDs, glucocorticoid dosage, and smoking, plus potentially outcome specific covariates. For a detailed description of model covariates, see Table 4 , In the ever-exposed approach, once patients are exposed, they will always remain at risk, i.e., exposure does not stop when a therapy is discontinued/switched. In the ever-exposed with latency period approach, the ever-exposed approach is employed but exposure starts with a latency of six months, i.e., events occurring during the first six months after therapy start are not assigned to the therapy.
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; HR, hazard ratio; LCL, lower confidence limit; NMSC, non-melanoma skin cancer; UCL: upper confidence limit.

Pregnancies

Two pregnancies were allocated to the tofacitinib cohort, one associated with maternal exposure and one associated with paternal exposure (Table 20).

The pregnancy associated with maternal tofacitinib exposure was a singleton pregnancy that ended in a live birth. There were two non-serious maternal events during this pregnancy. The woman was treated with tofacitinib for 22 months, and her therapy was stopped when the pregnancy was identified. Two months after therapy stop, the woman had non-serious nausea and 4 months after therapy stop, gestational diabetes was diagnosed.

The singleton pregnancy associated with paternal tofacitinib exposure ended with a live birth. The therapy with tofacitinib was not discontinued due to pregnancy intention. Due to abnormal heart sounds of the fetus, a Caesarean section was performed. Due to increased inflammatory markers, the neonate was in the intensive care unit for one week.

A total of 32 pregnancy-related events were reported for 109 pregnancies associated with maternal exposure to bDMARDs. Twenty of these events were classified as serious (Table 20). There were also 6 serious neonatal events in the bDMARD cohort. Of 9 singleton pregnancies in the bDMARD cohort occurring in association with paternal exposure, 6 were live births and for 3 the outcome was unknown.

In the nbDMARD cohort, one serious pregnancy-related event was reported among 4 pregnancies. Of 4 (2) pregnancies occurring in association with maternal (paternal) exposure, three (all) were live births, for one pregnancy with maternal exposure, this information was missing.

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Table 20. Counts of Pregnancies, pregnancy-related outcomes, and pregnancy-related events

	Tofacitinib	bDMARD	nbDMARD
Pregnancies with maternal exposure			
Number of total pregnancies	1	109	4
Number of patients (mothers)	1	83	3
Singleton pregnancies	1	107	4
Twin pregnancies	0	2	0
Pregnancy outcomes			
Live births	1	83	3
Abortion, fetal death, stillbirth	0	23	0
Unknown	0	3	1
Pregnancy related events			
Maternal events, serious and non-serious	2	32	1
thereof serious	0	20	1
Neonatal events	0	6	0
thereof serious	0	6	0
Pregnancies after paternal exposure (pregnancies of partners)			
Number of total pregnancies	1	9	2
Singleton pregnancies	1	9	1
Twin pregnancies	0	0	1
Pregnancy outcomes			
Live births	1	6	2
Abortion, fetal death, stillbirth	0	0	0
Unknown	0	3	0

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; nbDMARD, non-biologic disease-modifying anti-rheumatic drug.

10.5. Other Analyses

For regression models, a sensitivity analysis was performed where initiation of the new medication did not censor the 90-day risk window and events occurring after the switch were attributed to the prior therapy (Table 18). Almost all results from the main analysis were consistent with the results of this sensitivity analysis, except for the outcome lung cancer. In the main analysis, the difference between tofacitinib and bDMARDs was elevated (HR 1.86; 95%

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CI: 0.72 – 4.82), but statistically not significantly different. In contrast, in the sensitivity analysis, the risk for lung cancer statistically was significantly higher using tofacitinib compared to bDMARD (HR 2.50; 95% CI: 1.07 – 5.84).

10.6. Adverse Events/Adverse Reactions

This study involved data that exist as structured data by the time of study start. In these data sources, individual patient data were not retrieved or validated by Pfizer, and for Pfizer 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 AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) were not met for Pfizer.

11. DISCUSSION

11.1. Key results

Baseline characteristics

Patients who received tofacitinib and bDMARDs were quite similar in several characteristics, including age, proportion of females and rheumatoid factor/ACPA positivity, glucocorticoid use, smoking status and mean number of comorbidities. However, some differences reflect the recommendations from therapy guidelines, as outlined in the next paragraph. More patients received combination therapy in the bDMARD cohort (51.9%) compared to patients who were in the tofacitinib cohort (41.4%). RA disease duration was longer and fewer patients were b/tsDMARD naive in the tofacitinib cohort (i.e., in the tofacitinib cohort, a higher percentage of patients previously had therapy switches, mainly due to therapy failure and / or adverse events prior to starting tofacitinib). Disease activity (as measured by DAS28-ESR at therapy start) was higher in the tofacitinib cohort compared to the bDMARDs group, due to higher 28 swollen and tender joint count as well as higher ESR. This poorer state of health was reflected by a lower percentage of full physical function (measured with the FFbH), and patients starting tofacitinib on average reporting more pain. Restricting the cohorts to b/tsDMARD naive patients indicated that especially patients with contraindication to combination therapy were selected for tofacitinib therapy when they were bionaive, as only 38.6% in the b/tsDMARD naïve tofacitinib cohort but 57.4% in the b/tsDMARD naïve bDMARD cohort received combination therapy. The main difference between tofacitinib and bDMARD cohorts in this study sample was the year of therapy start, reflecting the recommendations and warnings.

Baricitinib and tofacitinib have been available in Germany since 2017, and upadacitinib and filgotinib since 2020. In the EULAR recommendations published online in January 2020, the task force revised the preference of bDMARDs over tsDMARD due to evidence regarding the safety and successful efficacy of JAKis [35]. Furthermore, tsDMARDs and interleukin-6 inhibitors were recommended for patients who cannot use conventional synthetic (cs) DMARDs (henceforth called non-biological DMARDs) as co-medication. However, already in May 2019, the EMA sent a warning regarding the use of Tofacitinib in patients who were at high risk of VTE [36]. This safety issue was included in the EULAR recommendation informing that JAKis should be used with caution in patients with high risk of VTEs, such as patients with history of prior VTEs, obesity, hormone replacement therapy and higher age [35]. It was emphasized that further research was required as evidence was scarce [35]. A higher risk of HZ infections on JAKis was furthermore mentioned [36]. In 2021, different agencies (EMA, US Food and

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Drug Administration) and Pfizer (Direct Healthcare Professional Communications, DHPCs, in Germany so called “Rote Hand Briefe”) sent warnings about first evidence for an increased risk of MACE and malignancies (excluding NMSC) associated with the use of tofacitinib compared to TNFis. In February 2022, the EMA restricted the prescription of the JAKi class for patients over 65 years of age, ever smokers, and/or patients at increased risk of cardiovascular disease, neoplastic or thromboembolic complications. Likewise, the EULAR task force revised the current recommendations, published in November 2022 [37]. In the new recommendations, a bDMARD should be added after nbDMARD failure, whereas JAKis may be considered only after risk assessment. Risk factors to be considered now include risk factors for cardiovascular events as well as malignancies. Since the end of 2022, JAKis should be given only to patients below 65 years of age, to never smokers, to patients with no other cardiovascular risk factors (no diabetes, obesity, hypertension) and no other risk factors for malignancies (no prior or current malignancy other than successfully treated NMSC). Additionally, patients should not have risk factors for thromboembolic events (no history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders / a history of blood clots, no combined hormonal contraceptives or hormone replacement therapy, no major surgery, and patients should not be immobile).

Therefore, while the EULAR recommendations from 2019 considered JAKis at a similar level as bDMARDs in terms of safety, the EULAR recommendations from November 2022 considered JAKis to be risky for patients with specific risk factors [37]. The warning was expanded to the entire class of JAKis as a similar risk could not be excluded for JAKis other than tofacitinib. Since March 2023, the EMA recommendation that JAKis should only be prescribed to patients with specific risk factors if there are no suitable therapy alternatives has been followed in Germany.

Therefore, the changing recommendations and warnings influenced the initiation of tofacitinib over time and substantial imbalance in time of cohort entry was found even after weighting. As a result, time of cohort entry was added as covariate to all regression models.

Aside from the year of therapy start, further differences in the patient characteristics were visible for the comparison between tofacitinib and nbDMARDs in the b/tsDMARD naive cohort: Among tofacitinib patients, RA disease duration on average was more than 2 years longer than among nbDMARD patients, and imbalance in RA disease duration was still found after weighting for a majority of outcomes when comparing tofacitinib vs. nbDMARDs. Therefore, RA disease duration was added as covariate to those regression models. Furthermore, disease activity was higher, and percentage of full physical function was lower among tofacitinib patients than among nbDMARD patients, generally reflecting a poorer state of health for patients initiating tofacitinib. The percentage of patients diagnosed with CKD was higher in the tofacitinib cohort (10% compared to 4.2% in the nbDMARD cohort), reflecting the contraindication for continuing nbDMARD therapy. As it is uncommon for the treating physician to have to choose between tofacitinib and nbDMARDs after nbDMARD failure but before bDMARD failure, the results of the tofacitinib vs. nbDMARDs comparison are presented in this report, but are not discussed in detail.

Main results using the on-drug and the ever-exposed approach

Until now, most studies compared JAKis versus TNFis. Only one study was found comparing JAKis versus bDMARDs with other modes of action after failure of therapy with TNFis [38]. In

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that study, both groups had comparable safety profiles over 24 months of follow-up, however, unfortunately, due to the small sample size (163 patients in the JAKi group and 142 patients in the comparator group) results have to be interpreted cautiously.

This PASS compared the safety of tofacitinib use with bDMARD use among RA patients, however, therapy episodes were only included if there was no exposure to the specific active substance 365 days prior to prescription of the drug to minimize prevalent user bias. Thus, of 1,268 tofacitinib therapy episodes initiated either at enrolment or during follow-up, only 1235 episodes were included. Likewise, of 10,373 bDMARD therapy episodes initiated either at enrolment or during follow-up, only 9,087 episodes were considered in the analysis (see flowchart, Figure 1). For the subgroup “at least one other prior JAKi therapy” only around 100 episodes in the tofacitinib cohort were available, thus the results have to be interpreted cautiously. Likewise, the sample was very small for therapy start on or after 30-JUNE-2021 (only around 50 episodes).

1. Serious infections

In this PASS, the crude IR for serious infection (overall) was higher for the tofacitinib cohort compared to that of the bDMARD cohort, except for the subgroup with at least two prior b/tsDMARD therapies, which was a quite large group (47.8% in the tofacitinib and 33.6% in the bDMARD cohort). A higher crude IR for the tofacitinib cohort was noted for patients aged 65 years or older, corresponding to around 33% of the patients. There was no statistically significant difference between the tofacitinib and the bDMARD cohort using adjusted Cox regression analysis.

An increased risk for serious infections ([39], only for 10 mg twice daily), adjudicated opportunistic infections (including opportunistic HZ and TB both for 5 and 10 mg twice daily [39]) and all infections (for tofacitinib compared to TNFi, both for 5 and 10 mg twice daily [40]) was found in the high-risk population of the ORAL Surveillance trial. An increased risk of serious infections was likewise found by a meta-analysis based on observational studies in patients with RA [41]. A statistically significant higher risk of serious infection compared to adalimumab was documented for baricitinib but not tofacitinib in a recently published study [42]. According to an analysis using Japanese claims data, a lower risk for TNFi versus JAKis was found especially for respiratory tract infections, urological and gynecological infections and sepsis whereas no difference was observed for infections of the GI tract, of the skin and subcutaneous tissue and other infections [42]. A higher risk for serious opportunistic infections for JAKi compared to TNFi was found by [43], with the risk of viral infections being particularly high.

As for serious infection (overall), IR for pneumonia was also higher in the tofacitinib cohort relative to the bDMARD cohort, except for the subgroup with at least two prior b/tsDMARD therapies. Likewise, the difference was not statistically significant using adjusted Cox regression analysis.

For sepsis, the IR was higher for tofacitinib compared to bDMARDs, except for patients with no or only one prior b/tsDMARD therapy and for patients aged below 65 years. The HR was close to the null using adjusted Cox regression analysis.

For the outcome other infections, the IR was higher for tofacitinib compared to bDMARDs, except for patients with combination therapy, aged 65 years or older, no prior b/tsDMARD

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therapy or with at least two prior b/tsDMARD therapies. Again, there was no statistically significant difference between the tofacitinib and the bDMARD cohorts using adjusted Cox regression analysis.

For the outcomes of other infections of respiratory system, infections of CNS, bone / joint infections and opportunistic infections, the number of events in the tofacitinib cohort was too small to perform further subgroup and regression analyses.

In conclusion, the hazard of serious infections when examined overall and by subtypes statistically was not significantly different in patients exposed to tofacitinib compared to patients exposed to bDMARDs.

2. TB

In this PASS, the incidence of TB was very low, mirroring the low incidence of TB in Germany. There was only one case of TB in the bDMARD cohort and no case in the tofacitinib cohort. Therefore, no further analyses were performed.

No statistically significant difference for tofacitinib compared to TNFis was found for adjudicated TB in the high-risk population of the ORAL Surveillance trial [39]. A lower risk of TB for patients treated with JAKis compared to patients treated with bDMARDs/TNFis was described by three Korean studies [43-45]. No lower risk was found for tofacitinib vs tocilizumab [46].

3. HZ

In this PASS, the crude IR for HZ (serious and non-serious events) was higher for the tofacitinib cohort compared to the bDMARD cohort. This was supported by the statistically significant, more than 2-fold increased hazard for tofacitinib compared to bDMARDs in the crude and the adjusted model.

An increased hazard for serious and non-serious HZ under therapy with tofacitinib compared to TNFis was found in the high-risk population of the ORAL Surveillance trial [39,40]. Likewise, an increased HZ hazard was found for JAKis vs. nbDMARDs, tofacitinib vs. bDMARDs and tofacitinib vs. tocilizumab in unselected real-world patients [44,46-48].

4. Fractures

In this PASS, the IR for fractures was higher in the tofacitinib cohort compared to the bDMARD cohort except for the subgroup with one prior b/tsDMARD therapy where it was slightly lower. However, in sex-stratified analyses, the higher IR for tofacitinib was only found for women. For men, lower IRs were found for the tofacitinib cohort compared to the bDMARD cohort. Using adjusted Cox regression analysis, no statistically significant difference was found for the tofacitinib cohort compared to the bDMARD cohort. In sex-stratified analyses, the fully adjusted HR for tofacitinib compared to bDMARD was 1.33 (95% CI 0.93 – 1.90) in women

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and 0.68 (95% CI 0.25 – 1.84) in men. The percentage of osteoporosis as comorbid condition was slightly higher in women in the tofacitinib cohort (21.2%) compared to the bDMARD cohort (18.1%) and similar in men of both therapy groups (10.2% and 10.5%, respectively).
No study was found investigating safety of tofacitinib use among RA patients with respect to fractures.

5. Cardiac disorders

In this PASS, the IR for cardiac disorders (overall) was higher for the tofacitinib cohort compared to the bDMARD cohort regarding both the overall cohorts and all considered stratifications. This was reflected by the numerically increased hazard (without statistical significance) under tofacitinib therapy using regression analysis.

There are only few studies on subtypes of cardiac disorders. Several studies reported no statistically significant difference between tofacitinib/JAKis and TNFis for (acute) myocardial infarction [49-54] and for heart failure [52,54]. An increased risk for ischemic heart disease (IHD) and a protective effect for heart failure for JAKis vs bDMARDs was found by [55]. No difference between tofacitinib and tocilizumab was observed for coronary heart disease [46].

For heart failure, the IR was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup without prior b/tsDMARD therapy and for combination therapy. There was an elevated hazard for tofacitinib using adjusted Cox regression analysis, but this was not statistically significant.

For coronary artery disease, the overall IR was lower for the tofacitinib cohort compared to the bDMARD cohort. The IR was only higher for the tofacitinib cohort for patients without prior b/tsDMARD therapy or with only one prior b/tsDMARD therapy, for patients younger than 65 years and for patients without CV risk factors. This was supported by an HR of 0.97 (95% CI 0.42 – 2.25) in the adjusted regression analysis.

For myocardial infarction, the IR was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup with at least two prior b/tsDMARD therapies, where the IR was quite similar. Surprisingly, the IR for the tofacitinib cohort was higher for patients below 65 years of age compared to patients at or above that age. Accordingly, there was a borderline, statistically not significantly increased hazard for myocardial infarction using tofacitinib compared to bDMARDs performing adjusted Cox regression analysis.

For other cardiac disorders, the IR was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup with one prior b/tsDMARD therapy and no CV risk factor. Likewise, the HR of the adjusted regression analysis was not numerically increased (without statistical significance).

In conclusion, in this PASS, there was a potential safety concern for an increased hazard of cardiac disorders for tofacitinib compared to bDMARD. This hazard was mainly seen for myocardial infarction and further investigations are recommended.

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MACE (Major Cardiovascular events)

In this PASS, the IR for MACE was higher for patients in the tofacitinib cohort compared to patients in the bDMARD cohort for all stratifications. This was supported by a statistically significant increased hazard for MACE in the tofacitinib cohort compared to the bDMARD cohort using adjusted Cox regression analysis (HR: 1.78; 95% CI: 1.04 – 3.06).

The increased risk (without statistical significance) for MACE for tofacitinib compared to TNFis, found in the high-risk population of the ORAL Surveillance trial [39], was not supported by other studies. A statistically not significantly lower risk was observed by a meta-analysis based on observational studies in patients with RA [41]. A recently published study performed in Korea likewise found a lower risk for JAKis (consisting of over 90% tofacitinib) vs. TNFis in stratified analyses based on a high-risk population [54,56]. In RABBIT, lower risks (without statistical significance) were likewise found for JAKis compared to TNFis both overall and for a high-risk population, but a numerically higher risk was found for tofacitinib vs. TNFis, particularly for the overall cohorts [57].

6. Hematologic disorders

In this PASS, the IR for hematologic disorders (overall) was higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients receiving monotherapy, patients aged below 65 years and patients with at least one prior b/tsDMARD, respectively. No discrepancy between the hazards of both groups was found employing adjusted regression analysis (HR 1.06).

No literature was found for this outcome of interest.

For other blood dyscrasia, the IR was higher in the tofacitinib cohort compared to the bDMARD cohort. Using adjusted regression analysis, the HR was 1.33, but the difference between the groups was not statistically significant and the number of events in the tofacitinib group was small (6 events).

For bone marrow depression and hypoplastic anaemia, there were 7 events in the bDMARD cohort and no case in the tofacitinib cohort. Likewise, for platelet disorders, there were 4 events in the bDMARD cohort and no case in the tofacitinib cohort. For decreased white blood cells, there was one case in the tofacitinib cohort and there were 8 events in the bDMARD cohort. The number of events in the tofacitinib cohort was too low to perform regression analyses.

In conclusion, the number of events was small for this outcome and their subtypes, and robust conclusions cannot be drawn.

7. Disorders of the nervous system

In this PASS, the IR for disorders of the nervous system (overall) was higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients receiving combination therapy with nbDMARDs/MTX, patients aged below 65 years and patients with no or only one

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prior b/tsDMARD therapy. This was reflected in the HR around 1 for the adjusted regression analyses.

For stroke, no increased risk for JAKis in general and tofacitinib in particular compared to TNFis was found by some studies [41,48,50,53,54]. In contrast, a statistically significant, increased reporting of stroke for JAKis compared to bDMARDs was published by Goldman et al. (2024) [55], with a higher risk for upadacitinib and baricitinib compared to tofacitinib. Fang et al. (2024) [46] found a statistically not significantly increased risk for tofacitinib vs tocilizumab for stroke. Studies on other subtypes of disorders on the nervous system are scarce. One case of reversible multifocal CNS demyelination on tofacitinib has been reported [58]. In patients with low disease activity or remission, a reduction in anxiety and depression with JAKi compared to TNFis after one year of therapy was shown by Fujii et al (2025) [59].

For stroke, the IRs were clearly higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients with one prior b/tsDMARD and those with combination therapy with nbDMARDs, for which the IRs were quite similar. The regression analysis estimated an increased hazard for stroke for patients under tofacitinib compared to bDMARD therapy, with a HR of 1.93 being borderline not statistically significant (p=0.056).

For central demyelination, there was one event in the bDMARD cohort and no case in the tofacitinib cohort. Therefore, no further analyses were done.

For other disorders of the CNS, the IR was higher in the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups of patients below 65 years, patients with no prior b/tsDMARD therapy, and patients with combination therapy with nbDMARD/MTX. No difference was found using adjusted regression analysis.

For disorders of the peripheral nervous system, the IR was lower in the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups of patients with at least two prior b/tsDMARD therapies, patients receiving monotherapy and patients aged at least 65 years. Again, the HR was around 1 for the adjusted regression analyses.

For psychiatric disorders, the IR was lower in the tofacitinib compared to the bDMARD cohort. Of the 5 events relevant for calculating the IR in the tofacitinib cohort, one event occurred after reporting of this event in the bDMARD group, leaving only 4 events in the tofacitinib cohort when censoring patient time after the first event. Therefore, no regression analysis was done.

In conclusion, the outcome “disorders of the nervous system” showed a very heterogeneous picture. The only outcome with a possible signal for a higher hazard under tofacitinib therapy was stroke.

8. PML

In this PASS, there were no PML events in the tofacitinib cohort, no PML events in the nbDMARD cohort, and only one event PML in the bDMARD cohort. No further analyses were done.

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Two case reports of PML with subsequent immune reconstitution inflammatory syndrome in patients taking tofacitinib have been published [60,61]. No further publications were found for this outcome of interest.

9. Allergic conditions and hypersensitivity

In this PASS, only 3 events occurred in the tofacitinib group. The IRs were similar (around 1.3) for patients in the tofacitinib and the bDMARD group. No further analyses were done.

No literature was found for this outcome of interest.

10. Hepatic failure

In this PASS, there were 7 hepatic events in the bDMARD cohort and no case in the tofacitinib cohort. Therefore, no further analyses were performed.

Adjudicated hepatic events have been found to be more frequent with patients taking tofacitinib at a high dose (10 mg twice daily) compared to those taking TNFis [39].

11. GI perforations

In this PASS, the IR for GI perforations (overall) was lower in the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups of patients with at least 2 prior b/tsDMARD therapies and with combination therapy with MTX. Of the 5 events relevant for calculating the IR in the tofacitinib cohort, one event occurred after reporting of this event in the bDMARD group, leaving only 4 events in the tofacitinib cohort when censoring patient time after the first event. Therefore, no regression analysis was done.

No statistically significantly higher risk for tofacitinib compared to TNFis was found for adjudicated GI perforations in the high-risk population of the ORAL Surveillance trial [39]. Likewise, no difference was found for JAKis compared to nbDMARDs [62] and adalimumab [51]. In contrast, a higher risk was reported for tofacitinib compared to bDMARDs by Goldman et al (2024) [55]. Furthermore, Xie et al. (2016) [63] found a higher risk for tofacitinib vs. TNFis for the lower GI tract and Goldman et al. (2024) [55] for all JAKis vs. bDMARDs for the upper and the lower GI tract.

For other GI perforations (e.g., diverticulitis, GI haemorrhage, peritonitis), the IR was slightly higher in the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups of patients with no or one prior b/tsDMARD therapy, patients with monotherapy and patients aged below 65 years. Of the 5 events relevant for calculating the IR in the tofacitinib cohort, one event occurred after reporting of this event in the bDMARD group, leaving only 4 events in the tofacitinib cohort when censoring patient time after the first event. Therefore, no regression analysis was done.

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There was no lower intestinal perforation in the tofacitinib cohort and there were 13 events in the bDMARD cohort. No subgroup and regression analyses were done.

In conclusion, in this PASS, there was no indication of a higher hazard of GI perforations for tofacitinib compared to bDMARDs, but results are based on small numbers of events and no regression analysis was performed.

12. Pregnancy

In this PASS, a total of 2 pregnancies were reported after tofacitinib exposure, one after maternal and one after paternal exposure. In case of the maternal exposure, end of tofacitinib exposure and begin of pregnancy were reported for the same month (without exact date). Both pregnancies resulted in live births without complications or neonatal malformations. For the pregnancy with maternal exposure, 2 maternal non-serious events and no neonatal event were reported.

Data are scarce for pregnancy outcomes and only two studies with investigations on tofacitinib in pregnancies were found. Outcomes under tofacitinib exposure in RA / psoriasis patients appear to be similar to those observed in patients with different inflammatory diseases treated with biologics [64]. Likewise, no signal was found using the World Health Organization global pharmacovigilance database of individual case safety reports, however, the finding should be interpreted cautiously [65].

13. Embolic and thrombotic events

In this PASS, the number of embolic and thrombotic events in the tofacitinib cohort was small (7 events). The IR for embolic and thrombotic events (overall) was higher in the tofacitinib cohort compared to the bDMARD cohort, which was reflected in the HR of 1.25 (model C, without statistical significance) for the adjusted regression analysis. However, for the subgroups of patients receiving combination therapy with nbDMARDs/MTX, patients presenting no VTE risk factors and patients with therapy start on or after 31-JAN-2020, the IR was higher in the bDMARD cohort compared to the tofacitinib cohort. For patients aged below 65 years, IRs were similar for both groups.

An increased risk of venous thromboembolism (VTE**)** [39,66] and adjudicated PE [39] for tofacitinib compared to TNFis was found in the high-risk population of the ORAL Surveillance trial, reaching statistical significance for the higher dose of 10 mg twice daily, but not for 5 mg twice daily. Regarding adjudicated DVT, a numerically increased risk for tofacitinib compared to TNFis was observed in the same population [39]. A statistically significant increased risk of VTE for JAKi vs TNFis was likewise found by a meta-analysis based on observational studies in patients with RA [41]. Recently published studies considering bDMARDs [55], all other drugs [67] or tocilizumab [46] as comparator, respectively, found an increased risk for VTE [46,55,67], DVT [46,67] and PE [67] for tofacitinib.

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Likewise, for VTE, the IR was higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients receiving combination therapy with nbDMARD/MTX, patients presenting no VTE risk factors, patients with therapy start on or after 31-JAN-2020 and patients with one prior b/tsDMARD therapy.

For DVT, there were 18 events in the bDMARD cohort (IR 1.03) and only 2 events in the tofacitinib cohort (IR 0.85).

In contrast to the results for VTE and DVT, for PE, the IRs were higher in the tofacitinib compared to the bDMARD cohort both overall and for most subgroups of patients, except for patients who were receiving combination therapy with nbDMARD/MTX, with one prior b/tsDMARD therapy and with therapy start on or after 31-JAN-2020. In the tofacitinib cohort, the IR for PE was clearly higher compared to the IR for DVT. This strong difference between the subtypes was not seen for the bDMARD cohort and was also reflected in the HRs of the adjusted regression analyses. The HR was 1.55 for PE and 1.14 for VTE, whereas analyses for DVT could not be done due to the small number of events.

In conclusion, our analyses indicate a numerically increased hazard for embolic and thrombotic events in patients receiving tofacitinib vs. bDMARDs, particularly regarding PE, which is consistent with the warnings for patients aged at least 65 years and having VTE risk factors. After the warnings issued on January 2020, there was no further event documented in the tofacitinib cohort compared to 19 events in the bDMARD cohort. The channeling of the patients occurring after the warnings may explain the lack of statistical significance in the results of the regression analysis.

14. Operations and hospitalizations

In this PASS, the IR for operations and hospitalizations (overall) was higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients with one prior b/tsDMARD therapy and patients aged below 65 years. However, for men, IRs were lower for tofacitinib compared to bDMARD, but the number of events was small. Using adjusted regression analysis, no difference was found comparing tofacitinib with bDMARD.

Only one study was found investigating operations and hospitalizations. No statistically significant difference in total hip and total knee replacement was found for tofacitinib vs. tocilizumab [46].

For bone and joint surgery and other joint therapeutic procedures, the IR was lower in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients with no prior b/tsDMARD therapy, patients with combination therapy with nbDMARD/MTX and patients aged at least 65 years. The HR was below 1 (0.94) but not statistically significant.

For other operations and therapeutic procedures that led to hospitalization, the IR was higher in the tofacitinib compared to the bDMARD cohort, except for the subgroups of patients with one prior b/tsDMARD therapy and patients with combination therapy with nbDMARD/MTX. The HR was increased (HR 1.28) but not statistically significant.

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In conclusion, we could not find any statistically significant difference for this outcome between tofacitinib and bDMARD cohorts.

15. Other serious diagnoses, symptoms, and syndromes

In this PASS, the IR for other serious diagnoses, symptoms and syndromes (overall) was higher in the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup of patients with one prior b/tsDMARD therapy. However, for men, the IRs were lower for tofacitinib compared to bDMARDs. Using adjusted regression analysis, no statistically significant difference was found between tofacitinib and bDMARDs. However, the HR statistically was significantly higher for the tofacitinib cohort compared to the nbDMARD cohort using adjusted regression analysis (HR 1.92).

No study was found investigating safety of tofacitinib use among RA patients with respect to other serious diagnoses, symptoms, and syndromes.

16. NMSC

Using the ever-exposed approach, in this PASS, the IR for NMSC was always higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup of patients with one prior b/tsDMARD therapy. Likewise, using the on-drug approach, the IR for NMSC was always higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup of patient with one prior b/tsDMARD therapy. The higher IR was supported by the statistically significant, more than 2-fold increased hazard for tofacitinib compared to bDMARDs estimated by crude and adjusted Cox regression analysis, but only using the on-drug approach. Using the ever-exposed approach, the hazard was increased for tofacitinib vs. bDMARD therapy (HR 1.57; 95% CI 0.84 – 2.93), but not statistically significant.

A statistically significant increased risk for tofacitinib compared to TNFis was found for adjudicated NMSC in the high-risk population of the ORAL Surveillance trial [39]. This result was supported by the studies of Huss et al. (2023) and Huss et al. (2026) [68,69], finding an increased risk for JAKis vs. TNFis, especially for prolonged time since therapy initiation. In contrast, a statistically significant increased risk was not found in the study of Min et al. (2023) [53] for JAKis vs TNFis and in the study of Kremer (2021) [70] for tofacitinib vs. bDMARDs.

17. Malignancies excluding NMSC

In this PASS, using the ever-exposed approach, the IR for malignancies (overall) was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroup of patients aged below 65 years and for patients with one prior b/tsDMARD. Likewise, using the on-drug approach, the IR for the whole cohorts was higher for the tofacitinib cohort compared to the bDMARD cohort, but not for the subgroup of patients aged below 65 years, for patients with one prior b/tsDMARDs and furthermore for combination therapy with nbDMARD/MTX. For men, IRs were slightly smaller for tofacitinib compared to the bDMARD cohort using the ever-

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exposed and the on-drug approach, however, the sample of men was small. Using adjusted regression analysis, no statistically significant difference was found between tofacitinib and bDMARD regardless of the approach. It could however be noted that the HR was larger using the ever-exposed plus latency period approach than using the on-drug approach.

A statistically significant higher risk for tofacitinib compared to TNFis was found for cancer (excluding NMSC) in the high-risk population of the ORAL Surveillance trial [39]. This result was supported by the Korean claims data base study from Cho et al. (2025) [56] as well as the RABBIT analysis of Schaefer et al. (2025) [34], both finding an increased risk for JAKis vs. bDMARDs overall. Schaefer et al. (2025) [34] additionally considered the high-risk population for which an increased risk was also found. In contrast, no statistically significant difference between JAKis and TNFis for overall cancer was observed by Xu et al. (2025) [71] and by the Swedish register ARTIS [69]. The Danish register DANBIO [72] found a HR for tofacitinib vs. bDMARDs that was numerically comparable to the one detected in ORAL Surveillance and in RABBIT, however, due to the small numbers of events for JAKis the result was not statistically significant. A meta-analysis recently performed by Solitano et al. (2025) [41] did not result in a statistically significant increased risk, but this analysis did not include results from Schaefer et al. (2025) [34] and Xu et al. (2025) [71]. A detailed overview on studies was presented by Schaefer et al. (2025) [34], discussing possible reasons for conflicting results. No statistically significant difference was found for tofacitinib vs tocilizumab by Fang et al (2024) [46].

Data are scarce for individual cancer subtypes. While in ORAL Surveillance primarily an increased risk for lung cancer was seen [73], Schaefer et al. (2025) [34] found statistically significant risk increases for prostate and gynecological cancers comparing JAKis versus bDMARDs. Xu et al. (2025) [71] reported a reduced risk of incident digestive organ cancer, but an increased risk of respiratory and intrathoracic organ cancer among females for JAKis compared to TNFis.

In conclusion, there was no statistically significant difference for malignancies (excluding NMSC) between tofacitinib and bDMARDs in the ever-exposed approach for the whole cohort. However, if restricting the population to patients aged at least 65 years, a statistically significant increased hazard of overall malignancies was found for tofacitinib compared to bDMARDs (HR 2.04; 95%CI: 1.18 – 3.51).

18. Lymphoma

Using the ever-exposed approach, there were 3 cases of lymphoma (overall) in the tofacitinib cohort, 2 non-Hodgkin lymphoma and one chronic lymphatic leukemia. From the 5 cases of overall lymphoma in the bDMARD cohort, 3 were Hodgkin lymphoma and 2 chronic lymphatic leukemia. Using the on-drug approach, there were 2 cases of lymphoma (overall) in the tofacitinib cohort, one non-Hodgkin lymphoma and one chronic lymphatic leukemia. From the 6 cases of overall lymphoma in the bDMARD cohort, 4 were Hodgkin lymphoma and 2 chronic lymphatic leukemia. Due to the small number of events, no regression analysis was performed. There was no evidence for a higher risk for these outcomes for tofacitinib compared to bDMARD.

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19. Lung cancer

In this PASS, the overall IR was higher for the tofacitinib cohort compared to the bDMARD cohort, regardless of the approach. Using adjusted regression analysis, there was a numerically increased hazard (without statistical significance) for tofacitinib compared to bDMARD in the ever-exposed approach (HR 1.70; 95% CI: 0.75 – 3.87) and the on-drug approach (HR 1.86; 95% CI: 0.72 – 4.82), but a statistically significant increased hazard in the on-drug sensitivity approach (HR: 2.50; 95% CI: 1.07 – 5.84).

20. All-cause mortality

In this PASS, using the ever-exposed approach, the IR for all-cause mortality was higher for tofacitinib compared to bDMARDs, except for the subgroup of patients receiving monotherapy. Using the on-drug approach, the IR was higher for tofacitinib compared to bDMARDs as well, except for the subgroups of patients receiving monotherapy and one prior b/tsDMARD, respectively. When accounting for the differing patient characteristics by using adjusted regression analysis, the HR was below 1 for tofacitinib compared to bDMARDs, regardless of the approach, however, the protective effect was not statistically significant.

No statistically significant increased risk for JAKis compared to bDMARDs, TNFi or tocilizumab for all-cause mortality was documented by Sepriano et al. (2022), Xu et al. (2025) and Fang et al. (2024), respectively [46,48,71]. Likewise, no difference was found using JAKi / TNFi naive patients, whereas there was a statistically significant increased risk for JAKi among all patients with total follow-up in the study of Min et al. (2023) [53].

21. Leukemia

In this PASS, the number of events was very low for this outcome. Using the ever-exposed approach, there was only one event in the tofacitinib cohort. Using the on-drug approach, there was no event in the tofacitinib cohort. In conclusion, there was no evidence for a higher hazard for tofacitinib compared to bDMARD, but results are based on small numbers of events and no regression analysis was performed.

22. Other haematopoietic neoplasms (malignant and benign)

In this PASS, the number of events was very low. Using the ever-exposed approach, there was no event for other haematopoietic neoplasms in the tofacitinib cohort. Using the on-drug approach, there was no event in the tofacitinib cohort. In conclusion, there was no evidence for a higher hazard for tofacitinib compared to bDMARD, but results were based on small numbers of events and no regression analysis was performed.

23. Solid malignancies (overall)

In this PASS, the IR was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups one prior b/tsDMARD therapy and patients aged below 65 years,

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using the ever-exposed approach. A higher overall IR was likewise found for the on-drug approach, except for the subgroup one prior b/tsDMARD therapy and combination therapy. Using adjusted regression analysis, no statistically significant difference was found between tofacitinib and bDMARD, regardless of the approach.

24. Glioblastoma

In this PASS, there was no event in both cohorts, regardless of the approach.

25. Benign neoplasms

In this PASS, using the ever-exposed approach, the IR was higher for the tofacitinib cohort compared to the bDMARD cohort, except for the subgroups with at least 2 prior b/tsDMARD therapies and combination therapy with a nbDMARD. Likewise, overall and for several subgroups the IR was higher for the tofacitinib cohort compared to the bDMARD cohort using the on-drug approach. Using adjusted regression analysis, no statistically significant difference was found between tofacitinib and bDMARD, regardless of the approach.

26. Unspecified neoplasms and precanceroses

In this PASS, there was no event in the tofacitinib cohort using the on-drug approach and 3 events using the ever-exposed approach. In conclusion, there was no evidence for a higher hazard for tofacitinib compared to bDMARDs, but results were based on small numbers of events and no regression analysis was performed.

27. Metastases, cancer related and morbidities and associated syndromes

In this PASS, there was no event in the tofacitinib cohort using the on-drug approach and 3 events using the ever-exposed approach. In conclusion, there was no evidence for a higher hazard tofacitinib compared to bDMARDs, but results were based on small numbers of events and no regression analysis was performed.

28. Interstitial lung disease

In this PASS, the IR was lower for tofacitinib (IR 1.28, based on 3 events) compared to bDMARD (IR 2.58, based on 45 events) and nbDMARDs (IR 1.30, based on 7 events). Due to the small number of events in the tofacitinib group, no further subgroup and regression analyses were performed.

No statistically significant higher hazard for tofacitinib compared to TNFis was found for interstitial lung disease in the high-risk population of the ORAL Surveillance trial [39]. In patients with prevalent RA-ILD, a lower estimate, with no statistically significant difference was found for JAKis compared to TNFis regarding mortality as outcome using data from RABBIT [74], however, the sample size was small. In contrast, Shih et al. (2025) [75] found a higher all-cause mortality for JAKis compared to TNFis.

In conclusion, there was no indication of an altered hazard of interstitial lung disease for tofacitinib compared to bDMARD. Results were based on small numbers of events and no regression analysis was performed.

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11.2. Limitations

General limitations derive from the study design on which this final report was based. Observational cohort studies on drug therapy examine unselected patients in daily care. Due to non-randomisation of patients to defined therapy arms, these studies are prone to confounding by indication [22]. Therapy decisions and therefore exposures to DMARDs are usually based on the availability of drugs, the provider's experience in treating patients with them and on patients' characteristics such as age, severity of symptoms, disease course and specific comorbidities. Very likely there was a channeling of patients with a more severe disease of RA to certain therapies. Even after careful adjustment, such confounding can never be entirely ruled out. Since observational studies follow patients over very long time periods, they are also prone to attrition bias, i.e. selective loss to follow-up.

In the ever-exposed approach, the proportions of potentially informative dropout (e.g., a patient did not return to his/her institution for visits and/or could not be reached, or a patient did not wish to continue in the study) were similar among the therapy cohorts (13.7% in the tofacitinib cohort vs. 13.1% in the bDMARD cohort when analyzing the outcome mortality, for which no additional censoring at the first event was done). In the on-drug approach, the proportions of potentially informative dropout were 15.1% for the tofacitinib cohort, 12.5% for the bDMARD cohort and 15.9% for the nbDMARD cohort for the outcome mortality. To adjust for possibly informative dropout, IPCW was used.

Limitations based on the RABBIT study's design include the documentation of relevant comorbidities only every 2.5 years. For episodes not initiated at enrolment but during follow-up, measurement error could not be ruled out, as the time point of comorbidity diagnosis during these 2.5 years may be unknown. As 32.2% of the tofacitinib episodes and 48.7% of the bDMARD episodes were initiated at enrolment, a relevant percentage of misclassification regarding comorbidities could have shifted the result to a higher hazard for patients in the tofacitinib cohort for outcomes markedly influenced by comorbidities. In general, residual confounding may be present: If a patient switched therapies during the follow-up, covariates for the PS calculation in the Cox regression models were taken from the visit date occurring most recently prior to the therapy start date, but not exactly from the time at switch.

Prevalent user bias was likely minimized, but not completely prevented, by excluding episodes from patients using this specific active substance during the 365 days prior to prescription of the drug. Possible effect modification was investigated using IRs, but not regarding HRs. However, several stratified analyses were done for IRs and for age/sex-standardized IRs. Missing data from possible confounders have been addressed by tenfold imputation.

Looking at the balance between the tofacitinib cohort and the bDMARD (or nbDMARD) cohort after carrying out IPW, the year of therapy start was the only variable with considerable remaining imbalance across all regression models. The reason could be that after the warnings issued by the EMA regarding tofacitinib use, channeling took place and therapy starts with tofacitinib declined considerably. Patients still prescribed tofacitinib after the warnings tended to be either younger patients without risk factors or patients with risk factors who however were potentially difficult to treat and received tofacitinib after other therapy options were not successful. Thus, these patients treated with tofacitinib consisted of two differing groups for which results when looked at jointly were difficult to interpret - even more so since their overall numbers were small.

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The only variable aside from year of therapy start that after weighting still had remaining imbalance for some models was RA disease duration in the tofacitinib vs. nbDMARD comparison. This implies that even after restricting both the tofacitinib and the nbDMARD cohort to b/tsDMARD naive patients, tofacitinib patients still tended to have a longer disease duration than nbDMARD patients.

Differences between the tofacitinib cohort and the comparator cohorts regarding the disease duration may also have affected overlap in the histograms showing the PS distributions. In particular, the overlap between the tofacitinib cohort and the comparator cohorts in the therapy PS distributions was limited for small PS values. There was thus a group of patients – perhaps patients with a shorter disease duration than others – who were considerably more likely to be prescribed an nbDMARD or a bDMARD (particularly a TNFi, the dominant mode of action in the bDMARD cohort) than a JAKi.

The main challenge for any comparison of tofacitinib with a bDMARD was that EULAR recommended the equivalent use of bDMARDs and tsDMARDs after nbDMARD failure only for a short period and only after careful consideration of the patient's risk factors, with the further restriction that JAKis and IL6i should be used as a first choice if combination therapy is contraindicated. Therefore, patients at the time of receiving their first-line b/tsDMARD after nbDMARD failure may differ in characteristics that probably could not be adjusted for in the regression models.

To minimize differences between therapy groups with respect to the line of therapy and more closely emulate a target trial, the main comparison should rather be between tofacitinib and non-TNFi bDMARDs after therapy failure with TNFis.

A limitation affecting some of the pre-defined outcomes concerns statistical power and feasibility of analyses. Despite the high number of patients, episodes and patient years, for a considerable set of outcomes there were limited numbers of events that prevented a regression-based analysis while in case of some other outcomes, fitting a regression model was possible but the analysis could be underpowered to detect true differences. This was the case in particular for the comparison of tofacitinib vs. nbDMARDs, for which both compared cohorts were restricted to b/tsDMARD-naive patients [76,77].

A further limitation concerns the proportional hazards assumption made for the Cox regression models. In Schoenfeld residual plots, no violations were observed regarding the therapy effect for the comparison of tofactitinib versus bDMARDs; however, the proportional hazards assumption was violated regarding the therapy effect for the comparison of tofacitinib versus nbDMARDs. Violations were also observed for the additional covariate year of therapy start for both the main comparison (tofacitinib versus bDMARDs) and the tofacitinib versus nbDMARD comparison. The sandwich estimator employed in the Cox models is robust against violations of the Cox proportional hazards assumption [76,77], so valid model inference was not affected by these violations. However, it should be kept in mind for the interpretation of the HR estimates for tofacitinib vs. nbDMARDs that these estimates are of time-averaged nature rather than constant over time. The hazard estimates for the main comparison tofacitinib vs. bDMARDs can be interpreted in the usual way (i.e., as constant over time).

Finally, for malignancy outcomes and all-cause mortality the ever-exposed approach was used as primary approach, with the on-drug approach as secondary approach. Comparing

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on-drug and ever-exposed results for those outcomes was complicated by some methodological differences that have to be considered for interpretation: For the ever-exposed approach, unlike the on-drug approach, only the first therapy episode of a patient was considered in the regression analyses, giving more weight to the b/tsDMARD-naive subgroup of tofacitinib patients and thus influencing the results. On the other hand, for malignancy outcomes, a latency period was applied only for the ever-exposed approach but not for the on-drug approach, affecting the comparability between them.

11.3. Interpretation

The risk for serious infections is a concern in patients with RA treated with bDMARDs and tsDMARDs. No statistically significant increased hazard was observed for tofacitinib for overall serious infections, including only events with hospitalization. The hazard of pneumonia was 1.5-fold increased for tofacitinib compared to bDMARD and 2.5-fold increased compared to nbDMARD, but this difference was not statistically significant, possibly due to the low number of events (tofacitinib: 17 events in the whole cohort; 6 events in the b/tsDMARD naive cohort). There were 9 events of sepsis and 3 events of opportunistic infections in the tofacitinib cohort and the largest number of events in this outcome group were other infections. The fully PS adjusted model accounted for known risk factors like functional status of the patient and glucocorticoid dosages, as well as the comorbid conditions of chronic obstructive pulmonary disease and renal disease. However, previous infections were not added as a covariable in this analysis (since this information was not reliably available for most patients), even though those with a history of severe infections may be more susceptible to infections [11,78]. In general, the PASS result for infections was in line with the literature [41,48]. The meta-analysis of the four tofacitinib PASS (Appendix 8) did not include a pooled estimate for the serious infection outcome; some outcomes could not be pooled since they were not captured in all studies or define differently across studies.

HZ is also a relevant infectious event for patients with RA. In line with several other studies including the ORAL Surveillance study, in this final study report a statistically significant, 2.4-fold increased hazard for tofacitinib compared to bDMARDs and a 5.8-fold increased hazard compared to nbDMARDs was found for (serious and non-serious) HZ. In the SmPC, only IRs are reported for HZ (derived from the ORAL Surveillance study): Tofacitinib 5 mg twice daily IR: 3.75 (3.22, 4.34), Tofacitinib 10 mg twice daily: IR; 3.94 (3.38, 4.57), and TNF inhibitors IR: 1.18 (0.90, 1.52). The meta-analysis of the four tofacitinib PASS (Appendix 8) also demonstrated a statistically significant increased hazard compared to bDMARDs in the pooled estimate (HR: 2.22, 95% CI: 1.65, 3.00) using the ”censor at switch” approach (details are provided in the meta-analysis SAP).

TB and PML were also investigated, but no events occurred in the tofacitinib cohort. Likewise, there were no hepatic failure events in the tofacitinib cohort, however, incidence was generally low in the RABBIT cohort.

The hazard of fractures was statistically significant and increased among patients taking tofacitinib only compared to nbDMARDs, but not compared to bDMARDs. However, the PASS results indicate a notable effect modification by sex, as a numerically increased HR was only seen for females, while for males a HR well below the null was observed. In line with this, the percentage of osteoporosis was slightly higher in the tofacitinib cohort compared to the bDMARD cohort in women, while it was similar in men. The SmPC indicates that “Tofacitinib

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should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage." The meta-analysis of the four tofacitinib PASS (Appendix 8) did not demonstrate a statistically significant increased hazard compared to bDMARDs in the pooled estimate (using 90-Day-Window, Double-Count approach) approach (details are provided in the meta-analysis SAP).

In contrast to several other studies (e.g. [41,48]), this PASS found a statistically significant, increased hazard for MACE. An increased hazard was previously detected for JAKis vs. TNFis in the independent RABBIT publication from Meissner et al. (2023) [57], and although that result was not statistically significant, the findings in this final study report appear consistent with the previous results: The HR for tofacitinib vs. TNFis from Meissner et al. (2023) was 1.36, which is smaller than the HR of 1.78 for tofacitinib vs. bDMARDs from this report. However, in Meissner et al. (2023) [57] the HR for other bDMARDs vs. TNFis (0.76) was also smaller than the HR for JAKis vs. TNFis (0.89) reported in the same analysis, indicating that other bDMARDs may have a more beneficial profile regarding MACE hazard than JAKis. This is relevant because in this report, other bDMARDs were added to TNFis to form the reference group bDMARDs, and it could thus be expected that the HR for tofacitinib vs. bDMARDs overall reported here is larger than the one for tofacitinib vs. TNFis reported in Meissner et al. (2023) [57]. Of note, both the IR and HR for tofacitinib from Meissner (2023) [57] were notably higher than the corresponding estimates for baricitinib and upadacitinb in the same publication (reported IRs: tofacitinib 0.98 (0.58-1.55), baricitinib 0.49 (0.25-0.85), upadacitinib 0.53 (0.15-1.36).

Overall, the results in this report are consistent with the findings from the ORAL Surveillance trial, which found a numerically increased risk of MACE [39] using a different reference group (i.e., bDMARDs instead of TNFis). The SmPC includes this HR estimate of 1.33 (0.91, 1.94), with the different reference group. The meta-analysis of the four tofacitinib PASS (Appendix 8) demonstrated an increased hazard that was not statistically significant compared to bDMARDs in the pooled estimate using the 90-Day-Window "Censor-at-Switch" approach (details provided in the meta-analysis SAP).

Furthermore, there was a numerically increased hazard for cardiac disorders (overall) and especially myocardial infarction among patients taking tofacitinib compared to bDMARDs, that was not statistically significant. A non-statistically significant increased hazard for stroke and heart failure was also found, whereas there was no increased hazard for coronary artery disease.

Numbers of embolic and thrombotic events in the PASS were small, possibly limiting the power to detect statistically significant differences. This is in line with the ORAL Surveillance trial, reporting an increased risk, but reaching statistical significance only for the 10 mg twice daily dose [39]. A higher hazard for PE (HR 1.55) compared to VTE (HR 1.14) was seen in this PASS, in line with the ORAL Surveillance trial (5 mg tofacitinib dose: PE: HR 2.93, VTE: HR 1.66 [39]). Likewise, Zhou et al. (2025; PE: ROR 1.90; DVT: ROR 1.36 [67]) and Molander et al. (2022/2023; PE HR 3.21; DVT: HR 0.83 [79]) showed a higher hazard for PE compared to DVT. A higher VTE hazard for baricitinib compared to tofacitinib was reported by different studies [41,55,79].

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There were only few hematological disorders. Bone marrow depression and hypoplastic anaemia, as well as platelet disorders have not been observed in the tofacitinib cohort. In one patient, decreased white blood cells were reported and 6 events of other blood dyscrasia. There was no signal for an increased hazard with tofacitinib therapy. Likewise, there was no indication of an increased hazard for central demyelination, disorders of the peripheral nervous system, psychiatric disorders and allergic conditions and hypersensitivity.

In contrast to some studies [55,63], no increased hazard was found for GI perforations. The number of events was too small to perform adjusted Cox regression analysis. Furthermore, no difference was found between tofacitinib and bDMARDs for operations and hospitalizations and other serious diagnoses, symptoms and syndromes. However, a statistically increased hazard for tofacitinib compared to nbDMARDs was found for other serious diagnoses, symptoms and syndromes.

Malignancies usually develop slowly and are diagnosed with latency. In addition, it is expected that the hazard to develop a malignancy continues after the actual therapy exposure. Even though IRs and HRs for malignancies were also investigated using the on-drug approach to capture therapy exposure, we consider the ever-exposed approach plus latency period as the most appropriate analysis to estimate the hazard for malignancies. This approach is predominantly used in pharmacovigilance research for this kind of analyses. When using the ever-exposed approach plus latency period as main analysis, no statistically significant increased hazard for tofacitinib was found in this PASS for any malignancy outcome. In line with results from the ORAL Surveillance study, the hazard of NMSC was higher for tofacitinib compared to bDMARDs, but using data from RABBIT, the hazard statistically was only significantly increased using the on-drug approach. In contrast to the ORAL Surveillance study but in line with several other studies, no statistically significant increased hazard of malignancies overall (excluding NMSC) was found regardless of the approach; however, there was a numerically higher hazard for lung cancer (HR 1.70; 95% CI: 0.75 – 3.87 for the ever-exposed approach plus latency period), even when it did not reach statistical significance. In addition, a statistically significantly higher hazard of lung cancer for tofacitinib compared to bDMARDs was found in this PASS in the on-drug sensitivity analysis without censoring at switch (HR 2.50; 95% CI: 1.07 – 5.84).

The HR for malignancies (without NMSC) in the overall cohorts in this report was 1.31, slightly smaller in numerical sense than the HR of 1.40 reported in Schaefer et al. (2025) [34] but nevertheless important to discuss. The lack of significance might be owed to the smaller size of the tofacitinib cohort compared to the JAKi group in Schaefer et al. (2025) [34] (1208 and 774 tofacitinib episodes in the on-drug and ever-exposed Cox models in this report, respectively, vs. 2285 JAKi episodes in Schaefer et al.) and, thus, the smaller statistical power. The HR for tofacitinib vs. TNFis in patients aged 65 years or older in the Oral Surveillance study was 1.70 (95% CI: 1.00 – 2.90) [33], while in Schaefer et al. (2025) [34] the HR for JAKis vs. bDMARDs among patients aged 60 years and older was 1.93 (95% CI: 1.43 – 2.60). The HR found for tofacitinib vs. bDMARDs among patients aged 65 years or older in this report was 2.04 (95% CI: 1.18 – 3.51), and it is plausible that the HR for patients aged 65 or older increases compared to the HR for patients aged 60 years and older. The lower HR obtained in ORAL Surveillance may be owed to the lack of a latency period there. The lower HR obtained in this report for the on-drug approach might be due to the same reason, since a latency period was only applied in the ever-exposed approach. Taking into account the long latency of malignancy outcomes and the possibility of reverse causation, a latency period of at least 6

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months is regarded as state of the art [80] and it could be argued that it should be even longer. The ORAL Surveillance study, Schaefer et al. and also Cho et al. (2025) [34,56,73] consistently show that the increased hazard for tofacitinib or JAKis vs. bDMARDs/TNFis becomes detectable only after 16-18 months of follow-up after JAKi therapy initiation, indicating that the HR is expected to be smaller when omitting the latency period.

While in Schaefer et al. (2025) [34] no statistically significant hazard increase was reported for lung cancer among JAKi patients compared to bDMARD patients in any model, the RABBIT analysis for this report - now focusing on tofacitinib but not the other JAKis – does detect such a hazard increase for the on-drug sensitivity analysis, in line with the ORAL Surveillance study.

The higher hazard for NMSC estimated for tofacitinib vs. bDMARDs when using the on-drug approach instead of the ever-exposed approach may be explained by the observation time added after discontinuing tofacitinib by using the ever-exposed approach instead of the on-drug approach. When proportionately more time at risk is added than events that may happen during this time, the hazard estimate decreases. Particularly in the time after the EULAR warnings, since few new tofacitinib therapies were initiated, time at risk was inflated by the time added exclusively due to using the ever-exposed approach.

We found no increased hazard of all-cause mortality in our regression analyses.

There were 2 pregnancies in the tofacitinib cohort, one after maternal and one after paternal tofacitinib exposure. Both resulted in live births and there was no serious pregnancy related maternal event.

As done in several other studies, tofacitinib was mainly compared to TNF inhibitors (66.8%). However, as outlined in the introduction and the limitation section, an equivalent use based on recommendations was restricted to a very short time period. The main and the stratified baseline tables show that patients initiating tofacitinib had a poorer state of health compared to patients initiating bDMARDs or nbDMARDs. An adjustment for more possible confounders was limited by the small number of events in most outcomes.

Based on the IRs, a numerically higher hazard for tofacitinib compared to bDMARDs especially (or only) in patients at least 65 years of age was seen for several investigated outcomes, including malignancies (overall, solid malignancy and benign neoplasms), NMSC, all-cause mortality, serious infections (overall, pneumonia and sepsis), HZ, fractures, operations and hospitalizations (overall) and other serious diagnosis. In contrast, higher hazards for tofacitinib compared to bDMARD particularly observed in patients with age below 65 years were scarce (other infections, coronary artery disease). Therefore, the results of this PASS support the guideline that tofacitinib should be given preferentially to patients below 65 years of age.

11.4. Generalizability

In general, RABBIT is a nationwide, population-based cohort study including non-selected patients with established RA in daily rheumatological care in Germany. No inclusion or exclusion criteria were applied, except that patients had to have a rheumatologically confirmed diagnose of RA, be at least 18 years old at enrolment, have experienced RA disease onset after the age of 15, and start a new DMARD therapy (after failure of at least one DMARD). The generalizability to the entire field of German rheumatology is limited by the imbalance in

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prescriptions between institutions. Furthermore, interpretation of these findings in an international context requires consideration of structural differences between healthcare systems and different ways of therapeutic decision-making.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

After adjusting for measured potential confounders, a statistically significant increased hazard of HZ, CV risk (MACE), and NMSC was observed among tofacitinib initiators vs. bDMARD initiators, under the on-drug approach. Using the ever-exposed approach, the hazard of NMSC was increased for tofacitinib vs. bDMARD therapy, but not statistically significant.
After adjusting for measured potential confounders, a statistically significant increased hazard of HZ, fractures, cardiac disorders (overall), and other serious diagnoses, symptoms and syndromes was observed among tofacitinib initiators vs. nbDMARD initiators, under the on-drug approach. These results are consistent with the known safety profile of tofacitinib, as HZ reactivation is an important identified risk and cardiovascular risk is an important potential risk in the EU Risk Management Plan (RMP). Increased hazards using the secondary analysis or the sensitivity analyses were seen for cardiac disorders, myocardial infarction, stroke, NMSC and lung cancer in adjusted models. Additionally, a statistically significant increased hazard for malignancies (excl. NMSC) in tofacitinib vs. bDMARDs was observed in patients aged 65 years or older. Overall, the results of this report are in line with findings from the ORAL Surveillance trial. The PASS results support the evidence that an increased hazard of VTE could be driven by an increased hazard of PE.

However, for several investigated outcomes, the numbers of events were too small to perform adjusted Cox regression analyses which limits interpretability given the differences in patient characteristics found in this study, indicating that patients initiating tofacitinib had a generally poorer state of health compared to patients initiating a bDMARD or an nbDMARD, which could confound crude results.

These results are consistent with the known safety profile of tofacitinib, as HZ, NMSC, and MI are important identified risks in the EU RMP, while CV risk (excl. MI) and fractures are important potential risks.

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15. APPENDIX

Table 21. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort

Follow-up visits (t)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Month of follow-up	0	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Date of visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient characteristics																						
Year of birth, sex, height	x																					
Rheumatoid factor, Erosive joint alterations, Rheumatoid nodules	x																					
Date of symptom onset	x																					
Comorbidities	x						x					x					x					x
Smoking habits (patient), weight	x			x		x		x		x		x		x		x		x		x		x
Therapy																						
Start/end of DMARDs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reasons for therapy change		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Anti-rheumatic comedications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, other outcomes																						
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy including outcome				x		x		x		x		x		x		x		x		x		x
Side effects (patient)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease activity																						
ESR, CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
28 Swollen/ tender joint counts	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morning stiffness	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease activity, numerical rating scale (physician)*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Functional capacity (FFbH) (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain severity, numerical rating scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fatigue severity, numerical rating scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
General health state, numerical rating scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

X = measured variable at the indicated visit. All measurements are reported by the physician if not otherwise indicated.

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Table 21. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort

*Physician reported disease activity was added to the questionnaires in 2013.
Abbreviations: CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire.

Table 22. Histograms of the propensity score distributions of the primary regression analyses

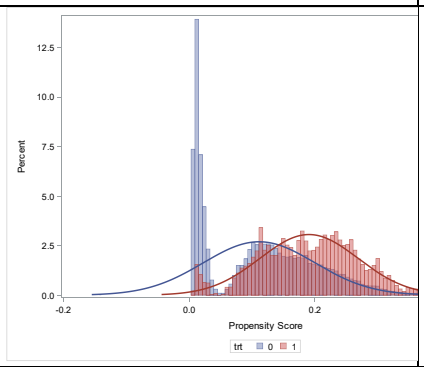
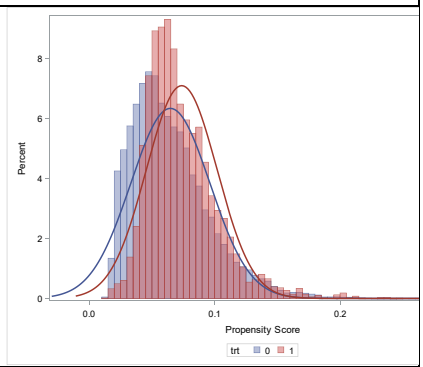
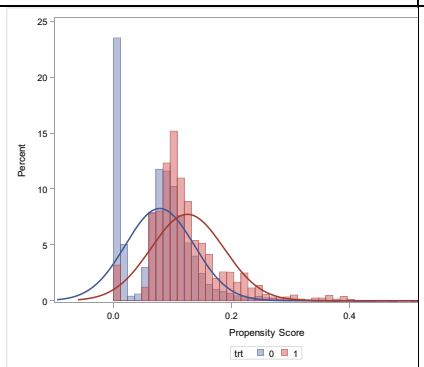
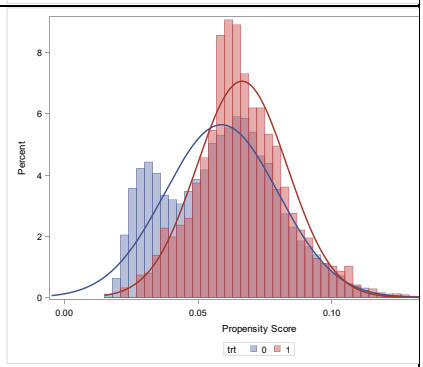
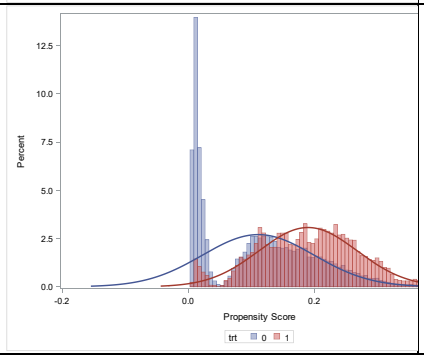
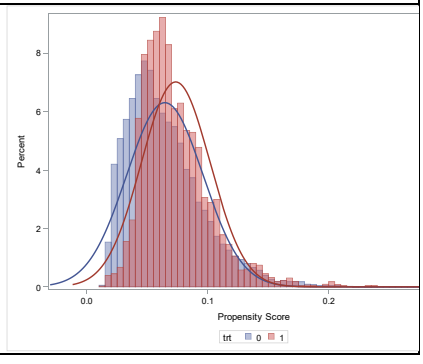
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
1. Serious infection (excluding TB)	bDMARD		
	nbDMARD		
Pneumonia	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

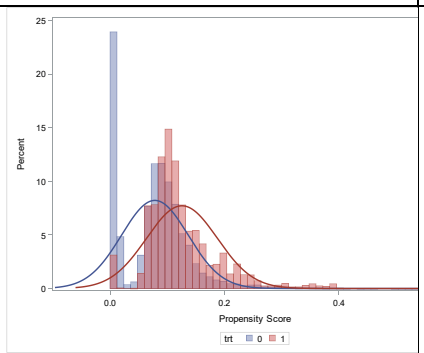
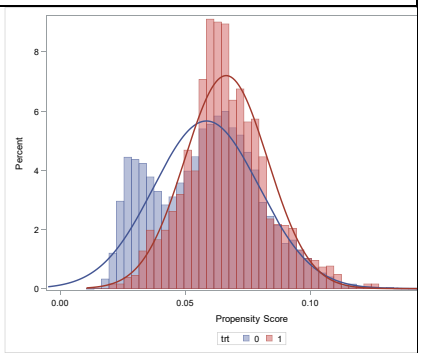
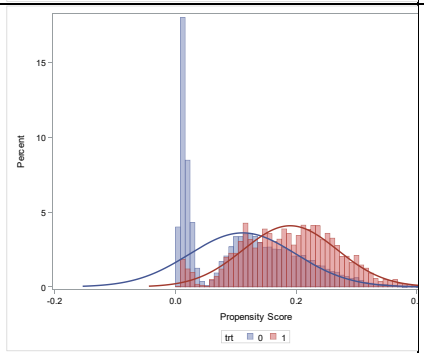
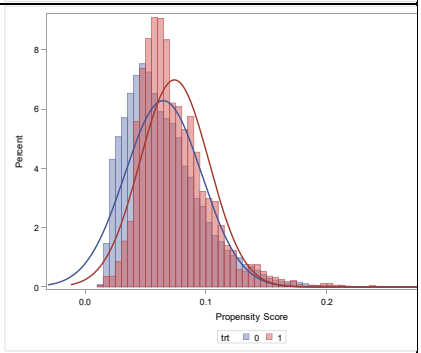
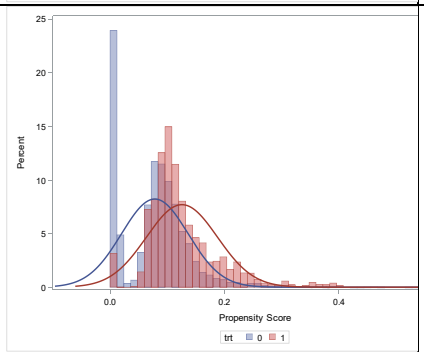
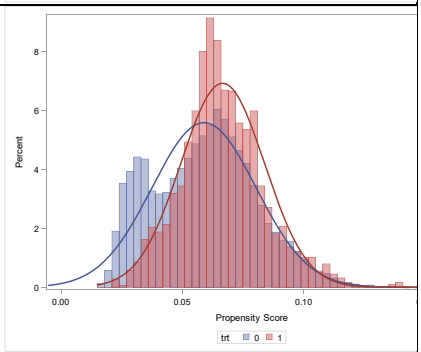
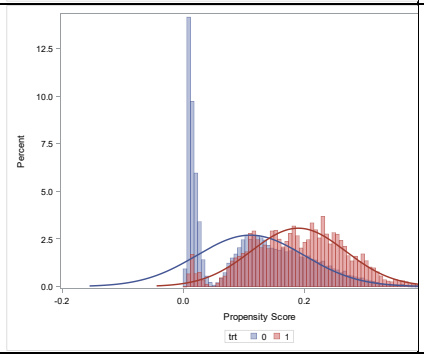
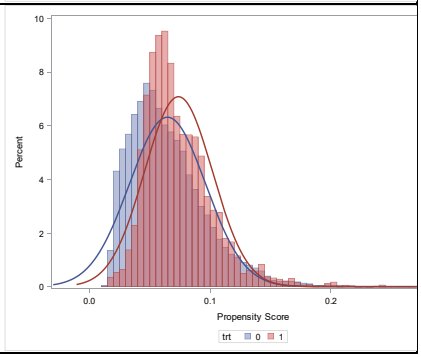
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
Sepsis	bDMARD		
	nbDMARD		
Other infections	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

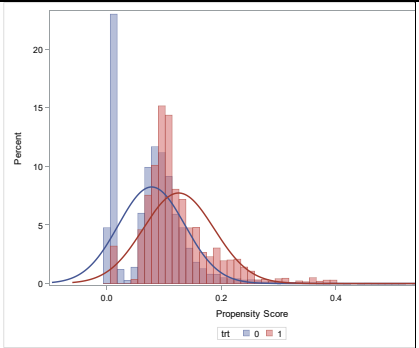
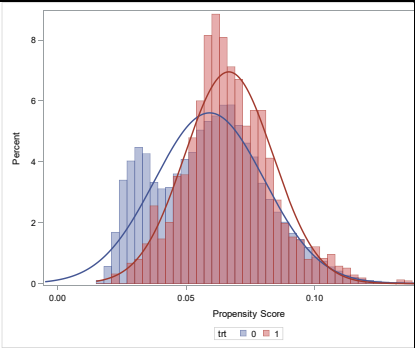
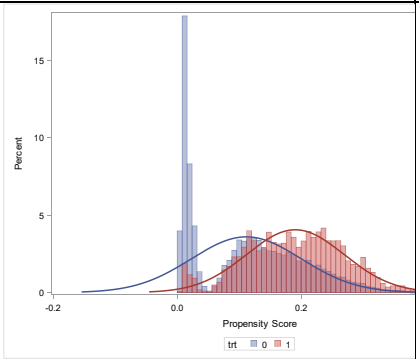
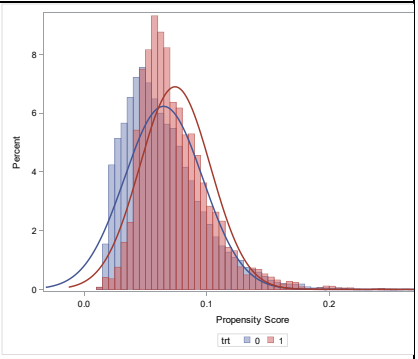
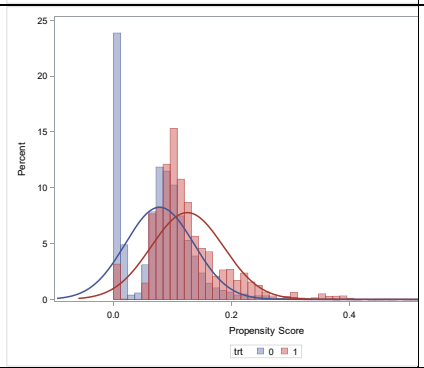
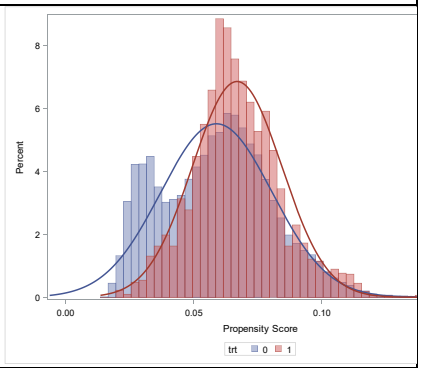
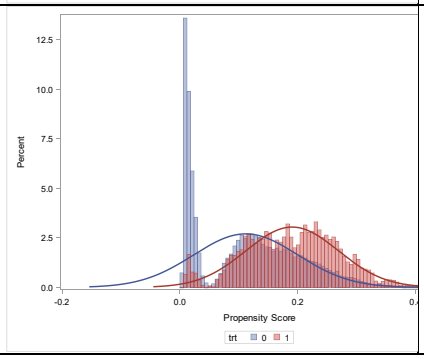
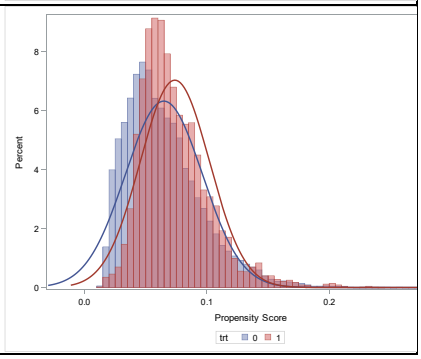
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
3. HZ	bDMARD		
	nbDMARD		
4. Fractures	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

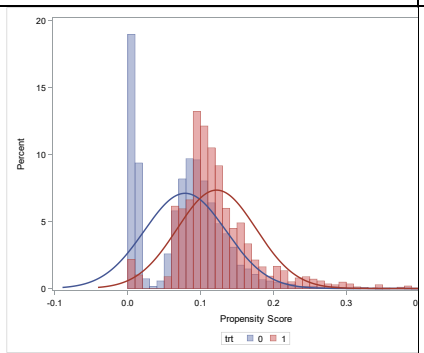
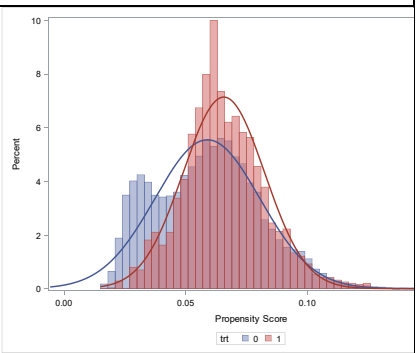
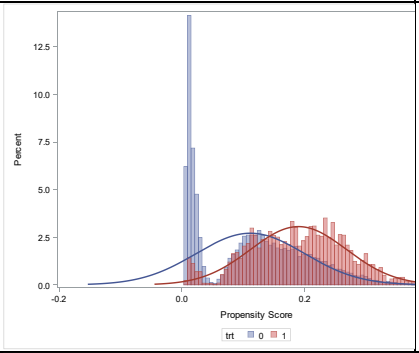
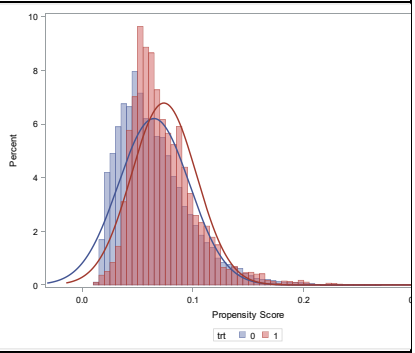
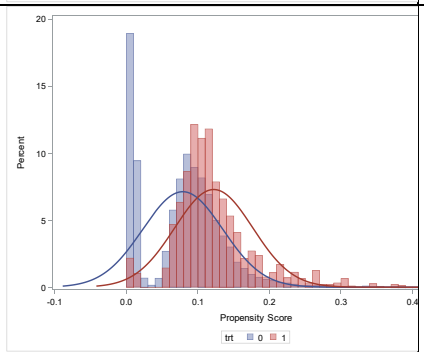
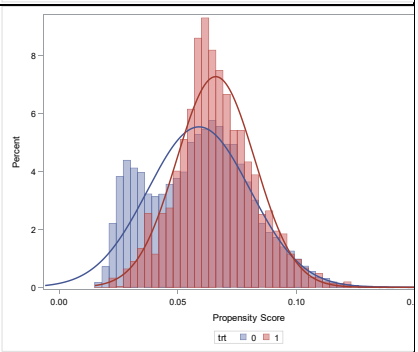
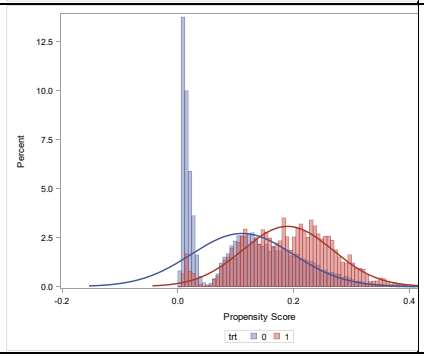
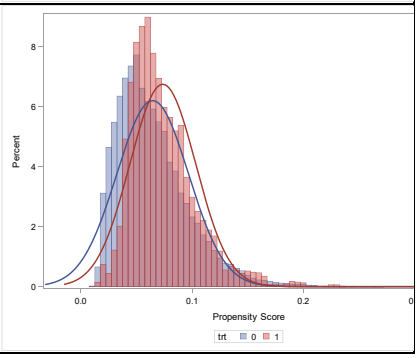
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
5. Cardiac disorders	bDMARD		
	nbDMARD		
Heart failure	bDMARD		

Table 22. Histograms of the propensity score distributions of the primary regression analyses

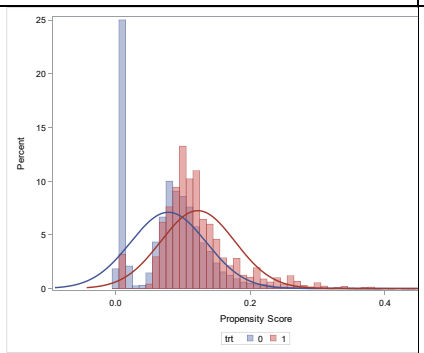
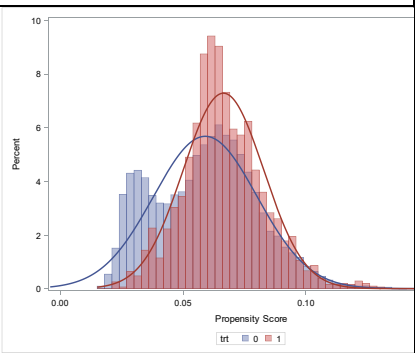
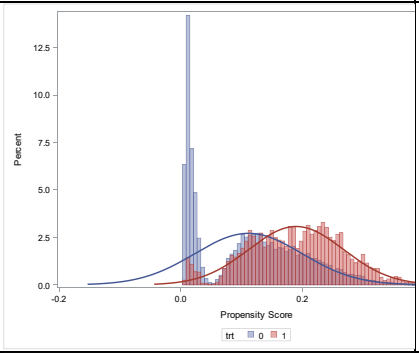
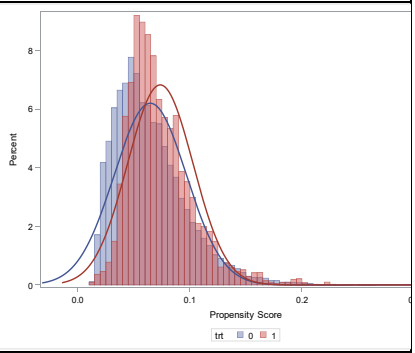
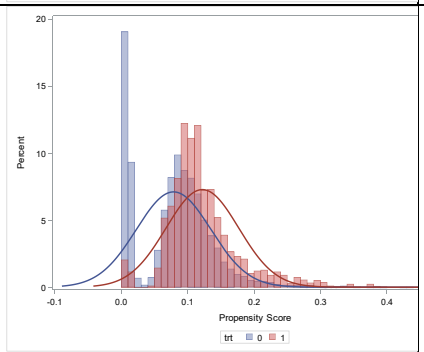
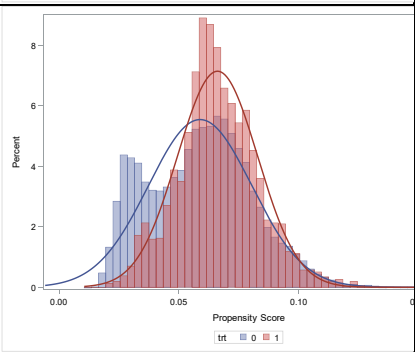
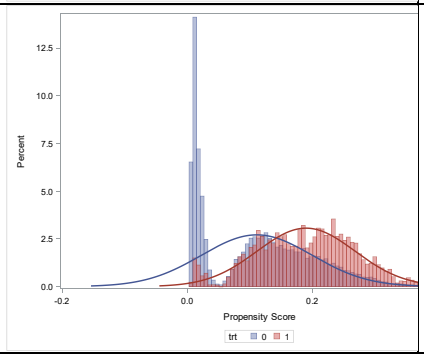
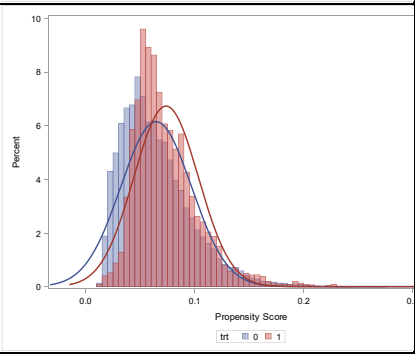
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
Coronary artery disease	bDMARD		
	nbDMARD		
Myocardial infarction	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

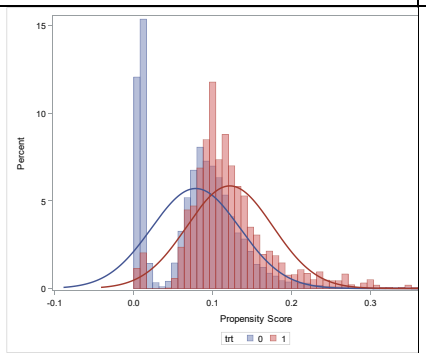
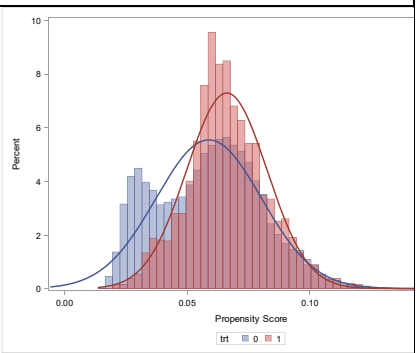
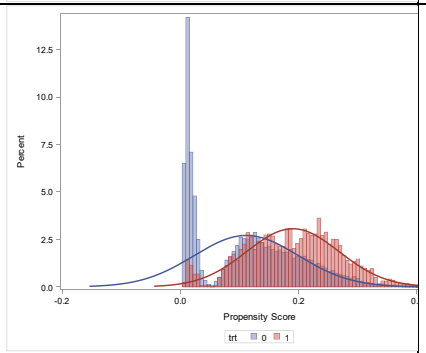
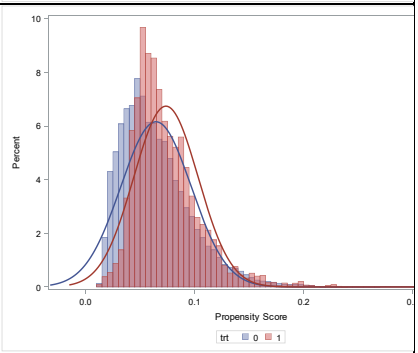
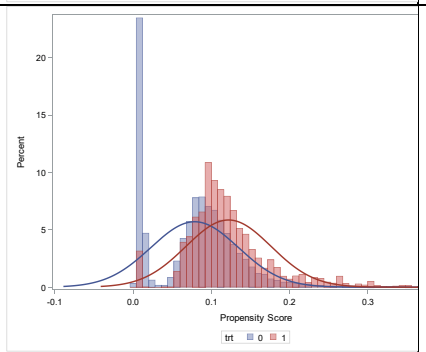
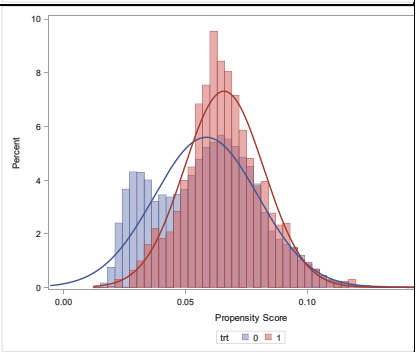
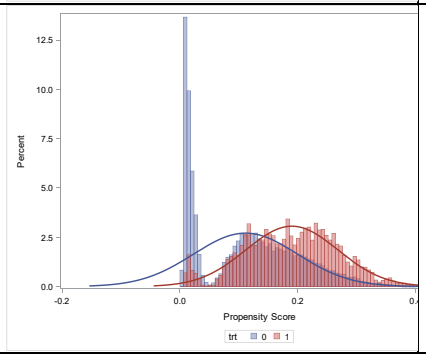
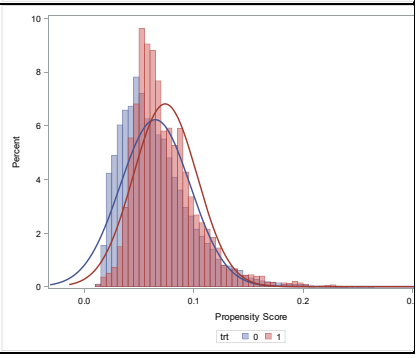
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
MACE	bDMARD		
	nbDMARD		
Other cardiac disorders	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

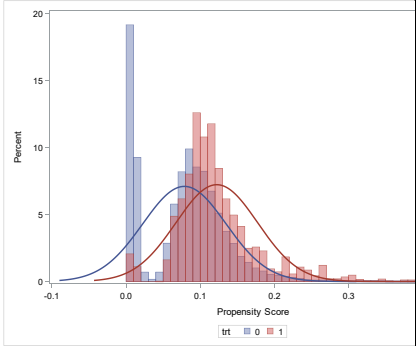
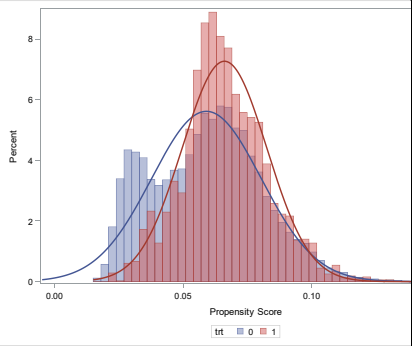
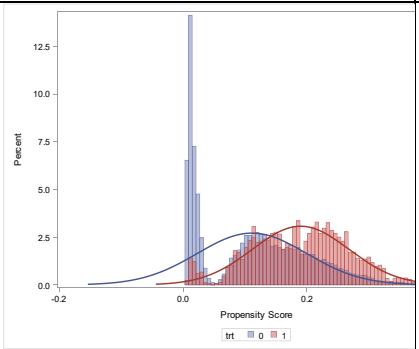
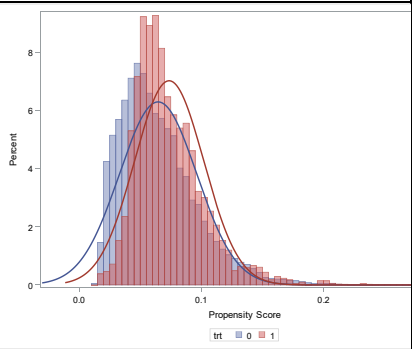
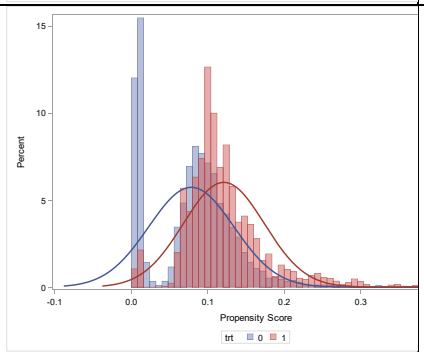
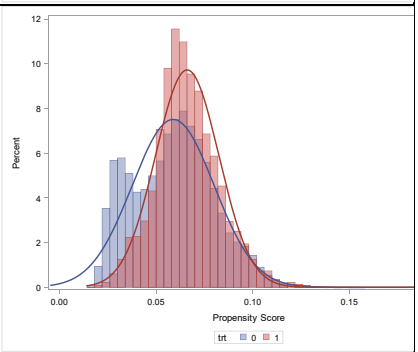
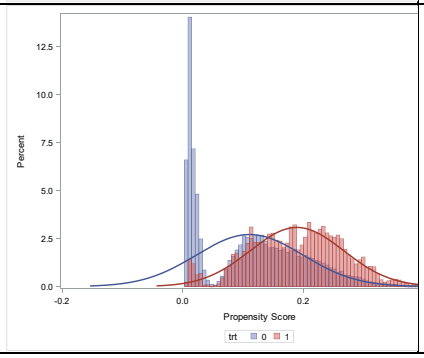
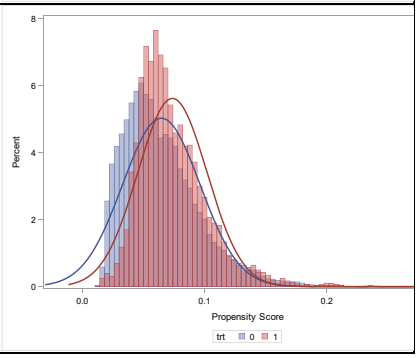
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
6. Hematologic disorders	bDMARD		
	nbDMARD		
Other blood dyscrasia	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

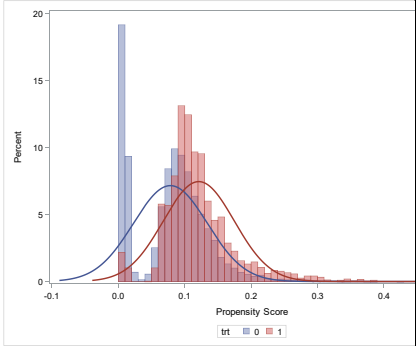
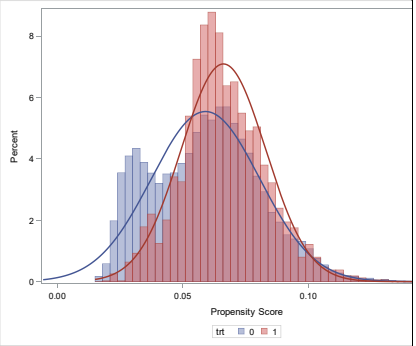
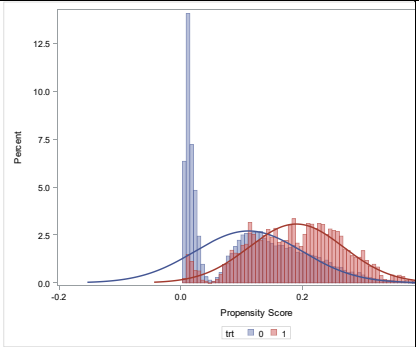
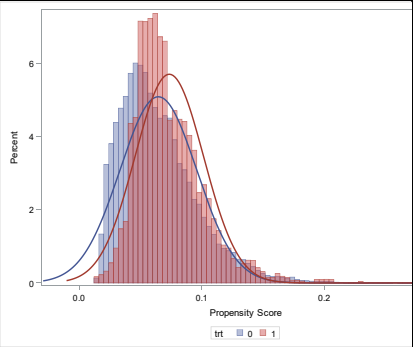
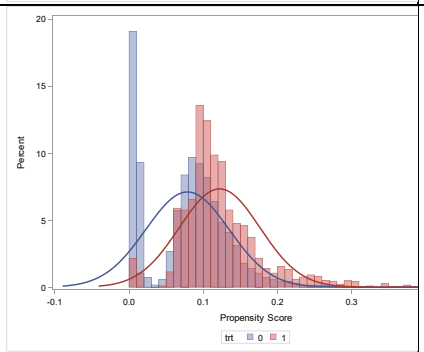
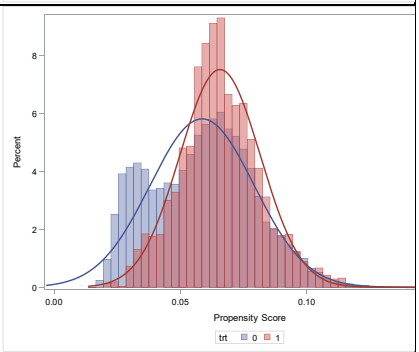
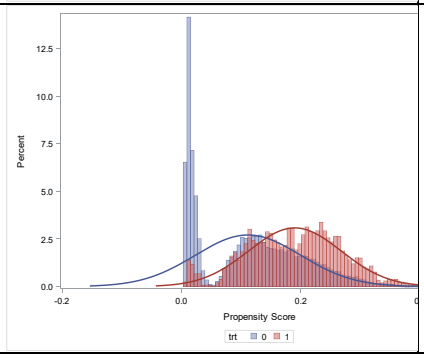
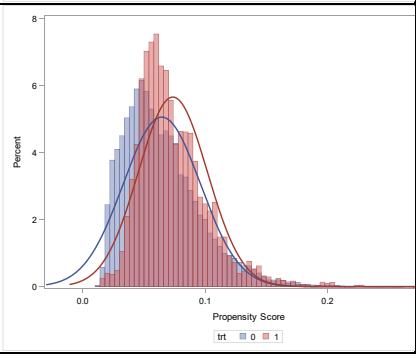
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
7. Disorders of the nervous system	bDMARD		
	nbDMARD		
Stroke	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

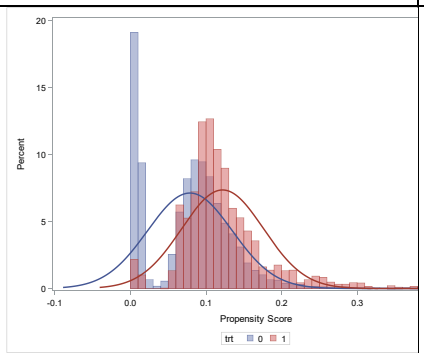
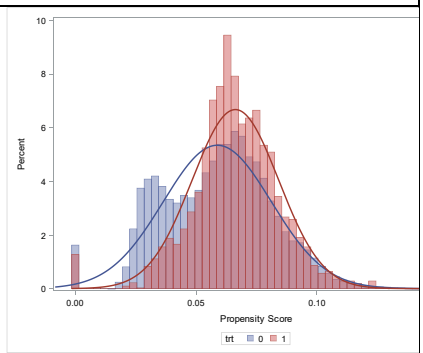
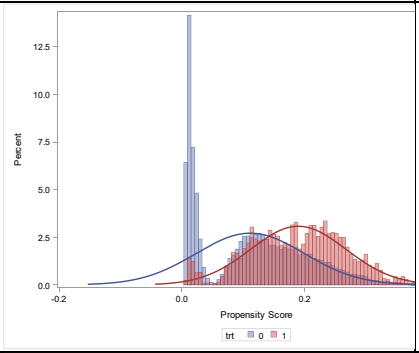
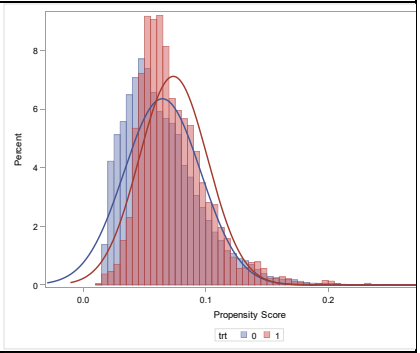
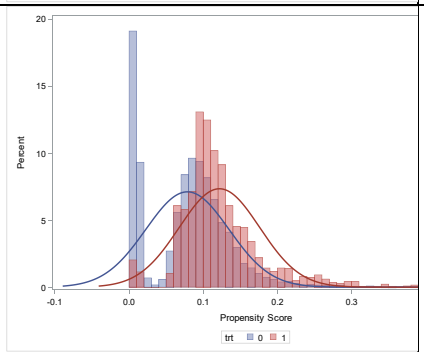
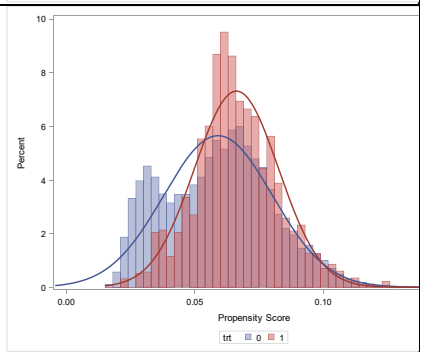
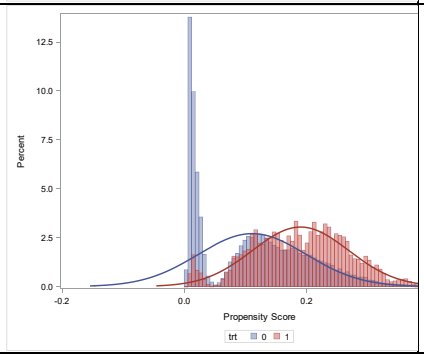
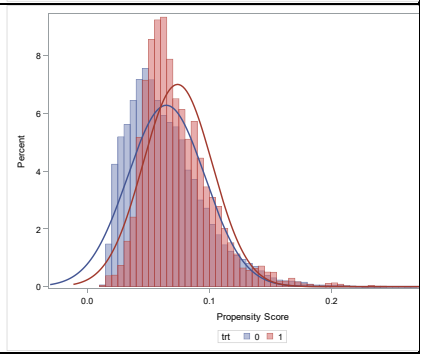
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
Other disorders of the CNS	bDMARD		
	nbDMARD		
Disorders of the peripheral nervous system	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

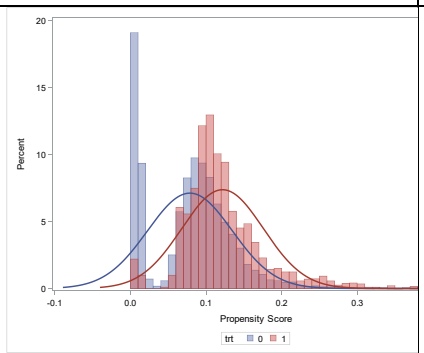
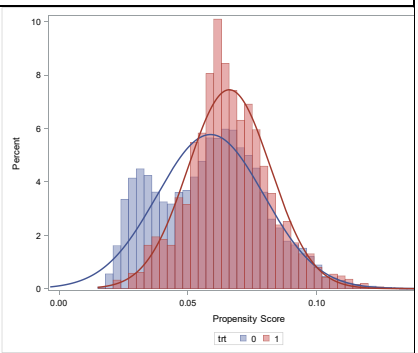
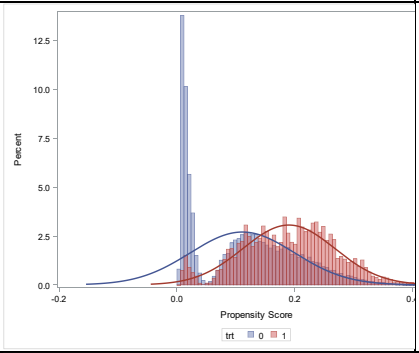
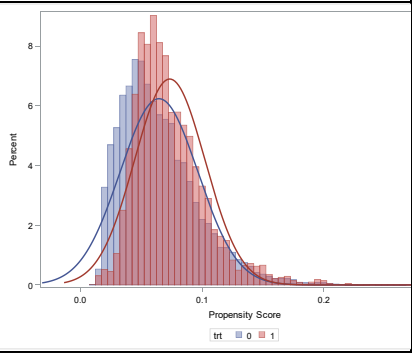
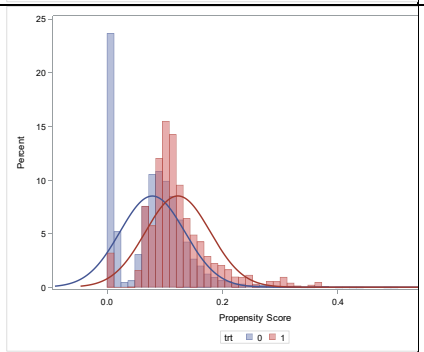
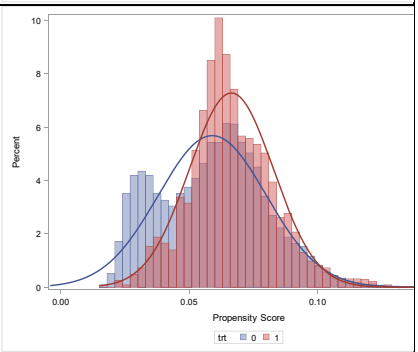
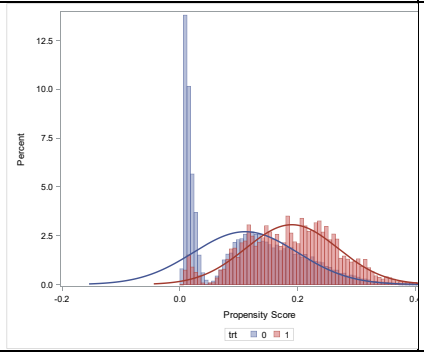
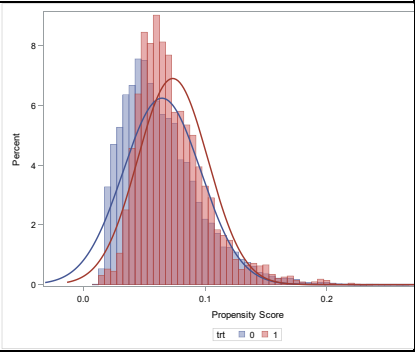
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
13. Embolic and thrombotic events	bDMARD		
	nbDMARD		
VTE	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

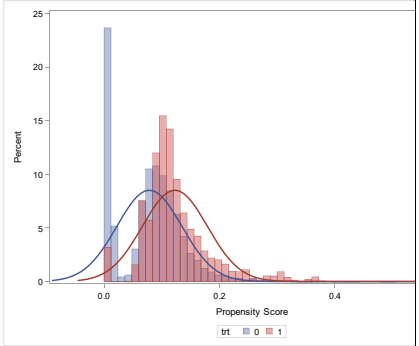
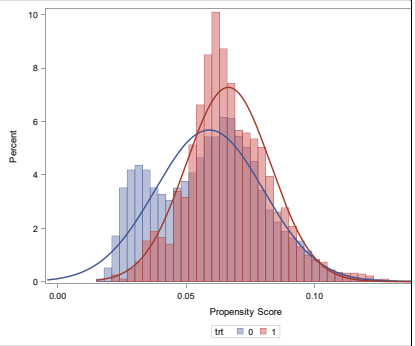
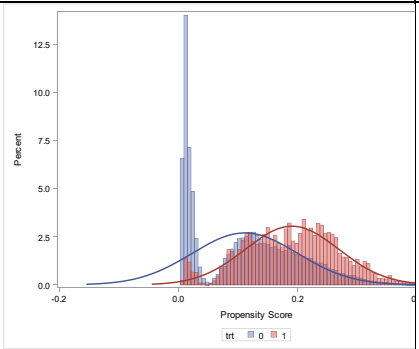
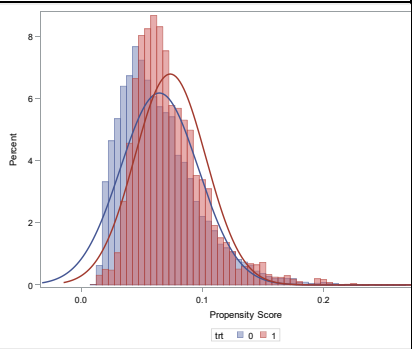
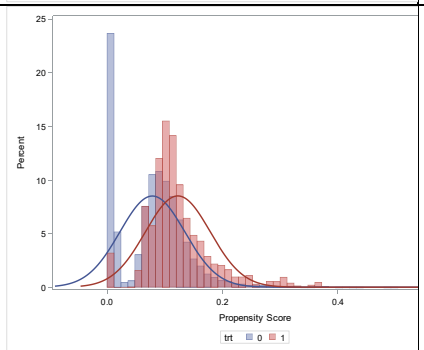
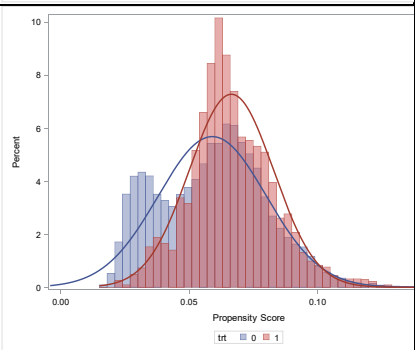
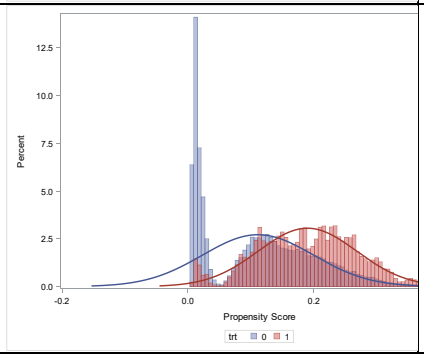
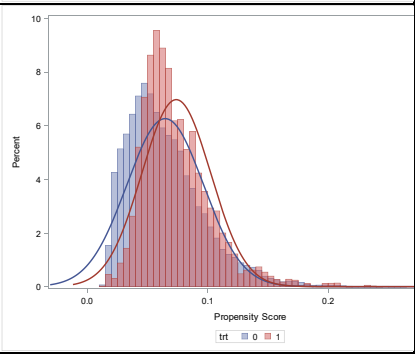
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
PE	bDMARD		
	nbDMARD		
14. Operations and hospitalizations	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

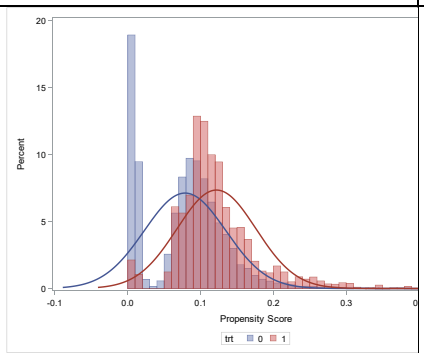
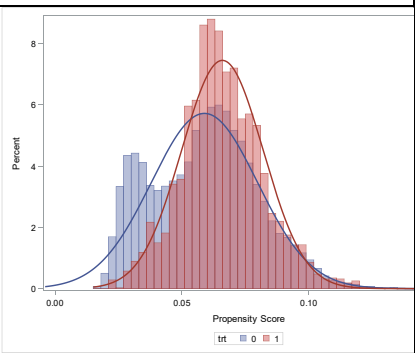
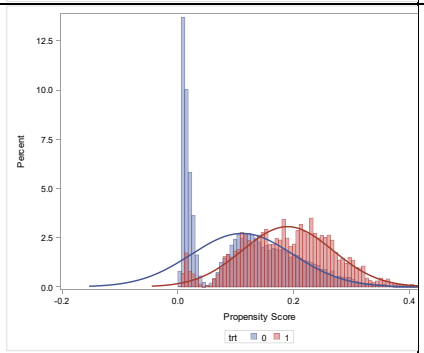
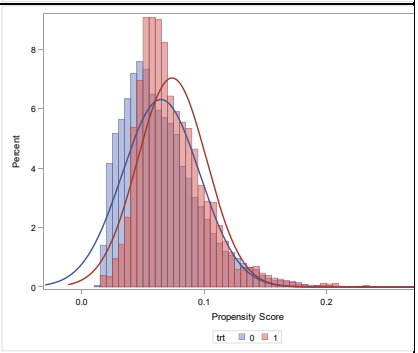
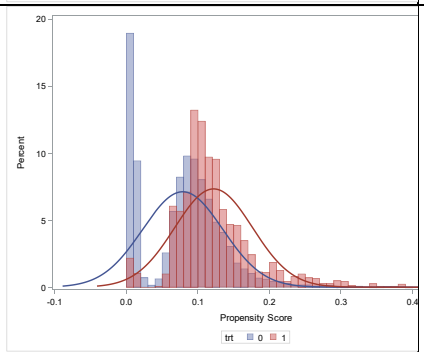
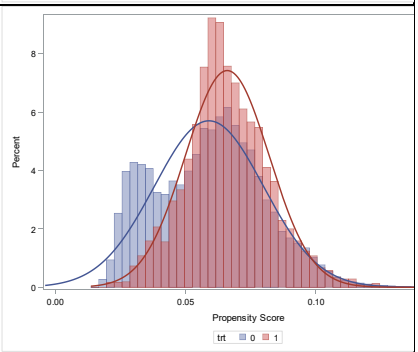
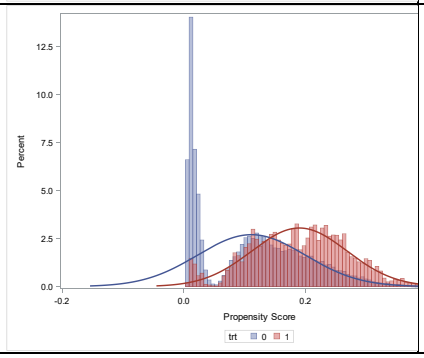
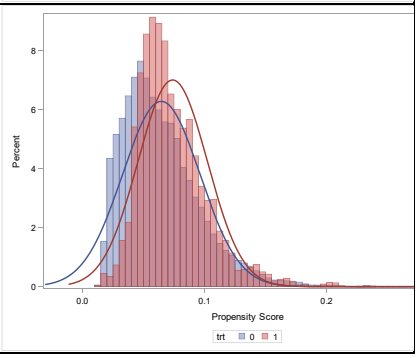
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
Bone and joint surgery and other joint therapeutic procedures	bDMARD		
	nbDMARD		
Other operations and (major) therapeutic procedures that lead to hospitalization	bDMARD		

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

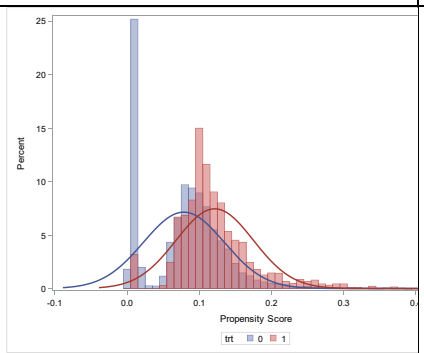
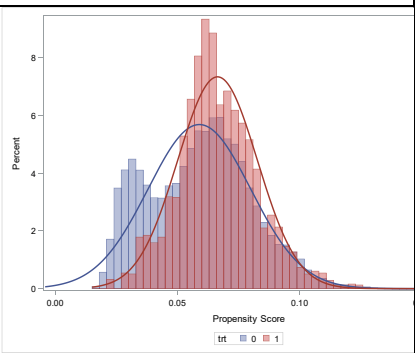
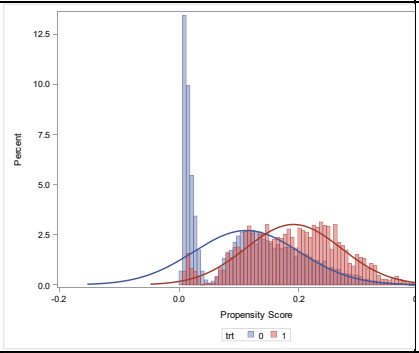
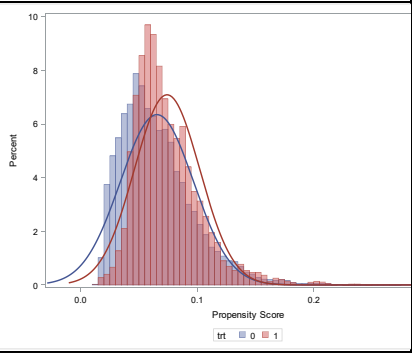
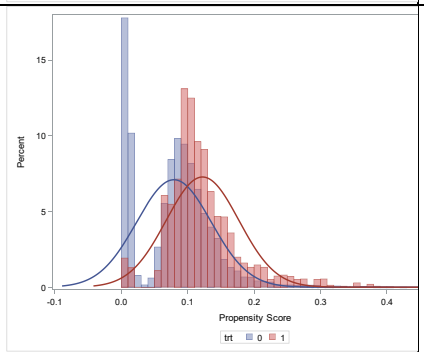
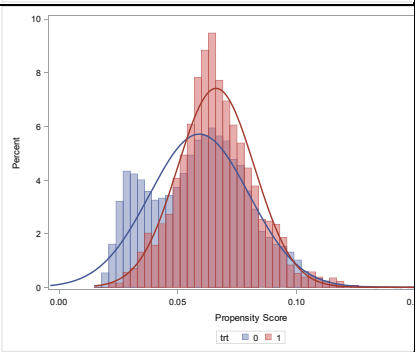
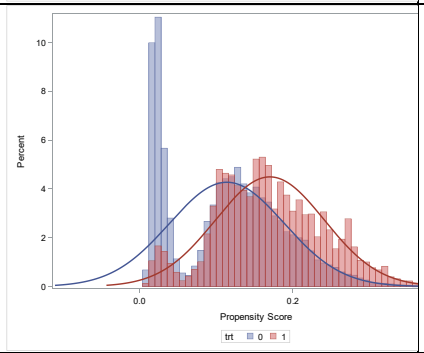
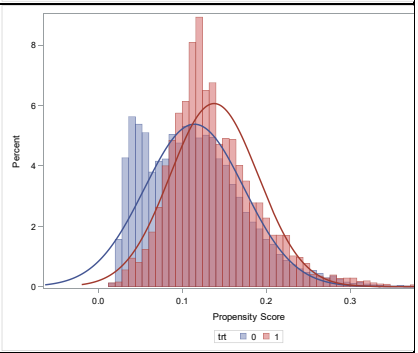
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
	nbDMARD		
15. Other serious diagnoses, symptoms, and syndromes	bDMARD		
	nbDMARD		
16. NMSC	bDMARD		
	nbDMARD	NA	NA

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Table 22. Histograms of the propensity score distributions of the primary regression analyses

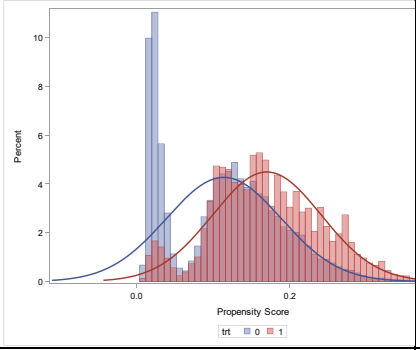
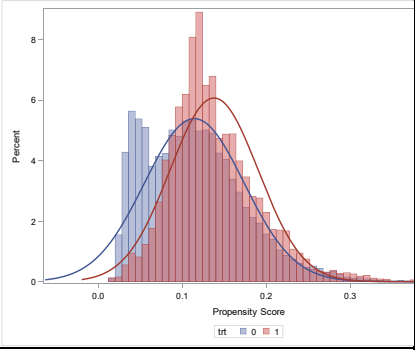
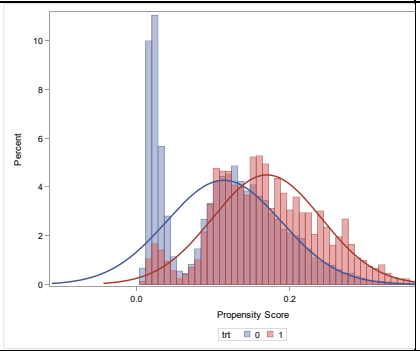
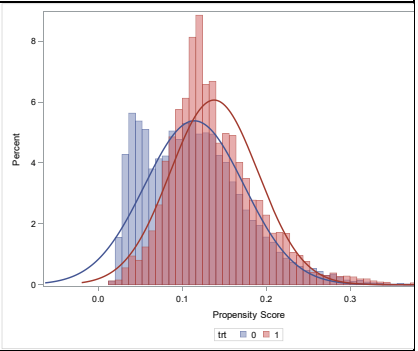
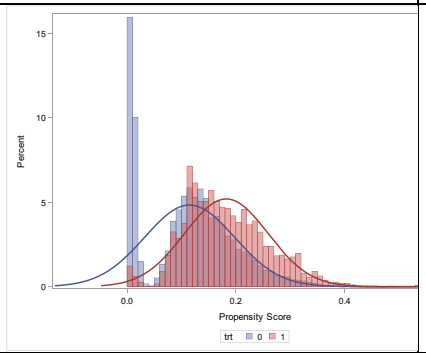
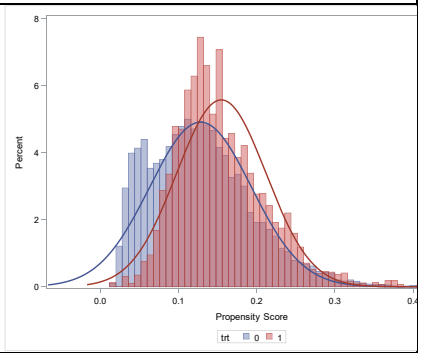
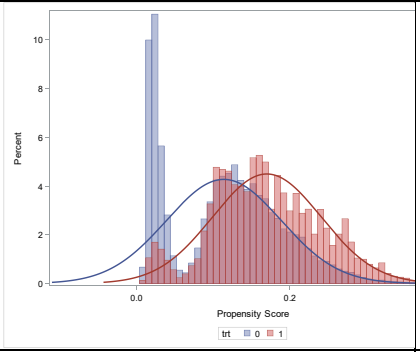
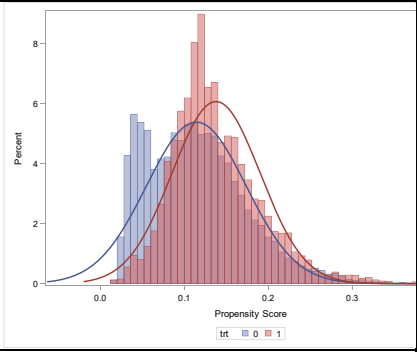
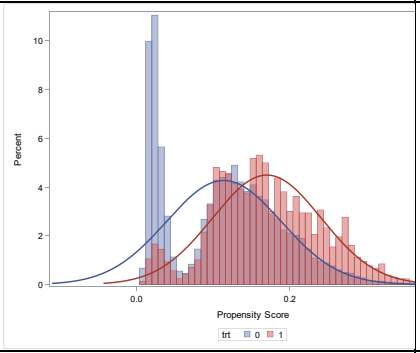
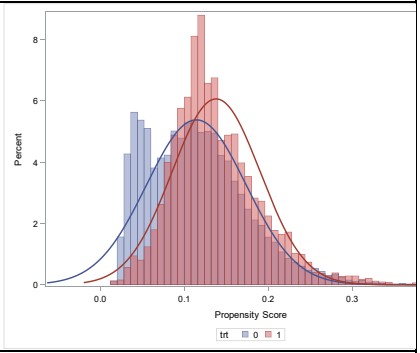
Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
17. Malignancies (overall, excluding NMSC)	bDMARD		
	nbDMARD	NA	NA
19. Lung Cancer	bDMARD		
	nbDMARD	NA	NA
20. All-cause Mortality	bDMARD		
	nbDMARD	NA	NA

Table 22. Histograms of the propensity score distributions of the primary regression analyses

Outcome	Comparator	PS distributions for	
		Therapy	Informative dropout
23. Solid malignancies (overall)	bDMARD		
	nbDMARD	NA	NA
25. Benign neoplasms	bDMARD		
	nbDMARD	NA	NA

For each outcome, the distributions of the therapy propensity score and the dropout propensity score from the main model are given for the tofacitinib cohort (trt=1) vs. the comparator cohort (trt=0), i.e., the bDMARD or the nbDMARD cohort, respectively. For malignancies outcomes as well as mortality, the model based on the ever-exposed approach (with and without latency period, respectively) is regarded as primary regression analysis, for all other outcomes the model based on the on-drug approach is regarded as primary regression analysis.
The main models are adjusted for age, sex, RA disease duration, RF/ ACPA positivity, year of therapy start, DAS28-ESR, FFbH, previous b/tsDMARDs, glucocorticoid dosage, and smoking, plus potentially outcome specific covariates. For a detailed description of model covariates, see Table 4.
Cox regression models using the ever-exposed approach were only calculated for comparing tofacitinib and bDMARDs. If no model was calculated, NA is given instead of PS distributions.
Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; CNS, central nervous system; HZ, herpes zoster; MACE, major cardiovascular events; NA, not applicable; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PS, propensity score; VTE, venous thromboembolism.

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
1. Serious infection	logit therapy PS	0.989	0.573	0.866	0.580
	logit dropout PS	0.407	0.348	0.473	0.440
	50 ≤ age < 60	0.083	0.020	0.020	0.045
	60 ≤ age < 70	-0.007	-0.017	-0.038	-0.046
	age ≥ 70	-0.037	-0.005	0.114	0.014
	DAS28-ESR	0.192	0.003	0.251	0.047
	disease duration	0.129	0.024	0.287	0.096
	sex	0.083	0.011	0.062	0.013
	FFbH	-0.210	-0.015	-0.183	-0.031
	0 < GC ≤ 5	0.031	-0.038	0.023	-0.031
	5 < GC ≤ 10	0.003	-0.023	-0.069	-0.068
	GC > 10	0.060	-0.009	0.111	-0.003
	One prior b/tsDMARD	0.109	0.054	NA	NA
	≥ 2 prior b/tsDMARDs	0.296	0.032	NA	NA
	Smoking	-0.045	-0.013	-0.115	-0.030
	RF/ACPA positive	-0.047	-0.013	0.022	-0.014
	Year of cohort entry	-0.873	-0.623	-0.753	-0.607
	History of COPD	-0.005	-0.002	-0.009	0.022
	History of CKD	0.045	0.035	0.226	0.052
Pneumonia	logit therapy PS	0.986	0.565	0.872	0.577
	logit dropout PS	0.402	0.339	0.491	0.446
	50 ≤ age < 60	0.081	0.019	0.018	0.044
	60 ≤ age < 70	-0.003	-0.020	-0.040	-0.049
	age ≥ 70	-0.041	-0.002	0.110	0.011
	DAS28-ESR	0.190	0.000	0.264	0.050
	disease duration	0.128	0.022	0.282	0.088
	sex	0.080	0.007	0.057	0.013
	FFbH	-0.203	-0.012	-0.175	-0.027
	0 < GC ≤ 5	0.033	-0.037	0.020	-0.032
	5 < GC ≤ 10	0.010	-0.023	-0.070	-0.070
	GC > 10	0.055	-0.012	0.113	-0.003
	One prior b/tsDMARD	0.109	0.053	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.031	NA	NA
	Smoking	-0.045	-0.014	-0.105	-0.027

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	RF/ACPA positive	-0.043	-0.012	0.027	-0.014
	Year of cohort entry	-0.872	-0.615	-0.758	-0.606
	History of COPD	-0.014	-0.002	-0.010	0.023
	History of CKD	0.042	0.035	0.225	0.049
Sepsis	logit therapy PS	0.985	0.562	0.872	0.576
	logit dropout PS	0.409	0.340	0.468	0.432
	50 ≤ age < 60	0.080	0.019	0.019	0.047
	60 ≤ age < 70	-0.002	-0.018	-0.040	-0.048
	age ≥ 70	-0.041	-0.004	0.109	0.010
	DAS28-ESR	0.193	0.002	0.260	0.050
	disease duration	0.127	0.021	0.282	0.086
	sex	0.081	0.010	0.058	0.014
	FFbH	-0.205	-0.014	-0.177	-0.026
	0 < GC ≤ 5	0.036	-0.035	0.022	-0.031
	5 < GC ≤ 10	0.009	-0.023	-0.070	-0.071
	GC > 10	0.054	-0.013	0.112	-0.004
	One prior b/tsDMARD	0.107	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.294	0.034	NA	NA
	Smoking	-0.044	-0.013	-0.111	-0.026
	RF/ACPA positive	-0.044	-0.013	0.030	-0.013
	Year of cohort entry	-0.870	-0.610	-0.758	-0.606
	History of COPD	-0.015	-0.003	-0.011	0.024
	History of CKD	0.042	0.035	0.222	0.044
Other infections	logit therapy PS	0.987	0.569	0.870	0.569
	logit dropout PS	0.410	0.348	0.461	0.426
	50 ≤ age < 60	0.083	0.019	0.022	0.050
	60 ≤ age < 70	-0.005	-0.016	-0.038	-0.050
	age ≥ 70	-0.040	-0.006	0.111	0.010
	DAS28-ESR	0.195	0.002	0.257	0.046
	disease duration	0.129	0.023	0.285	0.088
	sex	0.086	0.012	0.063	0.018
	FFbH	-0.206	-0.016	-0.188	-0.030
	0 < GC ≤ 5	0.029	-0.036	0.022	-0.034
	5 < GC ≤ 10	0.006	-0.022	-0.069	-0.069

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	GC > 10	0.058	-0.010	0.113	-0.005
	One prior b/tsDMARD	0.111	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.034	NA	NA
	Smoking	-0.044	-0.013	-0.111	-0.031
	RF/ACPA positive	-0.048	-0.013	0.025	-0.018
	Year of cohort entry	-0.872	-0.617	-0.755	-0.598
	History of COPD	-0.010	-0.002	-0.011	0.022
	History of CKD	0.044	0.034	0.224	0.045
3. HZ	logit therapy PS	0.984	0.554	0.869	0.574
	logit dropout PS	0.410	0.334	0.487	0.438
	50 ≤ age < 60	0.083	0.019	0.021	0.050
	60 ≤ age < 70	-0.005	-0.018	-0.038	-0.050
	age ≥ 70	-0.042	-0.005	0.104	0.008
	DAS28-ESR	0.191	-0.001	0.255	0.050
	disease duration	0.127	0.021	0.283	0.088
	sex	0.081	0.008	0.057	0.014
	FFbH	-0.206	-0.013	-0.177	-0.028
	0 < GC ≤ 5	0.035	-0.035	0.024	-0.034
	5 < GC ≤ 10	0.008	-0.024	-0.069	-0.070
	GC > 10	0.055	-0.012	0.115	-0.002
	One prior b/tsDMARD	0.106	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.298	0.034	NA	NA
	Smoking	-0.046	-0.013	-0.116	-0.029
	RF/ACPA positive	-0.052	-0.013	0.024	-0.018
	Year of cohort entry	-0.867	-0.603	-0.756	-0.603
	History of COPD	-0.011	-0.003	-0.009	0.023
	History of CKD	0.041	0.035	0.223	0.046
4. Fractures	logit therapy PS	0.982	0.559	0.853	0.587
	logit dropout PS	0.399	0.337	0.434	0.426
	50 ≤ age < 60	0.082	0.019	0.020	0.044
	60 ≤ age < 70	-0.003	-0.019	-0.040	-0.051
	age ≥ 70	-0.040	-0.001	0.108	0.018
	DAS28-ESR	0.190	0.005	0.259	0.052

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	disease duration	0.129	0.021	0.284	0.109
	sex	0.083	0.008	0.059	0.020
	FFbH	-0.208	-0.016	-0.175	-0.034
	0 < GC ≤ 5	0.035	-0.035	0.021	-0.041
	5 < GC ≤ 10	0.009	-0.022	-0.069	-0.062
	GC > 10	0.056	-0.012	0.112	0.000
	One prior b/tsDMARD	0.108	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.298	0.035	NA	NA
	Smoking	-0.041	-0.010	-0.115	-0.028
	RF/ACPA positive	-0.048	-0.013	0.028	-0.014
	Year of cohort entry	-0.866	-0.608	-0.757	-0.608
5. Cardiac disorders	logit therapy PS	0.980	0.557	0.851	0.579
	logit dropout PS	0.392	0.335	0.452	0.439
	50 ≤ age < 60	0.078	0.018	0.018	0.038
	60 ≤ age < 70	-0.001	-0.019	-0.041	-0.048
	age ≥ 70	-0.039	-0.001	0.111	0.017
	DAS28-ESR	0.195	0.003	0.254	0.051
	disease duration	0.129	0.020	0.283	0.101
	sex	0.080	0.007	0.057	0.020
	FFbH	-0.208	-0.017	-0.179	-0.035
	0 < GC ≤ 5	0.035	-0.034	0.022	-0.036
	5 < GC ≤ 10	0.010	-0.022	-0.072	-0.064
	GC > 10	0.055	-0.013	0.111	-0.004
	One prior b/tsDMARD	0.107	0.050	NA	NA
	≥ 2 prior b/tsDMARDs	0.296	0.034	NA	NA
	Smoking	-0.043	-0.012	-0.113	-0.025
	RF/ACPA positive	-0.044	-0.013	0.031	-0.016
	Year of cohort entry	-0.865	-0.607	-0.755	-0.603
	BMI ≥ 30	0.025	0.001	0.015	0.005
	CV risk	0.036	0.000	0.119	-0.009
Heart failure	logit therapy PS	0.983	0.560	NA	NA
	logit dropout PS	0.390	0.333	NA	NA
	50 ≤ age < 60	0.081	0.017	NA	NA

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	60 ≤ age < 70	-0.003	-0.019	NA	NA
	age ≥ 70	-0.041	-0.002	NA	NA
	DAS28-ESR	0.190	0.001	NA	NA
	disease duration	0.127	0.020	NA	NA
	sex	0.081	0.009	NA	NA
	FFbH	-0.204	-0.014	NA	NA
	0 < GC ≤ 5	0.034	-0.035	NA	NA
	5 < GC ≤ 10	0.011	-0.023	NA	NA
	GC > 10	0.054	-0.014	NA	NA
	One prior b/tsDMARD	0.108	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.031	NA	NA
	Smoking	-0.044	-0.011	NA	NA
	RF/ACPA positive	-0.045	-0.012	NA	NA
	Year of cohort entry	-0.870	-0.610	NA	NA
	BMI ≥ 30	0.023	-0.001	NA	NA
	CV risk	0.033	-0.002	NA	NA
	History of heart failure	0.014	-0.006	NA	NA
Coronary artery disease	logit therapy PS	0.982	0.558	NA	NA
	logit dropout PS	0.390	0.333	NA	NA
	50 ≤ age < 60	0.081	0.017	NA	NA
	60 ≤ age < 70	-0.002	-0.018	NA	NA
	age ≥ 70	-0.042	-0.003	NA	NA
	DAS28-ESR	0.188	0.002	NA	NA
	disease duration	0.129	0.019	NA	NA
	sex	0.080	0.007	NA	NA
	FFbH	-0.205	-0.014	NA	NA
	0 < GC ≤ 5	0.035	-0.036	NA	NA
	5 < GC ≤ 10	0.010	-0.023	NA	NA
	GC > 10	0.055	-0.012	NA	NA
	One prior b/tsDMARD	0.107	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.032	NA	NA
	Smoking	-0.044	-0.012	NA	NA
	RF/ACPA positive	-0.044	-0.013	NA	NA

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	Year of cohort entry	-0.869	-0.608	NA	NA
	BMI ≥ 30	0.026	0.001	NA	NA
	CV risk	0.033	-0.001	NA	NA
	History of CAD	0.022	0.007	NA	NA
Myocardial infarction	logit therapy PS	0.984	0.557	NA	NA
	logit dropout PS	0.397	0.338	NA	NA
	50 ≤ age < 60	0.081	0.018	NA	NA
	60 ≤ age < 70	-0.003	-0.020	NA	NA
	age ≥ 70	-0.042	-0.003	NA	NA
	DAS28-ESR	0.195	0.002	NA	NA
	disease duration	0.128	0.019	NA	NA
	sex	0.081	0.007	NA	NA
	FFbH	-0.202	-0.012	NA	NA
	0 < GC ≤ 5	0.034	-0.035	NA	NA
	5 < GC ≤ 10	0.010	-0.021	NA	NA
	GC > 10	0.053	-0.014	NA	NA
	One prior b/tsDMARD	0.108	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.030	NA	NA
	Smoking	-0.042	-0.010	NA	NA
	RF/ACPA positive	-0.044	-0.013	NA	NA
	Year of cohort entry	-0.870	-0.608	NA	NA
	BMI ≥ 30	0.024	-0.001	NA	NA
	CV risk	0.033	-0.002	NA	NA
MACE	logit therapy PS	0.984	0.559	0.853	0.584
	logit dropout PS	0.395	0.338	0.465	0.443
	50 ≤ age < 60	0.081	0.017	0.018	0.040
	60 ≤ age < 70	-0.002	-0.019	-0.041	-0.047
	age ≥ 70	-0.042	-0.003	0.110	0.015
	DAS28-ESR	0.192	0.002	0.253	0.052
	disease duration	0.127	0.019	0.282	0.103
	sex	0.081	0.008	0.057	0.021
	FFbH	-0.202	-0.014	-0.174	-0.035
	0 < GC ≤ 5	0.036	-0.034	0.020	-0.036
	5 < GC ≤ 10	0.010	-0.022	-0.070	-0.062
	GC > 10	0.052	-0.014	0.113	-0.001

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	One prior b/tsDMARD	0.108	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.031	NA	NA
	Smoking	-0.047	-0.014	-0.107	-0.027
	RF/ACPA positive	-0.044	-0.013	0.030	-0.016
	Year of cohort entry	-0.870	-0.609	-0.759	-0.607
	BMI ≥ 30	0.024	0.000	0.020	0.004
	CV risk	0.033	-0.001	0.118	-0.011
Other cardiac disorders	logit therapy PS	0.983	0.561	0.855	0.583
	logit dropout PS	0.396	0.339	0.449	0.434
	50 ≤ age < 60	0.079	0.017	0.018	0.039
	60 ≤ age < 70	-0.002	-0.018	-0.041	-0.048
	age ≥ 70	-0.039	-0.002	0.111	0.018
	DAS28-ESR	0.195	0.005	0.262	0.053
	disease duration	0.128	0.020	0.282	0.103
	sex	0.081	0.008	0.057	0.019
	FFbH	-0.207	-0.017	-0.176	-0.034
	0 < GC ≤ 5	0.035	-0.034	0.021	-0.036
	5 < GC ≤ 10	0.009	-0.022	-0.070	-0.063
	GC > 10	0.054	-0.013	0.112	-0.002
	One prior b/tsDMARD	0.108	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.033	NA	NA
	Smoking	-0.041	-0.010	-0.115	-0.027
	RF/ACPA positive	-0.044	-0.014	0.028	-0.013
	Year of cohort entry	-0.868	-0.610	-0.758	-0.607
	BMI ≥ 30	0.024	-0.001	0.018	0.005
	CV risk	0.035	0.000	0.118	-0.007
6. Hematologic disorders	logit therapy PS	0.984	0.563	NA	NA
	logit dropout PS	0.404	0.345	NA	NA
	50 ≤ age < 60	0.083	0.018	NA	NA
	60 ≤ age < 70	-0.004	-0.019	NA	NA
	age ≥ 70	-0.043	-0.002	NA	NA
	DAS28-ESR	0.191	0.001	NA	NA
	disease duration	0.128	0.020	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	sex	0.081	0.009	NA	NA
	FFbH	-0.202	-0.016	NA	NA
	0 < GC ≤ 5	0.034	-0.035	NA	NA
	5 < GC ≤ 10	0.011	-0.022	NA	NA
	GC > 10	0.051	-0.013	NA	NA
	One prior b/tsDMARD	0.109	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.032	NA	NA
	Smoking	-0.045	-0.013	NA	NA
	RF/ACPA positive	-0.041	-0.013	NA	NA
	Year of cohort entry	-0.870	-0.613	NA	NA
Other blood dyscrasia	logit therapy PS	0.984	0.564	NA	NA
	logit dropout PS	0.404	0.344	NA	NA
	50 ≤ age < 60	0.082	0.019	NA	NA
	60 ≤ age < 70	-0.004	-0.020	NA	NA
	age ≥ 70	-0.042	-0.001	NA	NA
	DAS28-ESR	0.190	0.003	NA	NA
	disease duration	0.127	0.019	NA	NA
	sex	0.081	0.008	NA	NA
	FFbH	-0.203	-0.016	NA	NA
	0 < GC ≤ 5	0.033	-0.036	NA	NA
	5 < GC ≤ 10	0.011	-0.022	NA	NA
	GC > 10	0.053	-0.013	NA	NA
	One prior b/tsDMARD	0.109	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.032	NA	NA
	Smoking	-0.043	-0.012	NA	NA
	RF/ACPA positive	-0.043	-0.012	NA	NA
	Year of cohort entry	-0.870	-0.614	NA	NA
7. Disorders of the nervous system	logit therapy PS	0.981	0.560	0.855	0.590
	logit dropout PS	0.403	0.343	0.462	0.440
	50 ≤ age < 60	0.082	0.019	0.018	0.041
	60 ≤ age < 70	-0.005	-0.019	-0.041	-0.047
	age ≥ 70	-0.038	-0.002	0.110	0.017

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	DAS28-ESR	0.192	0.001	0.262	0.055
	disease duration	0.127	0.020	0.283	0.111
	sex	0.082	0.008	0.058	0.019
	FFbH	-0.205	-0.017	-0.181	-0.037
	0 < GC ≤ 5	0.037	-0.033	0.022	-0.037
	5 < GC ≤ 10	-0.001	-0.024	-0.071	-0.063
	GC > 10	0.054	-0.013	0.114	0.003
	One prior b/tsDMARD	0.110	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.294	0.034	NA	NA
	Smoking	-0.042	-0.011	-0.115	-0.030
	RF/ACPA positive	-0.043	-0.014	0.027	-0.014
	Year of cohort entry	-0.867	-0.609	-0.758	-0.609
Stroke	logit therapy PS	0.983	0.564	NA	NA
	logit dropout PS	0.404	0.342	NA	NA
	50 ≤ age < 60	0.081	0.019	NA	NA
	60 ≤ age < 70	-0.002	-0.019	NA	NA
	age ≥ 70	-0.042	-0.002	NA	NA
	DAS28-ESR	0.190	0.003	NA	NA
	disease duration	0.127	0.021	NA	NA
	sex	0.081	0.008	NA	NA
	FFbH	-0.201	-0.014	NA	NA
	0 < GC ≤ 5	0.033	-0.037	NA	NA
	5 < GC ≤ 10	0.010	-0.022	NA	NA
	GC > 10	0.055	-0.012	NA	NA
	One prior b/tsDMARD	0.108	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.033	NA	NA
	Smoking	-0.043	-0.012	NA	NA
	RF/ACPA positive	-0.046	-0.012	NA	NA
	Year of cohort entry	-0.870	-0.613	NA	NA
	History of CeVD	-0.017	-0.007	NA	NA
Other disorders of the CNS	logit therapy PS	0.982	0.564	NA	NA
	logit dropout PS	0.402	0.344	NA	NA
	50 ≤ age < 60	0.081	0.019	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	60 ≤ age < 70	-0.003	-0.020	NA	NA
	age ≥ 70	-0.040	-0.001	NA	NA
	DAS28-ESR	0.191	0.002	NA	NA
	disease duration	0.128	0.021	NA	NA
	sex	0.080	0.007	NA	NA
	FFbH	-0.205	-0.015	NA	NA
	0 < GC ≤ 5	0.033	-0.036	NA	NA
	5 < GC ≤ 10	0.008	-0.022	NA	NA
	GC > 10	0.055	-0.013	NA	NA
	One prior b/tsDMARD	0.109	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.033	NA	NA
	Smoking	-0.043	-0.013	NA	NA
	RF/ACPA positive	-0.044	-0.012	NA	NA
	Year of cohort entry	-0.869	-0.614	NA	NA
Disorders of the peripheral nervous system	logit therapy PS	0.985	0.563	NA	NA
	logit dropout PS	0.409	0.344	NA	NA
	50 ≤ age < 60	0.082	0.019	NA	NA
	60 ≤ age < 70	-0.004	-0.019	NA	NA
	age ≥ 70	-0.041	-0.002	NA	NA
	DAS28-ESR	0.197	0.004	NA	NA
	disease duration	0.127	0.020	NA	NA
	sex	0.083	0.009	NA	NA
	FFbH	-0.207	-0.017	NA	NA
	0 < GC ≤ 5	0.036	-0.034	NA	NA
	5 < GC ≤ 10	0.005	-0.022	NA	NA
	GC > 10	0.054	-0.013	NA	NA
	One prior b/tsDMARD	0.109	0.052	NA	NA
	≥ 2 prior b/tsDMARDs	0.291	0.033	NA	NA
	Smoking	-0.045	-0.011	NA	NA
	RF/ACPA positive	-0.047	-0.012	NA	NA
	Year of cohort entry	-0.870	-0.612	NA	NA
13. Embolic and thrombotic events	logit therapy PS	0.986	0.565	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	logit dropout PS	0.388	0.337	NA	NA
	50 ≤ age < 60	0.081	0.018	NA	NA
	60 ≤ age < 70	-0.001	-0.021	NA	NA
	age ≥ 70	-0.043	0.000	NA	NA
	DAS28-ESR	0.190	0.002	NA	NA
	disease duration	0.126	0.020	NA	NA
	sex	0.081	0.011	NA	NA
	FFbH	-0.204	-0.016	NA	NA
	0 < GC ≤ 5	0.037	-0.038	NA	NA
	5 < GC ≤ 10	0.009	-0.023	NA	NA
	GC > 10	0.051	-0.010	NA	NA
	One prior b/tsDMARD	0.109	0.053	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.032	NA	NA
	Smoking	-0.043	-0.012	NA	NA
	RF/ACPA positive	-0.044	-0.014	NA	NA
	Year of cohort entry	-0.870	-0.613	NA	NA
	History of diabetes	0.046	0.001	NA	NA
	History of heart failure	0.011	-0.008	NA	NA
	History of malignancies	-0.067	-0.030	NA	NA
	History of hypertension	0.037	-0.009	NA	NA
VTE	logit therapy PS	0.986	0.565	NA	NA
	logit dropout PS	0.388	0.337	NA	NA
	50 ≤ age < 60	0.081	0.018	NA	NA
	60 ≤ age < 70	-0.001	-0.021	NA	NA
	age ≥ 70	-0.043	0.000	NA	NA
	DAS28-ESR	0.189	0.002	NA	NA
	disease duration	0.126	0.020	NA	NA
	sex	0.081	0.011	NA	NA
	FFbH	-0.204	-0.016	NA	NA
	0 < GC ≤ 5	0.037	-0.038	NA	NA
	5 < GC ≤ 10	0.009	-0.023	NA	NA
	GC > 10	0.051	-0.010	NA	NA
	One prior b/tsDMARD	0.109	0.053	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	≥ 2 prior b/tsDMARDs	0.292	0.032	NA	NA
	Smoking	-0.043	-0.012	NA	NA
	RF/ACPA positive	-0.045	-0.014	NA	NA
	Year of cohort entry	-0.870	-0.614	NA	NA
	History of diabetes	0.046	0.001	NA	NA
	History of heart failure	0.011	-0.008	NA	NA
	History of malignancies	-0.067	-0.030	NA	NA
	History of hypertension	0.037	-0.009	NA	NA
PE	logit therapy PS	0.985	0.564	NA	NA
	logit dropout PS	0.390	0.332	NA	NA
	50 ≤ age < 60	0.081	0.018	NA	NA
	60 ≤ age < 70	-0.002	-0.021	NA	NA
	age ≥ 70	-0.043	-0.001	NA	NA
	DAS28-ESR	0.190	0.003	NA	NA
	disease duration	0.126	0.021	NA	NA
	sex	0.081	0.010	NA	NA
	FFbH	-0.205	-0.017	NA	NA
	0 < GC ≤ 5	0.036	-0.037	NA	NA
	5 < GC ≤ 10	0.010	-0.022	NA	NA
	GC > 10	0.051	-0.010	NA	NA
	One prior b/tsDMARD	0.109	0.053	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.033	NA	NA
	Smoking	-0.045	-0.013	NA	NA
	RF/ACPA positive	-0.042	-0.013	NA	NA
	Year of cohort entry	-0.870	-0.612	NA	NA
	History of diabetes	0.047	0.001	NA	NA
	History of heart failure	0.011	-0.007	NA	NA
	History of malignancies	-0.067	-0.030	NA	NA
	History of hypertension	0.037	-0.009	NA	NA
14. Operations and hospitalizations	logit therapy PS	0.982	0.558	0.853	0.587
	logit dropout PS	0.407	0.341	0.459	0.442

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	50 ≤ age < 60	0.084	0.017	0.018	0.040
	60 ≤ age < 70	-0.004	-0.019	-0.039	-0.049
	age ≥ 70	-0.043	-0.001	0.110	0.018
	DAS28-ESR	0.195	0.003	0.257	0.050
	disease duration	0.126	0.020	0.283	0.108
	sex	0.083	0.008	0.059	0.017
	FFbH	-0.204	-0.014	-0.176	-0.035
	0 < GC ≤ 5	0.036	-0.035	0.022	-0.038
	5 < GC ≤ 10	0.010	-0.022	-0.070	-0.063
	GC > 10	0.052	-0.014	0.115	0.001
	One prior b/tsDMARD	0.107	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.032	NA	NA
	Smoking	-0.042	-0.011	-0.110	-0.024
	RF/ACPA positive	-0.044	-0.012	0.028	-0.014
	Year of cohort entry	-0.867	-0.608	-0.757	-0.609
Bone and joint surgery and other joint therapeutic procedures	logit therapy PS	0.982	0.561	0.852	0.589
	logit dropout PS	0.404	0.343	0.457	0.441
	50 ≤ age < 60	0.084	0.018	0.018	0.041
	60 ≤ age < 70	-0.004	-0.020	-0.039	-0.047
	age ≥ 70	-0.042	-0.001	0.110	0.016
	DAS28-ESR	0.194	0.003	0.256	0.047
	disease duration	0.126	0.020	0.283	0.108
	sex	0.083	0.009	0.059	0.017
	FFbH	-0.202	-0.016	-0.177	-0.035
	0 < GC ≤ 5	0.037	-0.034	0.020	-0.039
	5 < GC ≤ 10	0.009	-0.021	-0.069	-0.062
	GC > 10	0.054	-0.013	0.114	0.001
	One prior b/tsDMARD	0.107	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.293	0.033	NA	NA
	Smoking	-0.042	-0.012	-0.114	-0.026
	RF/ACPA positive	-0.048	-0.015	0.026	-0.014
	Year of cohort entry	-0.868	-0.611	-0.757	-0.611
	logit therapy PS	0.985	0.561	NA	NA
	logit dropout PS	0.414	0.347	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
Other operations and (major) therapeutic procedures that lead to hospitalization	50 ≤ age < 60	0.081	0.019	NA	NA
	60 ≤ age < 70	-0.003	-0.020	NA	NA
	age ≥ 70	-0.042	-0.001	NA	NA
	DAS28-ESR	0.197	0.004	NA	NA
	disease duration	0.127	0.020	NA	NA
	sex	0.081	0.008	NA	NA
	FFbH	-0.205	-0.017	NA	NA
	0 < GC ≤ 5	0.035	-0.035	NA	NA
	5 < GC ≤ 10	0.010	-0.022	NA	NA
	GC > 10	0.052	-0.013	NA	NA
	One prior b/tsDMARD	0.109	0.051	NA	NA
	≥ 2 prior b/tsDMARDs	0.292	0.031	NA	NA
	Smoking	-0.043	-0.013	NA	NA
	RF/ACPA positive	-0.040	-0.012	NA	NA
	Year of cohort entry	-0.870	-0.612	NA	NA
15. Other serious diagnoses, symptoms, and syndromes	logit therapy PS	0.974	0.553	0.847	0.581
	logit dropout PS	0.393	0.336	0.456	0.435
	50 ≤ age < 60	0.070	0.016	0.017	0.040
	60 ≤ age < 70	-0.002	-0.016	-0.045	-0.050
	age ≥ 70	-0.028	0.000	0.117	0.022
	DAS28-ESR	0.191	0.002	0.257	0.052
	disease duration	0.138	0.024	0.293	0.118
	sex	0.081	0.006	0.057	0.018
	FFbH	-0.219	-0.020	-0.181	-0.039
	0 < GC ≤ 5	0.041	-0.037	0.017	-0.041
	5 < GC ≤ 10	0.007	-0.023	-0.069	-0.062
	GC > 10	0.062	-0.009	0.109	0.002
	One prior b/tsDMARD	0.105	0.054	NA	NA
	≥ 2 prior b/tsDMARDs	0.311	0.037	NA	NA
	Smoking	-0.050	-0.009	-0.110	-0.026
	RF/ACPA positive	-0.046	-0.013	0.034	-0.012
	Year of cohort entry	-0.855	-0.605	-0.748	-0.600
16. NMSC	logit therapy PS	0.802	0.296	NA	NA
	logit dropout PS	0.518	0.249	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	50 ≤ age < 60	0.088	0.030	NA	NA
	60 ≤ age < 70	0.037	-0.025	NA	NA
	age ≥ 70	-0.055	-0.008	NA	NA
	DAS28-ESR	0.237	0.053	NA	NA
	disease duration	0.146	-0.008	NA	NA
	sex	0.064	0.006	NA	NA
	FFbH	-0.214	-0.046	NA	NA
	0 < GC ≤ 5	0.073	0.006	NA	NA
	5 < GC ≤ 10	-0.043	-0.025	NA	NA
	GC > 10	0.050	0.001	NA	NA
	One prior b/tsDMARD	-0.004	0.047	NA	NA
	≥ 2 prior b/tsDMARDs	0.314	0.016	NA	NA
	Smoking	-0.065	-0.018	NA	NA
	RF/ACPA positive	-0.049	-0.029	NA	NA
	Year of cohort entry	-0.697	-0.310	NA	NA
	BMI ≥ 30	0.037	0.023	NA	NA
	History of malignancies	-0.071	-0.036	NA	NA
17. Malignancies (overall, excluding NMSC)	logit therapy PS	0.802	0.295	NA	NA
	logit dropout PS	0.518	0.249	NA	NA
	50 ≤ age < 60	0.088	0.030	NA	NA
	60 ≤ age < 70	0.037	-0.025	NA	NA
	age ≥ 70	-0.055	-0.008	NA	NA
	DAS28-ESR	0.237	0.053	NA	NA
	disease duration	0.146	-0.008	NA	NA
	sex	0.064	0.006	NA	NA
	FFbH	-0.214	-0.046	NA	NA
	0 < GC ≤ 5	0.073	0.006	NA	NA
	5 < GC ≤ 10	-0.043	-0.025	NA	NA
	GC > 10	0.050	0.001	NA	NA
	One prior b/tsDMARD	-0.004	0.047	NA	NA
	≥ 2 prior b/tsDMARDs	0.314	0.016	NA	NA
	Smoking	-0.065	-0.018	NA	NA
	RF/ACPA positive	-0.049	-0.029	NA	NA

090177e1a6a96f38\Approved\Approved On: 30-Jul-2026 20:55 (GMT)

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	Year of cohort entry	-0.697	-0.310	NA	NA
	BMI ≥ 30	0.037	0.023	NA	NA
	History of malignancies	-0.071	-0.036	NA	NA
19. Lung Cancer	logit therapy PS	0.802	0.296	NA	NA
	logit dropout PS	0.518	0.249	NA	NA
	50 ≤ age < 60	0.088	0.030	NA	NA
	60 ≤ age < 70	0.037	-0.025	NA	NA
	age ≥ 70	-0.055	-0.008	NA	NA
	DAS28-ESR	0.237	0.053	NA	NA
	disease duration	0.146	-0.008	NA	NA
	sex	0.064	0.006	NA	NA
	FFbH	-0.214	-0.046	NA	NA
	0 < GC ≤ 5	0.073	0.006	NA	NA
	5 < GC ≤ 10	-0.043	-0.025	NA	NA
	GC > 10	0.050	0.001	NA	NA
	One prior b/tsDMARD	-0.004	0.047	NA	NA
	≥ 2 prior b/tsDMARDs	0.314	0.016	NA	NA
	Smoking	-0.065	-0.018	NA	NA
	RF/ACPA positive	-0.049	-0.029	NA	NA
	Year of cohort entry	-0.697	-0.310	NA	NA
	BMI ≥ 30	0.037	0.023	NA	NA
	History of malignancies	-0.071	-0.036	NA	NA
20. All-cause Mortality	logit therapy PS	0.893	0.530	NA	NA
	logit dropout PS	0.533	0.379	NA	NA
	50 ≤ age < 60	0.091	0.007	NA	NA
	60 ≤ age < 70	0.018	-0.019	NA	NA
	age ≥ 70	-0.040	-0.006	NA	NA
	DAS28-ESR	0.242	0.001	NA	NA
	disease duration	0.124	0.009	NA	NA
	sex	0.053	0.002	NA	NA
	FFbH	-0.261	-0.024	NA	NA
	0 < GC ≤ 5	0.074	-0.021	NA	NA
	5 < GC ≤ 10	-0.060	-0.047	NA	NA
	GC > 10	0.071	0.009	NA	NA

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Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	One prior b/tsDMARD	-0.032	0.045	NA	NA
	≥ 2 prior b/tsDMARDs	0.316	0.034	NA	NA
	Smoking	-0.066	-0.020	NA	NA
	RF/ACPA positive	-0.030	-0.004	NA	NA
	Year of cohort entry	-0.771	-0.577	NA	NA
	History of diabetes	0.081	-0.007	NA	NA
	History of heart failure	0.044	-0.014	NA	NA
	History of CAD	0.040	-0.003	NA	NA
	History of CKD	0.050	0.048	NA	NA
23. Solid malignancies (overall)	logit therapy PS	0.802	0.294	NA	NA
	logit dropout PS	0.518	0.248	NA	NA
	50 ≤ age < 60	0.088	0.030	NA	NA
	60 ≤ age < 70	0.037	-0.025	NA	NA
	age ≥ 70	-0.055	-0.008	NA	NA
	DAS28-ESR	0.237	0.053	NA	NA
	disease duration	0.146	-0.008	NA	NA
	sex	0.064	0.006	NA	NA
	FFbH	-0.214	-0.047	NA	NA
	0 < GC ≤ 5	0.073	0.006	NA	NA
	5 < GC ≤ 10	-0.043	-0.025	NA	NA
	GC > 10	0.050	0.001	NA	NA
	One prior b/tsDMARD	-0.004	0.047	NA	NA
	≥ 2 prior b/tsDMARDs	0.314	0.016	NA	NA
	Smoking	-0.065	-0.018	NA	NA
	RF/ACPA positive	-0.048	-0.029	NA	NA
	Year of cohort entry	-0.697	-0.308	NA	NA
	BMI ≥ 30	0.037	0.023	NA	NA
	History of malignancies	-0.071	-0.036	NA	NA
25. Benign neoplasms	logit therapy PS	0.802	0.296	NA	NA
	logit dropout PS	0.518	0.250	NA	NA
	50 ≤ age < 60	0.088	0.030	NA	NA
	60 ≤ age < 70	0.037	-0.025	NA	NA

Table 23. SMDs of the primary regression analyses

Outcome	Variable	Tofacitinib vs. bDMARD		Tofacitinib vs. nbDMARD	
		Unweighted	Weighted	Unweighted	Weighted
	age ≥ 70	-0.055	-0.008	NA	NA
	DAS28-ESR	0.237	0.053	NA	NA
	disease duration	0.146	-0.008	NA	NA
	sex	0.064	0.006	NA	NA
	FFbH	-0.214	-0.046	NA	NA
	0 < GC ≤ 5	0.073	0.006	NA	NA
	5 < GC ≤ 10	-0.043	-0.025	NA	NA
	GC > 10	0.050	0.001	NA	NA
	One prior b/tsDMARD	-0.004	0.047	NA	NA
	≥ 2 prior b/tsDMARDs	0.314	0.016	NA	NA
	Smoking	-0.065	-0.018	NA	NA
	RF/ACPA positive	-0.049	-0.029	NA	NA
	Year of cohort entry	-0.697	-0.311	NA	NA
	BMI ≥ 30	0.037	0.023	NA	NA
	History of malignancies	-0.071	-0.036	NA	NA

For malignancies outcomes as well as mortality, the model based on the ever-exposed approach (with and without latency period, respectively) is regarded as primary regression analysis, for all other outcomes the model based on the on-drug approach is regarded as primary regression analysis.
Cox regression models using the ever-exposed approach were only calculated for comparing tofacitinib and bDMARDs. If no model was calculated, NA is given instead of standardized mean differences. Also, if a specific covariate was not considered for a model, NA is given instead of standardized mean differences.
Abbreviations: ACPA, anti-citrullinated protein antibodies; B-CLL, B-cell chronic lymphocytic leukemia; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DAS28-ESR, disease activity score 28 based on erythrocyte sedimentation rate; FFbH, % of full function by Hannover Functional Status Questionnaire; GC, glucocorticoids, HZ, herpes zoster; MACE, major cardiovascular events; NA, not applicable; nbDMARD, non-biologic disease-modifying anti-rheumatic drug; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PS, propensity score; RF, rheumatoid factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; VTE, venous thromboembolism.

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Document Approval Record

Document Name:	A3921317 Non-Interventional-Low-Interventional Study Type 1 Study Report
Document Title:	An Active Surveillance, Post-authorization Safety Study (pass) Of Serious Infection, Malignancy, Cardiovascular (cv) And Other Safety Events Of Interest Among Patients Treated With Tofacitinib For Moderately To Severely Active Rheumatoid Arthritis (ra) Within The German Registry Rheumatoide Arthritis: Beobachtung Der Biologika-therapie (rabbit)

Signed By:	Date(GMT)	Signing Capacity
Koram, Nana	30-Jul-2026 11:13:53	Manager Approval
De Bernardi, Barbara	30-Jul-2026 20:55:40	EUQPPV Approval

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Pfizer	CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE	
Identifier	**Version**	**Title**
CT24-WI-GL15-RF06	3.0	NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT/MANUSCRIPT SIGNATURES

APPENDIX 1. SIGNATURES

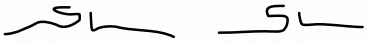
PROTOCOL NUMBER: A3921317

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 German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

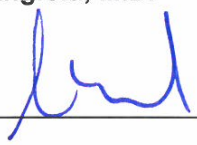
STUDY REPORT VERSION: 1.0

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
Shahar Shmuel, PhD

Signature:  **Date:** 27-Jul-2026

Principal investigator, medical doctor, epidemiologist
Prof. Anja Strangfeld, M.D.

Signature:  **Date: 24-JULY-2026**

Approval of study report

N/A

Signature: **Date:**

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NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	An Active Surveillance, Post--Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)
Protocol Number	A3921317
Protocol Version Identifier	7.0
Date	06 July2025
EU Post Authorisation Study (PAS) Register Number	EUPAS31164
Active Substance	L04AA29 Tofacitinib
Medicinal Product	Xeljanz® (tofacitinib)
Product Reference	EMEA/H/C/004214
Procedure Number	EMA/PAM/0000261850
Marketing Authorisation Holder (MAH)	Pfizer Europe
Joint PASS	No
Research Question and Objectives	**Research Question:** What are the rates of adverse outcomes of interest in RA patients treated with tofacitinib in relation to those treated with biologic disease modifying anti-rheumatics and non-biologic disease modifying anti-rheumatics?

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	Objectives: To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, MACE, MI, VTE (DVT and PE) and other specified outcomes, including fractures, among patients with RA who initiate tofacitinib in a German register. Rates will also be estimated among existing cohorts of biologic disease modifying antirheumatic drugs (bDMARDs) and non-biologic DMARDs (nbDMARDs) patients to provide context for rates observed on tofacitinib. Further, incidence rates will be estimated in elderly patients aged 65 years and older. Pending feasibility, hazard rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE and other events, 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(-ies) of Study	Germany
Author	Shahar Shmuel, PhD Pfizer, Inc. 66 Hudson Blvd E. New York, New York 10001

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Marketing Authorisation Holder(s)

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1. TABLE OF CONTENTS

1. TABLE OF CONTENTS....4
APPENDICES....5
2. LIST OF ABBREVIATIONS....6
3. RESPONSIBLE PARTIES....8
4. ABSTRACT....9
5. AMENDMENTS AND UPDATES....12
6. MILESTONES....21
7. RATIONALE AND BACKGROUND....22
8. RESEARCH QUESTION AND OBJECTIVES....24
9. RESEARCH METHODS....25
9.1. Study Design....25
9.2. Setting....25
9.2.1. Inclusion Criteria....26
9.2.1.1. Tofacitinib Exposed Cohort Inclusion Criteria....26
9.2.1.2. nbDMARD – b/tsDMARD naive Cohort Inclusion Criteria....26
9.2.1.3. nbDMARD Exposed Cohort Inclusion Criteria (previously exposed to b/tsDMARDs)....27
9.2.1.4. Tofacitinib Exposed Cohort Inclusion Criteria....27
9.2.1.5. nbDMARD Cohort Inclusion Criteria....27
9.2.1.6. bDMARD Exposed Cohort Inclusion Criteria....27
9.2.2. Exclusion Criteria....27
9.3. Index Date....27
9.4. Risk Window....28
9.5. Variables....30
9.5.1. Baseline Data....31
9.5.2. Follow-up....32
9.5.3. Endpoints....32
9.6. Data Sources....34
9.7. Study Size....34
9.8. Data Management....37
9.9. Data Analysis....37

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

9.10. Quality Control....39
9.11. Limitations of the Research Methods....40
9.12. Other Aspects....41
10. PROTECTION OF HUMAN SUBJECTS....42
10.1. Patient....42
10.2. Patient Consent....42
10.3. Patient Withdrawal....42
10.4. Institutional Review Board/Independent Ethics Committee....42
10.4.1. Cooperation Between Study Management, Advisory Board, and Sponsors....43
10.5. Ethical Conduct of the Study....43
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS....44
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS....44
13. REFERENCES....46
14. LIST OF TABLES....49
15. LIST OF FIGURES....49
ANNEX 1. LIST OF STAND ALONE DOCUMENTS....50
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS....51
ANNEX 3. ADDITIONAL INFORMATION....57

APPENDICES

Appendix 1. ICD and MedDRA Codes For Select Safety Endpoints....58

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABT	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
AEM	adverse event monitoring
ANK	anakinra
bDMARD	biologic disease modifying antirheumatic drug
BfArM	Bundesamt fur Arzneimittel und Medizinprodukte
BID	bis in die (twice a day)
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DAS	Disease Activity Score
DAS-28	Disease Activity Score 28
DFRZ	Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center)
DGRh	German Society for Rheumatology
DMARD	disease modifying antirheumatic drug
DVT	deep vein thrombosis
EBV	Epstein Barr virus
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	erythrocyte sedimentation rate
ETA	etanercept
EU	European Union
GI	gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	Health Assessment Questionnaire
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL	interleukin
INF	infliximab
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology

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Abbreviation	Definition
JAK	Janus kinase
MACE	major adverse cardiovascular events
MAH	market authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
MTX	methotrexate
nbDMARD	non-biologic DMARD[1]
NDA	New Drug Application
NHL	non-Hodgkin's lymphoma
NI	non-Interventional
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
OMERACT	Outcome Measures in Rheumatology
PAS	post authorization study
PASS	Post- Authorization Safety Study
PE	pulmonary embolism
PML	progressive multifocal leukoencephilitis
PRAC	Pharmacovigilance Risk Assessment Committee
PRIND	prolonged reversible ischemic neurological deficit
PY	person-years
RA	rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	risk management plan
RTX	rituxumab
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance and Epidemiology End Results
SIR	Standardised Incidence Ratio
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	tuberculosis
TIA	transient ischemic attack
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic DMARD
VAS	Visual Analog Scale
VTE	Venous thromboembolism

[1] Synonymous with csDMARD

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3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Dr. Martin Schäfer	Statistician	Deutsches Rheuma-Forschungszentrum Berlin Forschungsbereich Epidemiologie	Chariteplatz 1 10117 Berlin Germany
Dr. Anja Strangfeld	Epidemiologist	Deutsches Rheuma-Forschungszentrum Berlin Forschungsbereich Epidemiologie	Chariteplatz 1 10117 Berlin Germany

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 German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT).

Version: Final Protocol (v7.0).

Date: 06 July 2025

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

Research Question: What are the rates of safety events of interest in RA patients treated with tofacitinib in relation to those treated with biologic DMARDs (bDMARD) and non-biologic DMARDs (nbDMARD)[2]?

Objectives: To enable assessment of safety events of interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data in RABBIT. Further, the study will evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, major adverse cardiovascular events (MACE), myocardial infarction (MI), venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]), and other specified outcomes, including fractures, among patients with RA in a German register who initiate tofacitinib. Rates will also be estimated among existing cohorts of bDMARD and nbDMARD patients to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested in this descriptive study. Pending feasibility, hazard rates of malignancy (overall, excluding NMSC), lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE, and other events, including fracture, will be compared between tofacitinib-treated RA patients and the comparator cohort using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and MACE have been added as study endpoints (MI and lymphoma (overall) were already included as a study endpoints). Further, rates of events, including

[2] Defined as conventional synthetic DMARDs (csDMARDs)

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serious infections, MACE, MI and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

Study design: This active surveillance study is using data from 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 German Rheumatism Research Center (DFRZ), with industry funding.

Population: The study population will comprise all patients with RA enrolled within RABBIT who receive tofacitinib following European Medicines Agency (EMA) approval and German launch. For contextualization purposes, the study population will also include RABBIT patients treated with bDMARDs and nbDMARDs. As initiation of tofacitinib in RABBIT will be from 01 May 2017 onwards, only treatments initiated after this date will be included in the final report.

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), and heart disease (including MACE), and VTE (DVT and PE).

Data Sources: Core baseline and follow up data, including patient demographics, disease characteristics, and treatment will be based on data from the RABBIT.

Study size: This is a descriptive study without pre-specified hypotheses therefore sample size is not calculated. The targeted sample size for tofacitinib-treated patients is 500. Enrolment will not be capped at 500 but continue throughout the study period.

Data analysis: The initial analyses will consist of descriptive comparisons of baseline status and crude event rates between the different cohorts in the interim reports. The final analysis of endpoints will provide incidence rates overall and in subgroups defined by baseline characteristics. Pending feasibility, hazard rates of malignancy (overall, excluding NMSC), lymphoma (overall and by subtype), lung cancer, serious infection, CV event, VTE, and other events will be compared as hazard ratios 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, event and 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 and incidence rates will be stratified by type of event. Further, for the outcomes of MI and MACE, incidence rates of the safety events of interest will be stratified by patients with ≥1 CV risk factors versus no CV risk factors. Similarly, for the outcome of VTE, incidence rates of the safety events of interest will be stratified by patients with ⩾1 VTE risk factors versus no VTE risk factors.

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

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5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	September 2021	Substantial	Title Page	Updated to replace old Pfizer logo with new one Updated to include EU PAS Register Number Updated contact information for three protocol authors. Updated contact information for the MAH Contact Person	Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Study staff transition for the MAH's vendor
			Section 2	Updated to include new abbreviations	Editorial change
			Section 3	Updated contact information for a principal investigator of the protocol	Study transition for MAH's principal investigator.
			Section 4	Revised version and date. Updated Objective 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.	PRAC request and clarification.
			Section 7	Updated to include information on changes to protocol resulting from 2021 signal evaluation procedures Updated to include fractures as an additional safety event of interest	Editorial changes Based on available data, Pfizer has identified fractures as a potential risk
			Section 8	Updated objectives to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated objective to include	PRAC request and clarifications

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Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				estimation of event rates in the elderly aged 65 years and older.	
			Section 9.5.1	Updated to include CV risk factors	PRAC request and clarifications
			Section 9.5.3	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.
			Section 9.9	Updated analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes. Updated to specify 'elderly' as aged 65 years and older.	PRAC request and clarifications Editorial change.
			Section 9.11	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.
	August 2021	Substantial	Annex 2	Author name change. Signature and signature date updated. Instructions for form completion removed.	Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author. Editorial change
			Appendix 1	Updated to include definitions for additional endpoints.	PRAC request and clarifications

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Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
3.0	February 2022	Substantial	Title Page	Updated Research Questions and Objectives to include change in terminology from 'lymphoproliferative malignancy' to 'lymphoma' and to include VTE as an outcome of interest (VTE was already included as an outcome in the previous version of protocol. Included VTE in this section for consistency with the rest of protocol).	PRAC request and clarification
			Section 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. Removed 6-monthly reports from the Milestones.	Editorial change PRAC request and clarification PRAC request and clarification
			Section 7	Updated the Cardiovascular Disease section to remove MACE as an "important identified risk".	PRAC request and clarification
			Section 8	Updated Objective to replace the term 'lymphoproliferative malignancy' with	PRAC request and clarification

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Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				'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).	
			Section 9.5.1	Updated CV risk factors to include chronic kidney disease and hypercholesterolemia	PRAC request and clarification
			Section 9.5.3	Updated the Endpoints to replace the term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
			Section 9.9	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
			Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
			All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
			Annex 2	Signature date updated	Editorial change.
4.0	February 2023	Substantial	Section 6	Added footnote to milestone table to indicate anticipated data availability	To accommodate data lag
			Section 9.5.1	Removed Charlson Index	Data required to estimate the Charlson Index is not captured in the registry
			Section 9.5.1	Removed ACR rating scale from baseline covariates	Data required to estimate the ACR rating scale is not captured in the registry

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Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
			All sections where applicable	Updated language to 'safety events of interest' to be consistent with the study title	Editorial change
5.0	October 2023	Substantial	Title page, Author address, MAH Contact Person	Updated author address and name and address of MAH contact person	Editorial change
			Section 3.0	Updated Pfizer contact address; updated job title for other investigators	Editorial change
			Section 9.5.2	Deletion of text related to rheumatologist assessment of severity of reported adverse events	Updating to remove language regarding severity assessment as this is not well captured within registry
6.0	February 2025	Substantial	PASS Information, Abstract, Sections 8, 9.2.1, 9.5.3, 9.9	Distinguished between analyses conducted in the interim reports and final reports.	The protocol addresses both the interim reports and the final report. As the methods differ between the reports, a better differentiation of which analyses will be provided in which reports was necessary. When describing overall study objectives, the wording was aligned to correspond with the final report analyses which estimate incidence rates.
			List of abbreviations, Abstract, Section 8	Definition of nbDMARD	The group of non-biologic disease modifying antirheumatic drug (nbDMARD) usually comprises conventional synthetic disease modifying antirheumatic drugs (csDMARD) and targeted synthetic disease modifying antirheumatic drugs (tsDMARD). In this protocol, the term solely refers to csDMARDs, but not to tsDMARDs.

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Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
			Section 3	Corrected job title of one of the principal investigators	Job title needed correction
			Abstract	Deleted “including link data”	No data linkage possible in Germany
			Abstract, Section 9.2	Added start of observation time for final report	Start of observation for all cohorts will be from 01 May 2017 onwards
			Sections 8, 9.9	Stated that incidence rates will be estimated in the final report	Clarified which report will present incidence rates
			Section 9.2	Updated the number of patients in the registry	Updated number better reflects current enrollment in the registry
			Section 9.2	For final reports, no exposure to the active substance 365 days prior to index date	To reduce prevalent user bias
			Section 9.2.1	Prior tsDMARD exposure is no longer an exclusion criteria.	Applied similar inclusion criteria across cohorts with respect to prior therapy for the final report to reduce potential bias.
			Section 9.4	In the analyses where follow-up is censored after a switch to a different treatment class, the censoring event in the tofacitinib-treated cohort was changed from censoring from switch to non-JAK-inhibitor advanced systemic therapy to non-tofacitinib advanced systemic therapy.	Updated censoring event to account for non-tofacitinib JAK inhibitors, as there are drug-specific safety risks
			Section 9.4	Adaption of risk window definition	Improved clarity of the analysis.
			Section 9.5.1	Removed several VTE risk and CV risk factors Removed baseline variables that are not collected and provided	Data required to include these risk factors is not captured by the registry

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				additional detail on variables that are collected	Clarified which baseline data is collected by the registry
			Sections 9.5.2, 9.9	Removed listing of outcomes	Listing was redundant since all outcomes are listed in section 9.5.3
			Section 9.5.3	Several outcomes were added.	Reflected the additional outcomes provided in the interim reports.
			Sections 9.8, 9.10	Added additional detail	Additional detail helps clarify the RABBIT processes
			Section 9.9	Added clause of exclusion of patients with documented prior history of the safety endpoint of interest from analysis of that specific safety endpoint	To limit potential bias as patients with prior history of the safety endpoints are often at increased risk of future occurrences of the same endpoint
			Section 9.9	Added sensitivity analysis with stratification by prior use of non-tofacitinib JAK inhibitor therapies	Results from patients with prior non-tofacitinib JAK inhibitors may be confounded. The stratified analysis will examine potential risk of endpoints from only tofacitinib versus other JAK inhibitor therapies
			Section 9.9	Updated semi-annual report section	Clarification that semi-annual reports present event rates
			Section 9.11	Limitations section was revised to provide additional detail and clarity.	More limitations were identified and redundant sentences were deleted.
			Section 9.11	Deletion of "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	RABBIT is an ongoing cohort study recruiting new patients receiving TNF and DMARD therapy regimes after January 2020

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
				TNF and DMARD therapy regimens"	
			Section 11	Section was revised	Updated to reflect the processes applied in RABBIT
			Annex 2	Updated Section number references where appropriate	Corrected Section number references
7.0	06 July 2025	Substantial	Section 6	In the footnote, updated the start date for data availability for the final report based on data availability	Editorial update
			Section 8	Added clarification on estimation of event and incidence rates	Improved clarity of the analytic methods
			PASS information, Section 4, Section 8, Section 9.9, Section 9.11	Added clarification that comparative analyses will report hazard ratios since the adjusted regression models used are Cox proportional hazards models. Crude incidence rates will also be reported.	Improved clarity of the analytic methods
			Section 9.5.1	Updated 'hypercholesteremia' to 'hyperlipoproteinaemia'	This is the information collected in the questionnaire
			Section 9.9	Removed clause of exclusion of patients with documented prior history of the safety endpoint of interest from analysis of that specific safety endpoint. Specified that baseline comorbidities include history of the outcomes of interest (when data is available).	Per PRAC request. Prior history will be accounted for using model adjustment for baseline comorbidities.
			Section 9.9	Added clarification language on the data collection of the registry	Improved clarity

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
			Abstract	Added 'excluding NMSC'	For consistency with PASS Information and Objectives sections

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6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	1 September 2019
Start of data collection	15 September 2019
Interim report	14 March 2021
Interim report	14 March 2023
Interim report	14 March 2025
End of data collection	14 September 2025
Final Study Report	14 August 2026*

*Anticipated to include data from 01 May 2017 – 30 June 2025 to accommodate data lag.

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7. RATIONALE AND BACKGROUND

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

Tofacitinib is 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 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.[12,26] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[13] 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.

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.

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.[14] 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 event rates of major adverse cardiovascular events

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(MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients treated with tofacitinib for rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma (overall) were already included as study endpoints prior to the signal evaluation). It is therefore fundamentally important to describe the occurrence of these events among patients treated with newly approved therapies and among patients who remained on "conventional" therapy or received a different targeted agent.

To enable assessment of safety events of interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib exposed patients using actively collected prospective data embedded within the RABBIT 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 ≥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.[5,9] 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,[4,8,9,20] however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.[3,23] 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.[23]

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.[10,21,24,28]

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

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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.[18,22] 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.[14]

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 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

RABBIT collects data other safety events of interest in the RA population including central nervous system (CNS) events, fractures, pregnancy and mortality. Rates of these events will also be estimated to potentially identify new safety signals.

8. RESEARCH QUESTION AND OBJECTIVES

This study asks what are the rates of safety events of interest in RA patients treated with tofacitinib in relation to those treated with bDMARD and nbDMARD. In this study, nbDMARDs are defined as conventional synthetic DMARDs (csDMARDs). In the interim reports, event rates will be estimated, whereas, in the final report, incidence rates will be estimated. The bDMARD comparator cohort will be presented in the final report, while the nbDMARD comparator cohort will be included in both interim and final report reports. In

both reports, the group of nbDMARDs will only include csDMARDs and not tsDMARDs by definition.

Objectives:

To evaluate the rates of serious infections, malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, CV events, MACE, MI, VTE (DVT and PE) and other specified safety events of interest, including fractures, among patients with RA in a Germany -based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of bDMARD and nbDMARDs patients to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested in this descriptive study. Pending feasibility, hazard rates of malignancy (overall, excluding NMSC), subtypes of lymphoma, lung cancer, serious infection, CV events, MACE, MI, VTE, and other events, including fractures, will be compared as hazard ratios between tofacitinib -treated RA patients and other comparator cohorts using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities 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, incidence 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 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.

Rates of safety events of interest will be calculated in tofacitinib-exposed and comparator cohorts with 95% confidence intervals (CIs) and reported as descriptive analyses. No a priori hypotheses will be specified. Data capture and follow-up methods are the same for all cohorts within RABBIT. 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 German Biologics Register RABBIT has been active since May 2001 under the auspices of the “Kompetenznetz entzündlich-rheumatische Systemerkrankungen” (“Competence Network Rheumatology”). The content of the original study protocol as well as the extension protocol was agreed with the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology). Physicians aiming at taking part in RABBIT must sign a contract with the Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Center) (DRFZ). There is no influence on any treatment decision from the principal

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investigators, scientific advisory board or pharmaceutical companies sponsoring the study. The type of treatment administered, and the details of individual therapy, including dosages, is determined by the treating physician only. Participating patients have provided informed consent, have a diagnosis of RA according to American College of Rheumatology (ACR) criteria, have age at onset of RA at age 16 or older, and have initiated of an approved therapy for the treatment of RA.

Per RABBIT policy, adverse events (AE) and serious AEs (SAE) will be recorded according to the International Council for Harmonisation (ICH) guidelines. Therefore, any untoward medical occurrence observed in a patient has to be reported as AE. The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect has to be reported as SAE. These definitions of AEs and SAEs are also provided in the case report forms (CRFs). For non-serious AEs, severity grading will be performed according to the recommendations of the Outcome Measures in Rheumatology (OMERACT) Toxicity Working Group. For the coding of AE and SAE the Medical Dictionary for Regulatory Activities (MedDRA) will be used on the preferred term level. It is intended to update the AE/SAE database with every update of MedDRA.

Study Population

The active surveillance population includes rheumatoid arthritis patients enrolled in RABBIT who are newly treated with tofacitinib following EMA approval and German launch of the product (product fully available May 2017). For contextualization purposes, the study population will also include RABBIT patients treated with bDMARDs and nbDMARDs. There are currently over 24,000 patients observed in the register. Patients switching therapies are eligible to move between cohorts if inclusion/exclusion criteria are met.

9.2.1. Inclusion Criteria

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

For the **interim reports**, the inclusion criteria are as follows:

9.2.1.1. Tofacitinib Exposed Cohort Inclusion Criteria

1. Included in RABBIT.
2. Initiation of tofacitinib.

9.2.1.2. nbDMARD – b/tsDMARD naive Cohort Inclusion Criteria

1. Included in RABBIT.
2. Enrolled after 01 January 2009.
3. failure of at least one DMARD and initiation of a new csDMARD.

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4. No previous exposure to bDMARD or targeted synthetic DMARD (tsDMARD).

9.2.1.3. nbDMARD Exposed Cohort Inclusion Criteria (previously exposed to b/tsDMARDs)

1. Included in RABBIT.
2. Enrolled after 01 January 2009.
3. previous exposure to bDMARD or targeted synthetic DMARD (tsDMARD) but discontinued this treatment

For the **final report**, the inclusion criteria are as follows:

9.2.1.4. Tofacitinib Exposed Cohort Inclusion Criteria

4. Included in RABBIT.
5. Initiation of tofacitinib.

9.2.1.5. nbDMARD Cohort Inclusion Criteria

6. Included in RABBIT.
7. Initiation of csDMARD therapy after 01 May 2017.
8. failure of at least one DMARD and initiation of a new csDMARD.
9. No previous exposure to bDMARD or targeted synthetic DMARD (tsDMARD).
10. Patients with no exposure to any DMARD will be excluded

9.2.1.6. bDMARD Exposed Cohort Inclusion Criteria

11. Included in RABBIT.
12. Initiation of bDMARD therapy after 01 May 2017.

Definition of the included episodes in the final report for the tofacitinib and the bDMARD exposed cohort: episodes are only included if there is no exposure of the active substance 365 days prior to prescription of the drug.

9.2.2. Exclusion Criteria

1. Any patient with RA enrolled within RABBIT who does not meet one or more of the inclusion criteria will be excluded.

9.3. Index Date

The index date for the tofacitinib cohort is the date the first tofacitinib dose was taken. Similarly, the index dates for comparator cohorts are the date of the initiation of the first comparator treatment dose. Patients who switch to a subsequent therapy are eligible for

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enrollment as an initiator of the subsequent therapy, and the initiation date will be the date of initiating the subsequent therapy.

9.4. Risk Window

Follow-up definition: 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 patient's first occurrence of the event of interest, discontinuation of index treatment, death, loss to follow up, exit from the register or after 7 years of follow up. Exposure data in RABBIT is derived from the treating rheumatologist at follow-up visits at months 3, 6, 12, 18, 24, 30, 36, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114 and 120. 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.

Statistical approaches: For non-melanoma skin cancer (NMSC), lung cancer, lymphoma, and malignancies excluding NMSC, and all-cause mortality, the manifestation of which is expected to be delayed relative to the time of exposure, the safety events of interest will be evaluated using two different approaches, a once exposed always at risk approach as the primary analysis and an on-drug approach as a secondary analysis. PML rates will also be described using this approach. The on-drug approach will be used as primary analysis for non-malignancy and non-mortality outcomes and as secondary analyses for malignancy, mortality and PML.

A 90-day risk window will be applied to the on-drug approach. Starting with the first month after discontinuation, an additional three months of exposure (90-day risk window) will be added. 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 medications containing rituximab, a risk window of nine months will be added due to its pharmacologic properties (depletion of B-cells) when using the on-drug approach. The duration of follow up within the nbDMARD cohort does not rely on a 90-day risk window or the once-exposed at-risk paradigm.

The on-drug approach will be implemented applying the censor at switch principle: 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 only events prior to the new medication start will be assigned to the discontinued medication. For regression models, as a sensitivity analysis, initiation of the new medication will not stop the 90-day risk window, and follow-up time and events occurring after the switch will be attributed to prior therapy and not current therapy.

The once exposed always at risk paradigm is frequently used in study of malignancy risk due to bDMARDs and will be the primary approach for malignancy, mortality and PML.[26,14,15,24] 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.

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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.

Using this 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.[26,14,15,24]

Unless noted otherwise, assignment of exposure time and events to treatments will be handled as described for both incidence / event rates and Cox regression models (three different models will be conducted with different numbers of confounders, 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.

As a sensitivity analysis, follow up time after a switch to a different treatment class will also be censored for malignancy, mortality and PML outcomes. 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-tofacitinib 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.[26,14,15]

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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 for the outcomes malignancy, mortality and PML:

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

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

a. Patients are followed for another 90 days after index exposure discontinuation if they do not initiate another systemic therapy in a different class.

Note: if an event does not occur, person time will be allocated to rate denominator as described in table without corresponding event.

9.5. 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), and heart disease (including MACE), and VTE (DVT and PE).

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9.5.1. Baseline Data

The following information is collected within RABBIT, having been reported by the recruiting clinician, using a standardized form:

1. Diagnosis (including the presence or absence of those features listed in 1987 American College of Rheumatology (ACR) criteria for RA).

2. Age at treatment start, gender, year of recalled symptom onset.

3. Previous drug history of immunosuppressive conventional synthetic DMARDS (csDMARDs) and biologics, biosimilar or other new advanced therapy since enrolment, including duration of therapy recorded as start month/year and reasons for treatment change.

4. All current RA therapy.

5. Baseline disease activity including Disease Activity Score (DAS)-28, Health Assessment Questionnaire (HAQ; will be calculated by using Funktionsfragebogen Hanover (FFbH)[29]); Pain Visual Analog Scale (VAS), Global Health (VAS), Tender Joint Count, Swollen joint count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

6. Baseline history of disease including tuberculosis, malignancy, heart disease.

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
- 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 or current diabetes
- History of chronic kidney disease

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- History of hyperlipoproteinaemia
- History of or current hypertension
- History of or current coronary heart disease

9.5.2. Follow-up

Follow up data in RABBIT derive from follow-up visits at months 3, 6, 12, 18, 24, 30, 36, 48, 54, and 60.

All serious and non-serious events occurring during the observation are regularly reported from the rheumatologist and captured in the register (with judgement from the rheumatologist on causality to given medication). For events of interest detailed queries are sent out, to get more information on the events (and additional discharge letters from hospitals, or results from biopsies etc). The actual events of interests are outlined in Section 9.5.3.

There is no possibility to link RABBIT data with any other data due to strict data protection rules and due to the fact that there is no national cancer register or death register with the possibility of linkage. However, all events are carefully monitored and several national offices are sometimes contacted to get more information.

9.5.3. Endpoints

Endpoints in RABBIT derive from physician reports of the occurrence of any AE or event of interest. The events of interest, based on previously identified risks in the treated and untreated RA population, include:

1. Serious infections (excluding TB): pneumonia, other infections of the respiratory system, infections of the CNS, sepsis, bone or joint infections, OI, other infections.
2. TB.
3. Herpes Zoster.
4. Fractures.
5. Cardiac disorders: heart failure, coronary artery disease, myocardial infarction, MACE, other cardiac disorders.
6. Hematologic disorders: bone marrow depression and hypoplastic anaemia, decreased white blood cells, platelet disorders, other blood dyscrasia.
7. Disorders of the nervous system (excluding infections): stroke, central demyelination, other disorders of the CNS, disorders of the peripheral nervous system, psychiatric disorders.

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8. Progressive multifocal leukoencephalopathy.
9. Allergic conditions and hypersensitivity.
10. Hepatic failure.
11. Gastrointestinal (GI) perforations: Lower intestinal perforations, Other GI perforations.
12. Pregnancy.
13. Thromboembolic events: deep vein thrombosis (DVT) and pulmonary embolism (PE).
14. Operations and hospitalisations: bone and joint surgery and other joint therapeutic procedures, other operations and (major) therapeutic procedures that lead to hospitalization.
15. Other serious diagnoses, symptoms, and syndromes.
16. NMSC.
17. Malignancies, (overall, excluding NMSC).
18. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia).
19. Lung cancer.
20. All-cause Mortality.
21. Leukaemia (excl. B-CLL)
22. Other haematopietic neoplasms (malignant and benign)
23. Solid malignancies (overall))
24. Glioblastoma
25. Benign neoplasms
26. Unspecified neoplasms and precanceroses
27. Metastases, cancer related and morbidities and associated syndromes
28. Interstitial lung disease, pending feasibility.

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Event rates of these endpoints of interest and their 95% CI will be reported for tofacitinib exposed and comparator cohorts every six months and in the interim reports.

For the final report, IRs will be presented overall stratified by age <65 years and ≥65 years.

9.6. Data Sources

Core baseline and follow up data, including patient demographics, disease characteristics, and treatment will be based on data from the RABBIT.

9.7. Study Size

This active surveillance study is not intended to test a pre-specified statistical hypothesis. The size of the active surveillance population depends largely on use of tofacitinib in Germany. The targeted sample size for tofacitinib-treated patients is 500. Enrolment will not be capped at 500 but continue throughout the study period.

The bDMARD and nbDMARD populations used to contextualize event rates are well-established.

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:

- α=0.05;
- 3 different bDMARD-treated patient population sizes (reflecting roughly range of EU registers): n=11 100, 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

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bDMARD over the study period, as previously demonstrated in the EU for bDMARDs in Italy (Eposti, 2016).[30]

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 11 100 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, 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

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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, 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 ~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 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, 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

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Based on the first 16 months of enrolment of tofacitinib-exposed patients in RABBIT, 558 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.

9.8. Data Management

All data management activities occur within the overarching RABBIT study.

In RABBIT, outcome parameters and covariates are assessed by physicians and/or patients as applicable, on pre-defined case report forms (CRF) at study enrolment and follow-up visits. Data collection is paper-based, and all questionnaires (CRFs) are sent to the register holder by fax.

Patients are observed for at least 5 and up to 10 years. After enrolment, data is reported in month 3 and 6, and every 6 months thereafter. Apart from socio-demographic characteristics including education, occupation and smoking habits, data on disease duration, comorbid conditions and anti-rheumatic co-medications are assessed. The main outcome measures are the occurrence of adverse events, the course of disease activity assessed by physician- and patient-reported measures, the impairment in daily life activities reported by patients, the medical treatment adherence detected by physician-reported treatment duration and medical indications for initiation of therapy, therapy change or therapy discontinuation. Treatment starts, stops and switches are recorded as the dates on which they occurred.

Adverse event reporting is defined in Section 10.5. Data will be archived for at least ten years after the end of the study at the DRFZ in Berlin. No selected data or entire data sets will be disclosed without authorization to third parties, including the sponsors, but the sponsors will receive upon request additional analyses on their own products separate from the joint evaluations. The study management, advisory board and sponsors will decide jointly whether data may be passed on for pooling (international studies).

9.9. Data Analysis

The initial analyses will consist of descriptive comparisons of baseline status and crude event rates (interim report) between the different cohorts. The final report will provide incidence rates overall and in specified subgroups defined by baseline characteristics (see SAP, additional analyses). Pending feasibility, adjusted hazard ratios will be estimated for outcomes of interest with at least four events in the tofacitinib-treated group (see SAP for potential confounders).

For all safety endpoints of interest, when prior medical history for a particular safety endpoint is collected by the registry, the prior documented history of that particular safety endpoint will be included as binary variable (Y/N) in the adjusted analysis for that specific endpoint, but not for other endpoints At enrollment and then every 2.5 years, RABBIT collects medical history on the following conditions as comorbidity: hypertension, coronary heart disease, heart failure, cerebrovascular diseases (Apoplex/TIA/PRIND), hyperlipoproteinaemia, diabetes, malignant neoplasia, lymphoma/leucosis, chronic kidney diseases, psychological diseases/depression, and latent (inactive) TB. Adverse events are

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ascertained continuously after enrollment in RABBIT. As the overall goal of the study is to evaluate the safety profile of tofacitinib, overall incidence rates of the safety endpoints of interest will be estimated, and as a sensitivity analysis, results will be stratified by prior use of JAK inhibitors other than tofacitinib to account for potential prior use of these therapies impacting risk of the endpoints under study.

Semi-Annual Reports: Crude event rates, which can include multiple safety events of interest per patient, and corresponding 95% confidence intervals (CIs) per 1000 patient years (PY) will be estimated. Event rates will include all events (ie, patients who experience the event of interest will not be censored at the first event per patient group). Pfizer will receive one report on tofacitinib and two control group reports: one of biologics / tsDMARDs naïve patients and one of SAEs observed in patients under conventional treatment who were previously exposed to b/tsDMARDs. Copies of all summary reports are sent to the members of scientific advisory board and the spokesman of the commission drug therapy of the German Society for Rheumatology (DGRh).

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 hazard ratios for differences in severity of disease as well as other confounders and will be completed using appropriate multivariate, propensity score matching, or inverse probability weighting methods. The adjusted hazard ratios will include adjustment for sex, age, year of treatment start, treatment history, disease severity, comorbidities (including history of some of the outcomes of interest), and other potential confounders. Crude incidence rates and corresponding 95% CIs will be analyzed overall, and further stratified by previous b/tsDMARD use, by monotherapy and by combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs), specifically MTX. 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 final report. 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/sexstandardized- incidence rates, using the tofacitinib cohort as standard. Incidence rates will be restricted to the first event per patient per exposure group (ie, patients who experience the event of interest within one exposure cohort will be censored at the first event, however, further events after switch to another exposure cohort will be counted).

For lymphoma, event 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 safety events of interest 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 in the final report (see Section 9.5.1). Likewise, VTE event rates will be stratified by type of event (DVT and PE). Further, for the safety

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events of interest 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 in the final report. The incidence 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 30 June 2021).

The approved SAP will also describe the a priori determined common set of MedDRA codes and the MedDRA version to define serious infections, GI perforations, herpes zoster, fractures, and CV events (MACE). The codes and version will be harmonised with other registers conducting similar analysis. A draft set of MedDRA codes is included in Appendix 1.

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.

9.10. Quality Control

For the reports, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline will be followed. Furthermore, the results will be presented in a comprehensive way to enable the reader to follow them in detail.

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Quality control in the RABBIT register: After having received the CRF, the initial plausibility checks are performed. Missing or implausible variables are stratified into different groups: for some variables, missing values or implausible values are always queried, for other variables, missing or implausible values are only queried when values of other variables are also queried, and for some variables, missing or implausible values are not queried at all. Disease related information (joint count, inflammation markers, physician reported disease activity, etc.) and information related to DMARD treatment (start and stop dates, reasons for discontinuation of DMARDs, etc.) are always queried. There are no inquiries if physician reported weight or any patient reported variables (e.g., general health state, functional state, fatigue, pain, smoking habits, etc.) are missing. After the first monitoring steps, data are entered into the database. At regular intervals (every eight weeks) a new dataset is created by adding the new data. After this process the next monitoring steps are performed, mainly regarding longitudinal data plausibility.

If more than two follow-up time points are missing in one patient, an intensive drop out inquiry starts. First, the physician is queried to determine if anything is known about the patient's whereabouts. Secondly, the patient (or his/her relatives living in the same household) is contacted to determine why there have been no visits to the rheumatologist and whether the patient is still in rheumatologic care. If insufficient information is received after these first steps, authorities are asked (e.g., registration office) about new addresses, or whether the patient has died. In the latter case, health authorities are subsequently contacted to obtain causes of death.

9.11. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing RABBIT, a well-established Germany-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 to the overall RA population are of concern when comparing hazard 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 AEs. However, new therapies may perhaps also be used specifically for patients without multimorbidity. Biases resulting from channeling may present as increased or decreased rates of AEs. 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 in the final report. Trend analyses may be conducted to evaluate rates over time. Additionally, there is the potential for prevalent user bias since a true active comparator first-ever new user design could not be applied, given that most patients would not have a sufficient washout period to be included in the analysis.

To reduce the selection bias, the protocol was amended (Version 6.0, February 2025) so that use of prior therapies is handled similarly across cohorts. However, selective losses to follow-up may still lead to selection bias.

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The registry works to ensure data quality as described in Section 9.10. Nonetheless, there remains the potential for information bias if variables collected by the registry are mismeasured.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing AEs. The rates of AEs and their distribution among patient-types may have changed over time. Therefore, all comparators in the final report are contemporaneous to tofacitinib treated patients.

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, history of certain comorbidities (e.g. serious or opportunistic infections, herpes zoster, fractures are not documented at enrolment), characteristics which may influence VTE safety events (e.g. previous VTE, previous major surgery, 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).

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While RABBIT 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 follow patients for a period of 7-years of study initiation. Conclusions may not be generalizable outside of the 7-year period since initiation of therapy.

9.12. Other Aspects

Not applicable.

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10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient

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

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the institutional review board (IRB)/independent ethics committee (IEC) and Pfizer before use.

10.2. Patient Consent

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

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients have the right to leave the study at any time. The study coordinating office reserves the right to contact these patients by letter or phone to ask their reasons for discontinuing their participation.

10.4. Institutional Review Board/Independent Ethics Committee

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.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with

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the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.4.1. Cooperation Between Study Management, Advisory Board, and Sponsors

The study management team is supported by a scientific advisory board comprising four experienced community and hospital rheumatologists. The scientific advisory board was appointed by the governing board of the German Society for Rheumatology in agreement with the Professional Association of German Rheumatologists. The advisory board's duties are: regular review of the reports, consultation in case of serious events, discussion of the research agenda and the SAPs. The advisory board members meet personally at least once annually with the principal investigators and the study physicians and otherwise communicate by telephone conferences and email.

The sponsors are entitles to have two delegates with no voting rights present at the meetings of the scientific advisory board.

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

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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.

This study is a non-interventional PASS that will make secondary use of data collected by RABBIT, where individual patient data are de-identified within safety data.

In RABBIT, all serious and non-serious events occurring during the observation are regularly reported from the rheumatologist and captured in the register (with judgement from the rheumatologist on: severity (mild, moderate, severe; and causality to given medication). For events of special interest detailed queries are sent out, to get more information on the events (and additional discharge letters from hospitals, or results from biopsies etc).

Per RABBIT policy, AE and serious AEs (SAE) will be recorded according to the International Council for Harmonisation (ICH) guidelines. Therefore, any untoward medical occurrence observed in a patient has to be reported as AE. The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect has to be reported as SAE. These definitions of AEs and SAEs are also provided in the case report forms (CRFs). For non-serious AEs, severity grading will be performed according to the recommendations of the Outcome Measures in Rheumatology (OMERACT) Toxicity Working Group. For the coding of AE and SAE the Medical Dictionary for Regulatory Activities (MedDRA) will be used on the preferred term level. It is intended to update the AE/SAE database with every update of MedDRA. All events are carefully monitored.

There is no possibility to link RABBIT data with any other data source due to strict data protection rules and due to the fact that there is no national cancer register or death register with the possibility of linkage. However, in the case of death of a patient with unknown information about the date and cause of death, the respective national offices are contacted to get more information.

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 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 provided at 2, 4, 6 years after the start of data collection and submitted to EMA. The final report will be included in risk management plan (RMP) updates. Data may be used in regulatory

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communications external to Germany 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, 5-Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm....35

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, 30% Switch From Tofacitinib To bDMARD Per Year....36

15. LIST OF FIGURES

Not applicable.

090177e1a3faf9f5\Approved\Approved On: 10-Jul-2025 15:36 (GMT)

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

EU PAS Register® number: EUPAS31164
Study reference number (if applicable): A3921317

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	6
1.1.2 End of data collection[4]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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

Comments:

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

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

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Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	x☐	☐	☒	11

Comments:

No measure of association will be determined in this descriptive study. This is a secondary database study using structured data, no reporting of adverse events is required for this protocol.

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	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	☒	☐	☐	9.3.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1/9.2.2

Comments:

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

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

Comments:

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

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.5.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.5.3
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)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.11

Comments:

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

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	x☐	☒	☐	9.9

Comments:

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Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.5.3
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.5.1
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)	☒	☐	☐	9.5.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.5.1
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.5
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.9
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3	Are descriptive analyses included?	☒	☐	☐	9.9
10.4	Are stratified analyses included?	☒	☐	☐	9.9
10.5	Does the plan describe methods for analytic control of confounding?	☐	☒	☐	9.9
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?	☒	☐	☐	9.4, 9.9

Comments:

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

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Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8, 9.10
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.10

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒		☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
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).	☒	☐	☐	9.11
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.7

Comments:

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

Comments:

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

Comments:

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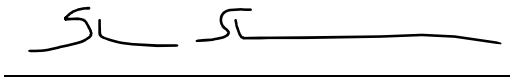
Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Shahar Shmuel

Date: 06 July 2025

Signature:



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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.
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 being the	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral

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	ARTIS		BIOBADASER, BSRBR, RABBIT
		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.	medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism; Fatal only 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type;;10006145 Brain stem haemorrhage;;10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus; 10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage; 10008076 Cerebral aneurysm ruptured syphilitic; 10008086 Cerebral arteriovenous malformation haemorrhagic; 10008089 Cerebral artery occlusion; 10008092 Cerebral artery thrombosis; 10008111 Cerebral haemorrhage; 10008118 Cerebral infarction; 10008132 Cerebral thrombosis; 10018985 Haemorrhage intracranial; 10022758 Intracranial aneurysm; 10022840 Intraventricular haemorrhage; 10022841 Intraventricular haemorrhage neonatal; 10024119 Left ventricular failure;

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	ARTIS		BIOBADASER, BSRBR, RABBIT
			10024242 Leriche syndrome; 10034476 Pericardial haemorrhage; 10036511 Precerebral artery occlusion; 10039163 Right ventricular failure; 10039330 Ruptured cerebral aneurysm; 10042316 Subarachnoid haemorrhage; 10042434 Sudden death; 10047279 Ventricle rupture; 10048380 Aneurysm ruptured; 10048761 Atrial rupture; 10049418 Sudden cardiac death; 10049993 Cardiac death; 10050403 Carotid artery dissection; 10051093 Cardiopulmonary failure; 10051328 Carotid aneurysm rupture; 10052019 Femoral artery occlusion; 10053633 Cerebellar artery occlusion; 10053649 Vascular rupture; 10053949 Vascular pseudoaneurysm ruptured; 10055803 Haemorrhage coronary artery; 10058178 Aortic occlusion; 10060874 Aortic rupture; 10060953 Ventricular failure; 10060964 Arterial haemorrhage; 10062585 Peripheral arterial occlusive disease; 10062599 Arterial occlusive disease; 10063081 Acute left ventricular failure; 10063082 Acute right ventricular failure ; 10063083 Chronic left ventricular failure; 10063084 Chronic right ventricular failure; 10064595 Haemorrhagic arteriovenous malformation; 10064601 Iliac artery occlusion; 10065441 Venous haemorrhage; 10065558 Aortic arteriosclerosis; 10067057 Basal ganglia haemorrhage; 10067116 Carotid arteriosclerosis; 10068119 Aortic dissection rupture; 10068119 Aortic dissection rupture; 10068230 Cardiorenal syndrome; 10069694 Brachiocephalic artery occlusion; 10069695 Subclavian artery occlusion; 10069696 Coeliac artery occlusion;10071716 Vertebral artery dissection; 10072043 Central nervous system haemorrhage; 10072789 Iliac artery rupture; 10073565 Intracranial artery dissection; 10073565 Intracranial artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure.
GI perforation	Hospitalizations in the Patient Register listing ICD10-codes: K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K31.6, K35.0, K35.1, K57.0, K57.2, K57.4, K57.8, K63.0, K63.1, K63.2.	See Serious Infections; Pharmacoepidemiol Drug Saf. 2011 Nov;20(11):1150-8. doi: 10.1002/pds.2215. Epub 2011 Aug 27. Validation of ICD-9-CM codes to identify gastrointestinal	10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheo-oesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924 Aorto-duodenal fistula; 10003012 Appendicitis perforated; 10009995 Colonic fistula; 10013536

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	ARTIS		BIOBADASER, BSRBR, RABBIT
		perforation events in administrative claims data among hospitalized rheumatoid arthritis patients.	Diverticular fistula; 10013538 Diverticulitis; 10013541 Diverticulitis intestinal haemorrhagic; 10013828 Duodenal fistula; 10013832 Duodenal perforation; 10013849 Duodenal ulcer perforation; 10013849 Duodenal ulcer perforation; 10013850 Duodenal ulcer perforation, nobstructive; 10017815 Gastric perforation; 10017835 Gastric ulcer perforation; 10017836 Gastric ulcer perforation, obstructive; 10017866 Gastritis haemorrhagic; 10017877 Gastrointestinal fistula; 10017954 Gastrointestinal gangrene; 10017955 Gastrointestinal haemorrhage; 10018001 Gastrointestinal perforation; 10021305 Ileal perforation; 10021310 Ileal ulcer perforation; 10022647 Intestinal fistula; 10022694 Intestinal perforation; 10023174 Jejunal perforation; 10023178 Jejunal ulcer perforation; 10023804 Large intestine perforation; 10030181 Oesophageal perforation; 10034354 Peptic ulcer perforation; 10034358 Peptic ulcer perforation, obstructive; 10034397 Perforated peptic ulcer oversewing; 10034649 Peritoneal abscess; 10034674 Peritonitis; 10038073 Rectal perforation; 10038975 Retroperitoneal abscess; 10041103 Small intestinal perforation; 10046274 Upper gastrointestinal haemorrhage; 10048946 Anal abscess; 10048947 Rectal abscess; 10049583 Douglas' abscess; 10049764 Appendiceal abscess; 10050362 Anovulvar fistula; 10050953 Lower gastrointestinal haemorrhage; 10051425 Enterocutaneous fistula; 10052211 Oesophageal rupture; 10052457 Perineal abscess; 10052488 Oesophageal ulcer perforation; 10052814 Perirectal abscess; 10052931 Colon fistula repair; 10052991 Intestinal fistula repair; 10053267 Rectal fistula repair; 10056086 Paraoesophageal abscess; 10056346 Anastomotic haemorrhage; 10056991 Enterocolonic fistula; 10056992 Oesophagobronchial fistula; 10058381 Oesophageal fistula repair; 10059175 Intestinal haemorrhage; 10060921 Abdominal abscess; 10061248 Intestinal ulcer perforation; 10061249 Intra-abdominal haemorrhage; 10061820 Diverticular perforation; 10061975 Gastrointestinal ulcer perforation; 10062065 Perforated ulcer; 10062070 Peritonitis bacterial; 10062570 Enterovesical fistula; 10065713 Gastric fistula; 10065879 Gastrointestinal anastomotic leak; 10066870

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	ARTIS		BIOBADASER, BSRBR, RABBIT
			Aorto-oesophageal fistula; 10066892 Rectourethral fistula; 10067091 Gastropleural fistula; 10068792 Gastrosplenic fistula; 10071647 Infectious peritonitis.
PML	Hospitalizations in the Patient Register listing ICD10-codes: A81.2.	See Serious Infections.	TBD based on reported events.
NMSC	Identified through the Cancer register as all malignancies with ICD-O/2 code C44, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers Alt: all invasive NMSC, identified as non-benign ICD-O/2 code C44, and no basal cell cancers.	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%.	10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059 Bowen's disease; 10007390 Carcinoma in situ of skin; 10064055 Lip squamous cell carcinoma; 10063693 Malignant neoplasm of eyelid; 10040808 Skin cancer; 10055115 Skin cancer metastatic 10041834 Squamous cell carcinoma of skin
Malignancy	All invasive malignancies recorded in the cancer register, excluding NMSC.	See NMSC.	Malignant or unspecified tumours (SMQ).
Lung Cancer	Identified through the Cancer Register. ICD-7: 162.1		HLTs: 10038723 Respiratory tract and pleural neoplasms malignant cell type unspecified NEC; 10024973 Lower respiratory tract neoplasms. LLT: 10023292 Kaposi's sarcoma, lung; Exclude PTs: 10043515 throat cancer; 10004280 benign lung neoplasm; 10061002 benign respiratory tract neoplasm, 10052247 bronchial neoplasm benign; 10014654 endobronchial lipoma; 10081106 sclerosing pneumocytoma.
Lymphoma	Identified through the Cancer Register. All non-Hodgkin Lymphoma: ICD-7: 200,202 All Hodgkin Lymphoma: ICD-7: 201 Chronic lymphocytic leukemia: ICD-7: 204.1	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%	Non-Hodgkin's lymphoma 10029547; Non-Hodgkin's lymphoma metastatic 10071535; Non-Hodgkin's lymphoma recurrent 10029600; Non-Hodgkin's lymphoma refractory 10029601; Non-Hodgkin's lymphoma stage I 10029602; Non-Hodgkin's lymphoma stage II 10029603; Non-Hodgkin's lymphoma stage III 10029604; Non-Hodgkin's lymphoma stage IV 10029605; Non-Hodgkin's lymphoma transformed recurrent 10061871; Non-Hodgkin's lymphoma unspecified histology aggressive 10063908; Non-Hodgkin's lymphoma unspecified histology aggressive recurrent 10029609; Non-Hodgkin's

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			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; Hodgkin's disease lymphocyte depletion stage I subdiaphragm 10020209; Hodgkin's disease lymphocyte depletion stage I supradiaphragm 10020210; Hodgkin's disease lymphocyte depletion stage II site unspecified 10020211; Hodgkin's disease lymphocyte depletion stage II subdiaphragm 10020212; Hodgkin's disease lymphocyte depletion stage II supradiaphragm 10020213; Hodgkin's disease lymphocyte depletion type recurrent 10020215; Hodgkin's disease lymphocyte depletion type refractory10020216; Hodgkin's disease lymphocyte depletion type stage III 10020217; Hodgkin's disease lymphocyte depletion type stage IV 10020218; Hodgkin's disease lymphocyte depletion type stage unspecified 10020219; Hodgkin's disease lymphocyte predominance stage I site unspec 10020220; Hodgkin's disease lymphocyte predominance stage I subdiaphragm 10020221; Hodgkin's disease lymphocyte predominance stage I supradiaphragm 10020222; Hodgkin's disease lymphocyte predominance stage II site unspec 10020223; Hodgkin's disease lymphocyte predominance stage II subdiaphragm 10020224; Hodgkin's disease lymphocyte predominance stage II supradiaphragm 10020225; Hodgkin's disease lymphocyte predominance type recurrent 10020227; Hodgkin's disease lymphocyte predominance type refractory 10020228; Hodgkin's disease lymphocyte predominance type stage III

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	ARTIS		BIOBADASER, BSRBR, RABBIT
			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 supradiaphragmatic 10020239; Hodgkin's disease mixed cellularity stage III 10020240; Hodgkin's disease mixed cellularity stage IV 10020241; Hodgkin's disease mixed cellularity stage unspecified 10020242; Hodgkin's disease nodular sclerosis 10020244; Hodgkin's disease nodular sclerosis recurrent 10020245; Hodgkin's disease nodular sclerosis refractory 10020246; Hodgkin's disease nodular sclerosis stage I 10073535; Hodgkin's disease nodular sclerosis stage II 10073534; Hodgkin's disease nodular sclerosis stage III 10020252; Hodgkin's disease nodular sclerosis stage IV 10020253; Hodgkin's disease recurrent 10020266; Hodgkin's disease refractory 10020267; Hodgkin's disease stage I 10020268; Hodgkin's disease stage II 10020269; Hodgkin's disease stage III 10020270; Hodgkin's disease stage IV 10061597; Hodgkin's disease unclassifiable 10020271; Chronic lymphocytic leukaemia 10008958; Chronic lymphocytic leukaemia (in remission) 10008959; Chronic lymphocytic leukaemia recurrent 10008961; Chronic lymphocytic leukaemia refractory 10008962; Chronic lymphocytic leukaemia stage 0 10008963; Chronic lymphocytic leukaemia stage 1 10008964; Chronic lymphocytic leukaemia stage 2 10008965; Chronic lymphocytic leukaemia stage 3 10008966; Chronic lymphocytic leukaemia stage 4 10008967; Chronic lymphocytic leukaemia transformation 10058717;

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	ARTIS		BIOBADASER, BSRBR, RABBIT
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 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.	The PPV for fractures in the Swedish NPR is extremely high: a validation of 647 patient charts the PPV of fracture in Swedish patient records was 1.00. There is high accuracy for both a diagnosis of hip fracture and a fracture of any type in the Swedish Patient Register	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 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

A3921317

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 German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

Statistical Analysis Plan

(SAP)

Version: 1.0

Authors: Meissner, Yvette

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**Epidemiology and Health Services Research,
German Rheumatology Research Center**

Date: 03-SEP-2025

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TABLE OF CONTENTS

LIST OF TABLES 4
1. LIST OF ABBREVIATIONS 5
2. RATIONALE AND BACKGROUND 7
3. STUDY OBJECTIVES AND HYPOTHESES 8
3.1. Primary objectives 8
4. RESEARCH METHODS 9
4.1. Study design 9
4.2. Study population 10
4.2.1. Main cohort and comparator cohorts 10
4.2.1.1. Interim reports 10
4.2.1.2. Final report 10
4.2.2. Subgroups 11
4.2.2.1. Interim reports 11
4.2.2.2. Final report 11
4.3. Variables 12
4.3.1. Exposure 12
4.3.2. Outcomes 13
4.3.3. Other variables (risk factors, co-morbidities, co-medications) 15
4.4. Data sources 23
4.5. Sample size and power calculations 26
4.6. Missing Data 28
4.6.1. Interim reports 28
4.6.2. Final report 28
4.7. Statistical methodology and analyses 29
4.7.1. Index date and follow-up 29
4.7.1.1. Interim reports 29
4.7.1.2. Final report 30
4.7.2. Risk window definitions 32
4.7.2.1. Interim reports 32
4.7.2.2. Final report 32
4.7.3. Primary analyses 33

090177e1a465bbe2\Approved\Approved On: 16-Sep-2025 14:12 (GMT)

4.7.3.1. Interim reports 33
4.7.3.2. Final report 34
4.7.4. Secondary analyses 35
4.7.4.1. Interim reports 35
4.7.4.2. Final report 35
4.7.5. Sensitivity analyses 39
4.7.5.1. Interim reports 39
4.7.5.2. Final report 39
4.7.6. Additional analyses 39
4.7.6.1. Interim reports 39
4.7.6.2. Final report 39
4.7.7. Post-hoc analyses 40
4.7.7.1. Interim reports 40
4.7.7.2. Final report 40
5. REFERENCES 40
6. APPENDICES 41

090177e1a465bbe2\Approved\Approved On: 16-Sep-2025 14:12 (GMT)

LIST OF TABLES

Table 1. Classification of Medications (ATC Codes) for the Treatment of RA. 13
Table 2. Definitions of baseline patient characteristics for the final report. 15
Table 3. Definitions of confounders for the final report. 19
Table 4. Definitions of VTE Risk Factors. 21
Table 5. Definitions of CV risk factors. 22
Table 6. Definitions of malignancy risk factors. 23
Table 7. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort 24
Table 8. 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 27
Table 9. 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 28
Table 10. Confounders for the Cox regression analysis for selected outcomes. 38

090177e1a465bbe2\Approved\Approved On: 16-Sep-2025 14:12 (GMT)

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
BAT	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
AEM	adverse event monitoring
ANK	anakinra
AE	adverse event
bDMARD	biologic disease modifying antirheumatic drug
BfArM	Bundesamt fur Arzneimittel und Medizinprodukte
BID	bis in die (twice a day)
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drug[a]
CV	cardiovascular
CVD	cardiovascular disease
DAS	Disease Activity Score
DAS-28	Disease Activity Score 28
DRFZ	Deutsches Rheuma-Forschungszentrum (German Rheumatology Research Center)
DGRh	German Society for Rheumatology
DMARD	disease-modifying antirheumatic drug
DVT	deep vein thrombosis
EC	European Commission
EBV	Epstein Barr virus
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Event rates
ESR	erythrocyte sedimentation rate
ETA	etanercept
EU	European Union
FFbH	% of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain
GI	gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	Health Assessment Questionnaire
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL	interleukin
INF	infliximab
IR	Incidence rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

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Abbreviation	Definition
IPTW	inverse probability weights
JAK	Janus kinase
MACE	major adverse cardiovascular events
MAH	market authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
MTX	methotrexate
nbDMARD	non-biologic DMARD[b]
NDA	New Drug Application
NHL	non-Hodgkin's lymphoma
NI	non-Interventional
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
OMERACT	Outcome Measures in Rheumatology
PAS	post authorization study
PASS	Post- Authorization Safety Study
PE	pulmonary embolism
PML	progressive multifocal leukoencephilitis
PS	propensity scores
PY	person-years
RA	rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	risk management plan
RTX	rituxumab
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance and Epidemiology End Results
SIR	Standardised Incidence Ratio
SMD	Standardized mean differences
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	tuberculosis
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic DMARD
VAS	Visual Analog Scale
VTE	venous thromboembolism

a. *synonymous with nbDMARD, b. synonymous with csDMARD*

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Glossary

Term	***Definition***
csDMARD	Identical to nbDMARD, includes Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide
nbDMARD	Identical to csDMARD, includes Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide
tsDMARD	Identical to JAK inhibitor, includes Tofacitinib, Baricitinib, Upadacitinib, Filgotinib.
JAK inhibitor	Identical to tsDMARD, includes Tofacitinib, Baricitinib, Upadacitinib, Filgotinib
3-months risk window	Identical to “90-day extension”.
90-day extension	Identical to 3-months risk window
Enrolment	The date on which the patient is included in the register.
Loss to follow-up	Identical to exit from the register.
Observation time	Comprises the entire time, the patient is observed in the register starting with enrolment and ending with loss to follow-up or death, or after 10 years of observation.
Treatment episode	Treatment episodes are defined as periods of use of the same treatment, defined by start and stop dates recorded in the register for any given treatment.
Index date	The index date for the tofacitinib cohort is the date the first tofacitinib dose was taken. Similarly, the index dates for comparator cohorts are the date of the initiation of the first comparator treatment dose. Patients who switch to a subsequent therapy are eligible for enrollment as an initiator of the subsequent therapy, and the initiation date will be the date of initiating the subsequent therapy. Index date can be either at enrolment or during the observation time.
Baseline	Baseline is equivalent to the index date.
End of study	Identical to end of data collection for this PASS study. The inclusion period for the final report is from 01 May 2017 to June 30, 2025.
Follow-up (time)	Comprises the time of every patient between index date until the occurrence of death, loss to follow-up, end of study, or after 7 years of observation, whichever occurs first.
Outcome	Identical to endpoint
Endpoint	Identical to outcome

2. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease and is characterized by inflammation, progressive disability, and joint destruction, which is frequently irreversible resulting in significant cumulative morbidity. Furthermore, patients experience a broad range of co-morbidities [1]. Compared with the general population, RA patients are at a higher risk of infections, cardiovascular (CV) disease (CVD) and

malignancies (including lymphoma). Patients with RA are 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 a potent, selective inhibitor of the Janus kinase (JAK) family with a high degree of selectivity relative to other kinases in the human genome. Tofacitinib was approved in the European Union (EU) in March 2017 at a dose of 5 milligrams (mg) administered twice daily (BID) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to, or who are intolerant to, one or more 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.

There is a need for active surveillance for all new biologic and other targeted therapies to identify higher than expected rates of safety events overall and within strata of disease severity, treatment history, and other concomitant therapy. Therefore, careful observation over several years of a large cohort of patients is needed to detect any increase or decrease in risk of malignancy, infection and other co-morbidities and mortality, possibly due to tofacitinib treatment.

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 embedded within the German register Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT). This study is designated as a post-authorization safety study (PASS) and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

This statistical analysis plan (SAP) describes the statistical methods to be used in addressing the objectives, such as demographic and baseline characteristics, treatment exposure, and safety outcomes of interest.

For the final report, end of data collection is 14 Sep 2025 (as noted in protocol, this data cut will include data through 30 Jun 2025 due to data lag) and delivery of the first draft of the final study report is 30 April 2026.

3. STUDY OBJECTIVES AND HYPOTHESES

No a priori hypotheses will be specified.

3.1. Primary objectives

The **primary objectives** are:

- 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) (DVT and PE) and other safety events of interest, including fractures, among patients with RA who initiated tofacitinib in a German register.
- Rates will also be estimated among existing cohorts of biologic disease modifying antirheumatic drugs (bDMARDs) and nonbiologic DMARDs (nbDMARDs) patients to provide context for rates observed on tofacitinib.

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- Further, incidence rates will be estimated in elderly patients aged 65 years and older[1].
- Pending feasibility, in the final report hazard ratios (HR) will be estimated with Cox proportional hazards regression models for the outcomes malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, MI, VTE, and other outcomes, including fractures, comparing tofacitinib-treated RA patients with patients treated with comparator drugs. The model will adjust for prespecified potential confounders, including sex, age, RA disease duration, year of treatment start, previous b/tsDMARDs, disease severity, and smoking. Additional covariates may be considered based on clinical relevance and data availability[1].

Different comparator cohorts will be used for the three interim reports and the final report.

The comparator cohorts for the interim reports will be:

- **b/tsDMARD-naive nbDMARD cohort:** patients who initiated a conventional synthetic (cs)DMARD and who were previously never exposed to bDMARDs or tsDMARDs but have received at least one prior csDMARD;
- **b/tsDMARD exposed nbDMARD cohort:** patients who initiated csDMARDs and who were previously exposed to bDMARDs or tsDMARDs but discontinued this treatment;

The comparator cohorts for the final report will be:

- **bDMARD exposed cohort:** patients who initiated a bDMARD;
- **nbDMARD exposed cohort:** patients who initiated a csDMARDs and who were previously never exposed to bDMARD or tsDMARD but that received at least one prior csDMARD (b/tsDMARD-naive nbDMARD);

4. RESEARCH METHODS

4.1. Study design

This is an active surveillance study using existing data within the German RABBIT register, an ongoing prospective observational cohort study that started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use (non-interventional post-authorization safety study). RABBIT is being conducted by Deutsches Rheuma-Forschungszentrum (German Rheumatology Research Center (DFRZ)) with industry funding. Patients may switch and /or discontinue therapies during observation time, which can be up to 10 years.

Data capture and follow-up methods are the same for all cohorts within RABBIT.

No time restrictions relating to the start of treatment initiation were applied. All patients enter at treatment initiation independent from previous treatments. Patients taking tofacitinib may enter as early as May 2017 (when the therapy was fully available in Germany). Patients on comparator treatments enter at time of treatment initiation (which can be earlier than May

[1] This will be presented in the final report only.

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2017) in the interim report. As initiation of tofacitinib in RABBIT will be from 01 May 2017 onwards, only treatments initiated after this date will be included in the final report.

4.2. Study population

The study population consists of patients with RA enrolled in RABBIT from 1 January 2009 onwards, and different exposure cohorts (main cohort and comparator cohorts) will be defined depending on the type of report

4.2.1. Main cohort and comparator cohorts

4.2.1.1. Interim reports

End of data collection for the first interim report was 31 October 2020, for the second interim report 30 April 2022 and for the third interim report 30 June 2024.

Inclusion criteria

Tofacitinib Exposed Cohort (main cohort):

- Included in RABBIT
- Initiation of tofacitinib (from 01 May 2017 onwards);

nbDMARD – b/tsDMARD-naive cohort:

- Included in RABBIT
- Enrolled after 01 January 2009;
- Failure of at least one DMARD and initiation of a new csDMARD;
- No previous exposure to bDMARD nor tsDMARD.

nbDMARD Exposed (previously exposed to b/tsDMARDs) Cohort:

- Included in RABBIT
- Enrolled after 01 January 2009
- Previous exposure to bDMARD or targeted synthetic DMARD (tsDMARD) but discontinued treatment[2]

4.2.1.2. Final report

End of data collection for the final report will be 30 June 2025. To allow the possibility of at least one follow-up visit, the initiation of tofacitinib, bDMARD and nbDMARD must be before 31 December 2024. As initiation of tofacitinib in RABBIT will be from 01 May 2017 onwards, only treatments initiated after this date will be included in the final report.

Inclusion criteria

Tofacitinib Exposed Cohort (main cohort):

- Included in RABBIT
- Initiated treatment with tofacitinib;

[2] (previously exposed to bDMARD or tsDMARD and received no bDMARD or tsDMARD for at least 3 months (9 months for rituximab))

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Treated with bDMARD RA Cohort (bDMARD cohort):

- Included in RABBIT.
- Initiation of bDMARD therapy after 01 May 2017.
- Eligible bDMARDs comprise abatacept, anakinra, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab.

Treated with nbDMARD RA Cohort (nbDMARD cohort):

- Included in RABBIT.
- Initiation of csDMARD therapy after 01 May 2017.
- Failure of at least one DMARD and initiation of a new csDMARD;
- No previous exposure to bDMARDs or tsDMARDs
- Patients with no exposure to any DMARD will be excluded.

  Definition of the included episodes in the final report for the tofacitinib and the bDMARD exposed cohort: episodes are only included if there is no exposure of the specific active substance (e.g., adalimumab, etanercept, infliximab, rituximab, certolizumab, golimumab, tocilizumab, sarilumab, abatacept for the bDMARD cohort, tofacitinib for the main cohort) 365 days prior to prescription of the drug.

Exclusion criteria

Any patient with RA enrolled within RABBIT who does not meet one or more of the inclusion criteria will be excluded

4.2.2. Subgroups

4.2.2.1. Interim reports

Patient characteristics and event rates (ER) will be presented overall and stratified by sex.

4.2.2.2. Final report

a) For the main cohort and the bDMARD cohort, patient characteristics and incidence rates (IR) of all outcomes will be presented stratified by the number of previous b/tsDMARDs (0, 1, ≥2)[3].
b) For the main cohort and the bDMARD cohort, patient characteristics and IR of all outcomes will be presented stratified by prior use of non-tofacitinib JAK-inhibitor therapy (0; >0).
c) For the main cohort and the bDMARD cohort, patient characteristics and IR of all outcomes will be presented stratified by monotherapy vs. combination therapy with

[3] The RABBIT team may deem it necessary to change the way in which the covariable previous b/tsDMARDs is considered in the model, for consistency the same categories will be used throughout the report. The mentioned categories might lead to considerable imbalances due to very different distributions of this confounders for the exposure groups, it might thus be necessary e.g. to change the category definition.

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concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs), specifically MTX. Combination therapy with MTX is defined as simultaneous use of MTX and bDMARD / tofacitinib for at least 30 days starting at index date. As begin and end dates of csDMARDs are only reported in the format month and year (without day), we approximate the above definition: If MTX was applied and treatment did not end in the same calendar month as the index date, we consider this episode as combined treatment. 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.

d) For all cohorts and all outcomes, IR will be presented stratified by age (<65 years and ≥65 years).
e) For all cohorts and the outcome of VTE, IR will be estimated stratified by the patients with ≥1 VTE risk factors vs. no VTE risk factors.

   VTE risk factors (evaluated at treatment initiation) which are taken into account are defined as: age (<65 years and ≥65 years), heart failure, malignancy, diabetes, hypertension.

f) If feasible, stratified analyses to estimate the IR for VTE stratified by time periods defined by the changes in the Summary of Product Characteristics (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).

g) For all cohorts and the outcomes of MACE and MI, IRs will be estimated stratified by patients with ≥1 CV risk factors vs. no CV risk factors.

   CV risk factors (evaluated at baseline) which are taken into account are defined as: age (patients ≥65 years versus <65 years), history of or current diabetes, history of hyperlipidemia, history of or current hypertension, history of or current coronary heart disease.

h) For all cohorts and the outcomes of malignancy, IR for malignancy outcomes in patients stratified by with and without prior history of malignancy.
i) Additionally, if feasible, the following analyses will be done: overall incidence rates (IR) for malignancy /CV risk and also presented stratified by 30 June 2021; overall IR for VTE and also presented stratified by 31 January 2020; IR for VTE among patients with VTE risk factors stratified by 31 January 2020; IR for malignancy /CV risk among patients with malignancy and CV risk factors stratified by 30 June 2021 For CV risk factors see e). Malignancy risk factors are defined as smoking and elevated BMI.

4.3. Variables

4.3.1. Exposure

This study will include different cohorts of interest, defined by their treatment for RA. The cohorts for the interim reports and the final reports are partially different, and respective inclusion criteria are defined in sections 4.2.1.1 and 4.2.1.2.

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Table 1 includes the Anatomical Therapeutic Chemical (ATC) codes for the medications used to treat RA.

Table 1. CLASSIFICATION OF MEDICATIONS (ATC CODES) FOR THE TREATMENT OF RA.

bDMARD		tsDMARD (JAK inhibitor)	csDMARD
Abatacept (L04AA24)	Anakinra (L04AC03)	Tofacitinib (Xeljanz, L04AA29)	Methotrexate (L01BA01, L04AX03, L04AX03)
Adalimumab (L04AB04)	Certolizumab pegol (L04AB05)	Baricitinib (L04AA37)	Sulfasalazine (A07EC01)
Etanercept (L04AB01)	Golimumab (L04AB06)	Upadacitinib (L04AA44)	Hydroxychloroquine (P01BA02)
Infliximab (L04AB02)	Rituximab (L01XC02)	Filgotinib (L04AA45)	Leflunomide (L04AA13)
Sarilumab (L04AC14)	Tocilizumab (L04AC07)		

4.3.2. Outcomes

Most outcomes are defined by the Medical Dictionary for Regulatory Activities (MedDRA) on the preferred term (PT) level.

Further details are provided in **Appendix Tables 1A** and **1B** of the APPENDICES.

Outcomes of the reports comprise:

1. Serious infections (excluding tuberculosis (TB)) (overall) and by subtype:
   - Pneumonia
   - Other infections of the respiratory system
   - Infections of the central nervous system (CNS)
   - Sepsis
   - Bone or joint infections
   - Opportunistic infections
   - Other infections
2. Herpes zoster (hospitalized)
3. TB
4. Hepatic failure
5. Fractures
6. Cardiac disorders (overall) and by subtype:
   - Myocardial infarction (MI)
   - Heart failure
   - Coronary artery disease

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- Other cardiac disorders.
7. Cardiovascular risk (defined as Major Cardiovascular Events (MACE))
8. Embolic and thrombotic events, venous or vessel type unspecified (overall) and:
- Thromboembolic events (VTE) and its components separately:
    - Deep vein thrombosis (DVT)
    - Pulmonary embolism (PE).
9. Hematologic disorders (overall) and by type:
- Bone marrow depression and hypoplastic anaemia
- Decreased white blood cells
- Platelet disorders
- Other blood dyscrasia.
10. Disorders of the nervous system (excluding infections) (overall) and by type:
- Stroke
- Central demyelination
- Other disorders of the CNS
- Disorders of the peripheral nervous system
- Psychiatric disorders.
11. Allergic conditions and hypersensitivity.
12. Progressive multifocal leukoencephalopathy (PML).
13. Gastrointestinal (GI) perforations (overall) and
- Lower intestinal perforations
- Other GI perforations.
14. Operations and hospitalizations (overall) and by type:
- Bone and joint surgery and other joint therapeutic procedures
- Other operations and (major) therapeutic procedures that lead to hospitalization.
15. Other serious diagnoses, symptoms, and syndromes.
16. Interstitial lung disease, pending feasibility.
17. NMSC
18. Neoplasms excl. NMSC (overall) and by type
- Leukaemia (excl. B-CLL)
- Other haematopietic neoplasms (malignant and benign)
- Solid malignancies (overall) and by subtype
    - Glioblastoma
    - Lung Cancer
- Benign neoplasms
- Unspecified neoplasms and precanceroses
- Metastases, cancer related and morbidities and associated syndromes
- Lymphoma (overall) and by subtype:
    - Non-Hodgkin lymphoma
    - Hodgkin lymphoma
    - Chronic lymphatic leukemia
19. All-cause Mortality.
20. Pregnancy (number of pregnancies, outcomes of pregnancies (defined as abortions, Live births, Caesarean sections)) and events associated with pregnancies (e.g., gestational diabetes, preeclampsia).

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4.3.3. Other variables (risk factors, co-morbidities, co-medications)

The data captured at the time of drug initiation include, but are not restricted to, the following: age, sex, years since diagnosis, disease severity, RA drug history, comorbidities (e.g., history of malignancies excluding NMSC, history of lymphoma,), history of therapeutic procedures and current concomitant medications.

Definitions of baseline patient characteristics are given in Table 2.

Table 2. Definitions of baseline patient characteristics for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
Number of features listed in 1987 American College of Rheumatology (ACR) criteria for RA	Questionnaire	For inclusion into RABBIT, a RA diagnosis by a rheumatologist is required. In addition number of fulfilled ACR criteria is asked.
Age at index date (ie, treatment initiation)	Calculation	Year of birth is recorded at enrolment. Every initiation of a DMARD treatment is registered with the date of treatment start. Age at index date will be calculated by subtracting the year of birth from the year of treatment initiation.
Sex [male/female]	Questionnaire	Recorded at enrolment, coded as male and female.
Calendar year of recalled RA symptom onset [< 1990, ≥ 1990 and < 2000, ≥ 2000 and < 2007, ≥ 2007 and < 2017, ≥ 2017]	Questionnaire	Recorded as month and calendar year.
Years since symptom onset	Calculation	Will be calculated by subtracting the year of symptom onset from the year of treatment initiation.
Previous drug history of cs/b/tsDMARDS (csDMARDs) and biologics, biosimilar or other new advanced therapy (Y/N)	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation. Will be 100% yes as all patients have a previous DMARD history in RABBIT
Reason for treatment change of previous therapy of cs/b/tsDMARDs	Questionnaire	Last reason of treatment change before treatment start (treatment failure and/or occurrence of adverse event / intolerance)
Previous use of bDMARDs [Y/N]	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.

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Table 2. Definitions of baseline patient characteristics for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
Number of previously used bDMARDs	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
Previous use of tsDMARDs [Y/N]	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
Number of previously used b/tsDMARDs [0/ 1/ ≥2][4]	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
Number of previously used csDMARDs	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
History of tuberculosis [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of diabetes mellitus [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of hypertension [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of coronary heart disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of malignancy events [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and

[4] The RABBIT team may deem it necessary to change the way in which the covariable previous b/tsDMARDs is considered in the model, for consistency the same categories will be used throughout the report. The mentioned categories might lead to considerable imbalances due to very different distributions of this confounders for the exposure groups, it might thus be necessary e.g. to change the category definition.

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Table 2. Definitions of baseline patient characteristics for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
		regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of lymphoma [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of chronic obstructive pulmonary disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of chronic kidney disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of heart failure [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
Number of comorbidities	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
Concomitant use of csDMARDs [Y/N]	Questionnaire	Recorded at every visit (at enrolment and during observation)
Concomitant use of MTX [Y/N]	Questionnaire	Recorded at every visit (at enrolment and during observation)
Dosage of concomitant use of glucocorticoids [<5, 5-<10, ≥ 10 mg/d]	Questionnaire	Recorded at every visit (at enrolment and during observation), measuring the average daily dose during the time since the last visit.

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Table 2. Definitions of baseline patient characteristics for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
Concomitant use of NSAIDs [Y/N]	Questionnaire	Recorded at every visit (at enrolment and during observation).
Smoking [current/previous/never/missing]	Questionnaire	Recorded at enrolment, patient-reported information.
Disease Activity Score (DAS)-28-ESR	Questionnaire	Calculated by using the following information, which is recorded at every visit (at enrolment and during observation): 28 counts of swollen and tender joints, ESR in mm/h, patient global health NRS (0-10).
Health Assessment Questionnaire (HAQ)	Calculation	Will be calculated by using FFbH [2].
Pain Visual Analog Scale (VAS) NRS (0-10)	Questionnaire	Recorded at every visit (at enrolment and during observation), patient-reported information.
Global Health Visual Analog Scale (VAS) NRS (0-10)	Questionnaire	Recorded at every visit (at enrolment and during observation), patient-reported information.
Funktionsfragebogen Hanover FFbH (% of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain)	Questionnaire	Recorded at every visit (at enrolment and during observation), patient-reported information.
28 Tender Joint Count	Questionnaire	Recorded at every visit (at enrolment and during observation).
28 Swollen Joint Count	Questionnaire	Recorded at every visit (at enrolment and during observation).
C-reactive protein (CPR) (mg/liter)	Questionnaire	Recorded at every visit (at enrolment and during observation).
Erythrocyte sedimentation rate (ESR) (mm/h)	Questionnaire	Recorded at every visit (at enrolment and during observation).
Rheumatoid factor positive [Y/N]	Questionnaire	Recorded at enrolment.
RA disease duration [<5/ ≥5 years]	Calculation	Will be calculated by using year of symptom onset and year of treatment initiation.
History of joint replacement surgery [Y/N]	Questionnaire	As recorded in the questionnaire
Year of treatment start [before 30 June 2021 / 30 June 2021 and afterwards]	Questionnaire	Every initiation of a DMARD treatment is registered with the date of treatment start.

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Table 2. Definitions of baseline patient characteristics for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, Erythrocyte sedimentation rate; FFbH, Funktionsfragebogen Hanover; HAQ, Health Assessment Questionnaire; *NRS, numeric rating scale;* VAS, Visual Analog Scale

Definition of potential confounders that are measured and will be accounted for in the adjusted Cox regression in the final report (secondary analysis) are provided in Table 3. A detailed descriptions which confounders will be included in specific Cox regression models is provided in Table 10.

Table 3. Definitions of confounders for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
Age at index date	Questionnaire	Year of birth is recorded at enrolment. Every initiation of a DMARD treatment is registered with the date of treatment start. Age at index date will be calculated by using year of birth and year of treatment initiation.
Sex [male/female]	Questionnaire	Recorded at enrolment, coded as male and female.
Years since symptom onset	Calculation	Will be calculated by using year of symptom onset and year of treatment initiation.
Previous use of b/tsDMARDs [0/ 1/ ≥2]	Questionnaire	Recorded until index. Variable is a composite from information at enrolment and during observation.
History of COPD [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of chronic renal disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
CV risk factors [0/ ≥1]	Calculation	CV risk factors are defined as history of or current diabetes, history of hyperlipidemia, history of or current

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Table 3. Definitions of confounders for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition
		hypertension, history of or current coronary heart disease.
History of diabetes mellitus [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of heart failure [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of coronary heart disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
Obesity [Y/N]	Calculation	Obesity is defined as BMI $\geqslant$30 kg/m^2. BMI is calculated by weight and height. Both are recorded at enrolment.
Dosage of concomitant use of glucocorticoids [<5, 5-<10, ≥ 10 mg/d]	Questionnaire	Recorded at every visit (at enrolment and during observation).
Smoking [current/previous/never]	Questionnaire	Recorded at enrolment, patient-reported information.
DAS28-ESR	Questionnaire	Calculated by using the following information, which is recorded at every visit (at enrolment and during observation): 28 counts of swollen and tender joints, ESR in mm/h, patient global health NRS (0-10).
FFbH (% of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain)	Questionnaire	Recorded at every visit (at enrolment and during observation), patient-reported information.
Rheumatoid factor and/or ACPA positive [Y/N]	Questionnaire	Recorded at enrolment.
Year of treatment start (before 30 June 2021, 30 June 2021 and afterwards)	Questionnaire	Every initiation of a DMARD treatment is registered with the date of treatment start.

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Table 3. Definitions of confounders for the final report.

Variable [including categories if applicable]	Data source(s)	Operational definition

Abbreviations: NRS, numeric rating scale

To facilitate the evaluation of the primary endpoint of VTE, the following VTE risk factors will be evaluated at baseline as specified in Table 4.

Table 4. Definitions of VTE Risk Factors.

Variable [including categories if applicable]	Data source(s)	Operational definition
Age at index date	Questionnaire	Year of birth is recorded at enrolment. Every initiation of a DMARD treatment is registered with the date of treatment start. Age at index date will be calculated by subtracting the year of birth from the year of treatment initiation.
History of diabetes mellitus [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of heart failure [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of malignancy [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of hypertension [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.

To facilitate the evaluation of the safety endpoints of MI and MACE, CV risk factors will also be evaluated at baseline (Table 5).

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Table 5. Definitions of CV risk factors.

Variable [including categories if applicable]	Data source(s)	Operational definition
Age at index date	Questionnaire	Year of birth is recorded at enrolment. Every initiation of a DMARD treatment is registered with the date of treatment start. Age at index date will be calculated by using year of birth and year of treatment initiation and age ≥65 years is defined as risk factor
History of or current diabetes mellitus [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of chronic renal disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of hyperlipidemia [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of hypertension [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.
History of coronary heart disease [Y/N]	Questionnaire	Comorbid conditions are indicated by the rheumatologist at enrolment and regularly during observation (every 2.5 years). They are reported as “no comorbidity” or as underlying comorbidity on a pre-defied list.

To facilitate the evaluation of the malignancy outcomes, the following malignancy risk factors will be evaluated at baseline as specified in Table 6.

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Table 6. Definitions of malignancy risk factors.

Variable	Data source(s)	Operational definition
Age at index date	Questionnaire	Year of birth is recorded at enrolment. Every initiation of a DMARD treatment is registered with the date of treatment start. Age at index date will be calculated by using year of birth and year of treatment initiation and age ≥65 years is defined as risk factor
Sex [male/female]	Questionnaire	Recorded at enrolment, coded as male and female.
smoking	Questionnaire	never vs. ever smokers.
Obesity [Y/N]	Calculation	Obesity is defined as BMI ≥30 kg/m^2. BMI is calculated by weight and height. Both are recorded at enrolment.

No effect measure modifiers are defined, but for specific outcomes results will be presented stratified by specified characteristics (see section 4.2.2).

4.4. Data sources

The German Biologics Register RABBIT has been active since May 2001 under the auspices of the “Kompetenznetz entzündlich-rheumatische Systemerkrankungen” (“Competence Network Rheumatology”). The content of the original study protocol (ie, not the PASS protocol) as well as the extension protocol was agreed with the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology). Physicians aiming at taking part in RABBIT must sign a contract with the DRFZ. There is no influence on any treatment decision from the principal investigators, scientific advisory board or pharmaceutical companies sponsoring the study. Participating patients have provided informed consent, have a diagnosis of RA, have age at onset of RA at age 16 or older, be 18 year of age or older at the time of enrollment, and have initiated of an approved therapy for the treatment of RA (either a bDMARD, tsDMARD, or a csDMARD after at least 1 prior DMARD). Note that until 2016 at least 4 out of the 7 criteria of the American College of Rheumatology (ACR) must have been fulfilled. Since 2017, a rheumatologist confirmed diagnosis of RA is required including the indication of the number of ACR criteria fulfilled.

Core baseline and follow up data, including patient demographics, disease characteristics, and treatment will be based on data from the RABBIT register.

In RABBIT, outcome parameters and covariates are assessed by physicians and/or patients as applicable, on pre-defined case report forms (CRF). Data is reported at predefined time points of follow-up (enrolment/baseline, at 3 and 6 months, thereafter every 6 months). Details are given in Table 7. Once enrolled, patients are followed regardless of treatment changes, treatment cessation or treatment initiation. The type of the treatment administered, and the conduct of individual therapy, including dosages, is solely determined by the treating

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physician in agreement with the patient. After five years of observation, observation time can be extended for another five years, if the patient consents.

Table 7. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort

Follow-up visits (t)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Month of follow-up	0	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Date of visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient characteristics																						
Year of birth, sex, height	x																					
Rheumatoid factor, Erosive joint alterations, Rheumatoid nodules	x																					
Date of symptom onset	x																					
Comorbidities	x						x					x					x					x
Smoking habits (patient), weight	x			x		x		x		x		x		x		x		x		x		x
Treatment																						
Start/end of DMARDs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reasons for treatment change		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Anti-rheumatic comedications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, other outcomes																						
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy including outcome				x		x		x		x		x		x		x		x		x		x
Side effects (patient)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease activity																						
ESR, CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
28 Swollen/ tender joint counts	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morning stiffness	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

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Table 7. Assessments at study enrolment (t0) and follow-up visits (t1 to t21) in the RABBIT cohort

Disease activity, NRS scale (physician)*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Functional capacity (FFbH) (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain severity, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fatigue severity, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
General health state, NRS scale (patient)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

X = measured variable at the indicated visit. All measurements are reported by the physician if not otherwise indicated.

**Physician reported disease activity was added to the questionnaires in 2013.*

Abbreviations: CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; FFbH = Hanover Functional Status Questionnaire; NRS = numeric rating scale.

All serious and non-serious events occurring during the observation are regularly reported from the rheumatologist and captured in the register (with judgement from the rheumatologist on: severity (mild, moderate, severe; and causality to given medication). For events of special interest detailed queries are sent out, to get more information on the events (and additional discharge letters from hospitals, or results from biopsies, etc.).

Per RABBIT policy, AE and serious AEs (SAE) will be recorded according to the International Council for Harmonisation (ICH) guidelines. Therefore, any untoward medical occurrence observed in a patient has to be reported as AE. The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect has to be reported as SAE. These definitions of AEs and SAEs are also provided in the case report forms (CRFs). For non-serious AEs, severity grading will be performed according to the recommendations of the Outcome Measures in Rheumatology (OMERACT) Toxicity Working Group. For the coding of AE and SAE the MedDRA dictionary will be used on the PT level. It is intended to update the AE/SAE database with every update of MedDRA.

There is no possibility to link RABBIT data with any other data due to strict data protection rules and due to the fact that there is no national cancer register or death register with the possibility of linkage. However, all events are carefully monitored and several national offices are sometimes contacted to get more information.

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Patients provide written informed consent before study entry. The original study protocol was approved on 1 March 2001 by the ethics committee of the Charité University Medicine, Berlin, Germany (Protocol number 1508/2001). A revised and updated study protocol received approval on 5 July 2021 (Protocol number EA4/123/21).

Further details are given in the RABBIT study protocol EA4/123/21. This document is not publicly available and cannot be included here.

4.5. Sample size and power calculations

This active surveillance study is not intended to test a single pre-specified statistical hypothesis. The size of the active surveillance population depends largely on use of tofacitinib in Germany. The targeted sample size for tofacitinib-treated patients is 500. Enrolment will not be capped at 500 but continue throughout the study period.

The bDMARD and csDMARD populations used to contextualize event rates are well-established.

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

Table 8 and Table 9 below describe the power to detect a 2-fold difference in event rates between tofacitinib-initiators and bDMARD-initiators using the following definitions:

- α=0.05;
- 3 different bDMARD-treated patient population sizes (reflecting roughly range of EU registers): n=11100, n=5050, n=1650;
- 4 different tofacitinib-treated patient population sizes: n=100, n=250, n=500, n=1000;
- Estimated rates on bDMARD of
    - 30/1000 person years (PY) (e.g., serious infection),
    - 10/1000 PY (e.g., malignancy excluding NMSC), and
    - 6/1000 PY (e.g., major adverse cardiovascular events (MACE) based on previous analysis with registers (Pfizer, internal data);

And the following assumptions:

- 7-year study period;
- Constant rate of accrual;
- 5% annual loss to follow up among tofacitinib-treated patients.

Additionally, Table 8 assumes an annual switch rate of 0 % for 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 9 assumes an annual switch rate of 30 % from tofacitinib to a bDMARD over the study period, as previously demonstrated in the EU for bDMARDs in Italy (Eposti, 2016).

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 8), while 500 tofacitinib exposed patients would be nearly sufficient if 30% of tofacitinib treated patients switched off of tofacitinib annually.

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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 8). 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 8) a sample size of 1000 tofacitinib patients within a registry with more than 5000 bDMARD patients would be required to make well-powered comparison. In a scenario with a 30% annual rate of switching off of tofacitinib, 1000 tofacitinib treated patients and 11 100 bDMARD patients would only provide 40% power to detect a 2-fold difference (Table 9).

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

Table 8. 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

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Table 9. 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 16 months of enrolment of tofacitinib-exposed patients in RABBIT, 558 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

4.6.1. Interim reports

In the interim reports, no information on number and proportion of missing data will be provided and no imputation of missing values will be performed.

4.6.2. Final report

In the final report, proportion of missing data will be provided for the main baseline variables and no imputation of missing values will be performed in the baseline tables.

For all confounders (Table 10), missing information will be assumed to be missing at random and is addressed by tenfold imputation. The multiple imputation will be performed by regression with fully conditional specification, including the covariates from Table 10 and the outcome. Statistical analyses will then proceed as normal for the multiple imputation strata and, results for the individual strata will be combined employing Rubin's rules. The robust sandwich variance estimator will be used for all Cox models to reduce the impact of the additional variance of the imputation method as well as of dependencies between treatment episodes of the same patient on the estimates.

When the date of an occurrence of an event is missing, the start date is assigned as the midpoint between the last two follow-up visits if the event did not lead to the death of the

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patient. If the event did lead to the death of the patient, the start date was assigned as the day of death. When the start or end date of a therapy was missing, the missing start or end date was estimated as the midpoint between the last two follow-up visits, or if another therapy was given, the date is estimated as just before or after the additional therapy, so that a parallel therapy of several b/tsDMARDs is avoided. When a therapy ended due to the patient's death, a missing end date is set to the day of death.

4.7. Statistical methodology and analyses

4.7.1. Index date and follow-up

The index date is the date of a new initiation of a drug from one of the drug-defined exposure cohorts (eg, new initiation of tofacitinib in the tofacitinib exposed cohort) if there is no exposure of the active substance 365 days prior to the new initiation. Patients who switch to a subsequent therapy from another exposure cohort are eligible for this other cohort (except for ever-exposed regression models). The date of initiation of this subsequent therapy is then referred to as index date within this subsequent exposure cohort. Information on censoring is given in Section 4.7.1.1 for the interim reports and 4.7.1.2 for the final report.

In the final report, if patients in the tofacitinib cohort or in the bDMARD cohort augment their initial treatment by initiating concomitant use of a csDMARD after cohort entry, they will maintain their initial cohort assignment (rather than being re-assigned to the nbDMARD cohort).

Events will be allocated to a treatment exposure cohort if the event occurs during the time at risk of the respective cohort.

4.7.1.1. Interim reports

Tofacitinib cohort (main cohort):

For patients initiating a treatment with tofacitinib, different definitions for the time at risk will be applied:

- **On-drug approach ("censoring at switch approach"; "censor follow-up time after a switch to a different treatment"):** Time at risk will be calculated from drug initiation until the stop of the respective drug treatment or switch to another therapy, death, loss to follow-up, or end of study, whichever occurs first. This approach will be applied to outcomes 1 to 16 listed in section 4.3.2.
- **Ever-exposed approach ("treatment at any time", "once exposed always at risk"):** Time at risk will be calculated from drug initiation at enrolment or during follow-up until the occurrence of death, loss to follow-up, or end of study, whichever occurs first. A patient is considered as once exposed, always at risk, despite stop of the respective drug treatment or switching to another drug during follow-up observation. This approach will be applied to outcomes 17 to 19 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy and one month before conception for women, and for men (for whose partner a pregnancy is reported) two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

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nbDMARD cohort – b/tsDMARD-naive cohort:

- **On-drug approach ("censoring at switch approach"; "censor follow-up time after a switch to a different treatment"):** Time at risk will be calculated for patients on a nbDMARD treatment as mono- or combination therapy but not in combination with a bDMARD or a tsDMARD from drug initiation until the initiation of a bDMARD or a tsDMARD during follow-up observation, death, loss to follow-up, or end of study, whichever occurs first. Time at risk will continue if patients stop csDMARDs and remained without any DMARD therapy. This approach will be applied to outcomes 1 to 16 listed in section 4.3.2.
- **Intention-to treat (ITT):** Time at risk will be calculated from drug initiation at enrolment until the occurrence of death, loss to follow-up, or end of study, whichever occurs first. A patient is considered as exposed despite stop of the respective drug treatment or switching to another drug during follow-up observation. This approach will be applied to outcomes 17 to 19 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy and one month before conception for women, and for men two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

nbDMARD cohort – not b/tsDMARD-naive cohort :

For nbDMARD cohort, the index date is the date 3 months after the discontinuation of a bDMARD or a tsDMARD (9 months after discontinuation of Rituximab).

- **On-drug approach ("censoring at switch approach"; "censor follow-up time after a switch to a different treatment"):** Patients will be eligible for inclusion if previously exposed to bDMARD or tsDMARD and received no bDMARD or tsDMARD for at least 4 months (10 months for rituximab). Time at risk will be calculated from months 4 (month 10 for rituximab) after stop of the b/tsDMARD until the initiation of a bDMARD or a tsDMARD during follow-up observation, death, loss to follow-up, or end of study, whichever occurs first. Time at risk will continue if patients stop nbDMARDs and remained without any DMARD therapy. This approach will be applied to outcomes 1 to 16 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy and one month before conception for women, and for men two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

4.7.1.2. Final report

Tofacitinib cohort (main cohort):

For patients initiating a treatment with tofacitinib, different definitions for the time at risk will be applied:

- **On-drug approach ("censoring at switch approach"; "censor follow up time after a switch to a different treatment"):** Time at risk will be calculated from drug initiation until the first occurrence of the event of interest, the discontinuation of the respective drug treatment or switch to another therapy, death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. This approach will be applied to outcomes 1 to 16 as primary analysis and to outcomes 17 to 19, as secondary analysis (listed in section 4.3.2).

- **Ever-exposed approach ("once exposed always at risk"):** Time at risk will be calculated from drug initiation until the first occurrence of the event of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. A patient is considered as once exposed, always at risk, despite stop of the respective drug treatment or switching to another drug. This approach will be applied as primary analysis to outcome 19 listed in section 4.3.2.
- **Ever-exposed approach plus latency period ("once exposed, always at risk"):** Time at risk will be calculated from the day six months after drug initiation until the first occurrence of the event of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. A patient is considered as once exposed, always at risk, despite stop of the respective drug treatment or switching to another drug. The latency period of 6 months after treatment initiation is respected to take into account the delayed onset of malignancy outcomes and to prevent reverse causation. This approach will be applied as primary analysis to outcomes 17 and 18 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy (no additional risk window is added after the end of pregnancy) and one month before conception for women, and for men two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

bDMARD cohort:

For patients initiating a treatment with bDMARD, different definitions for the time at risk (PY) will be applied:

- **On-drug approach ("censoring at switch approach"; "censor follow up time after a switch to a different treatment"):** Time at risk will be calculated from drug initiation until the first occurrence of the event of interest, the stop of the respective drug treatment or switch to another therapy, death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. This approach will be applied to outcomes 1 to 16 as primary analysis and to outcomes 17 to 19, as secondary analysis (listed in section 4.3.2).
- **Ever-exposed approach ("once exposed always at risk"):** Time at risk will be calculated from drug initiation until the first occurrence of the event of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. A patient is considered as once exposed, always at risk, despite strop of the respective drug treatment or switching to another drug. This approach will be applied as primary analysis to outcome 19 listed in section 4.3.2.
- **Ever-exposed approach plus latency period ("once exposed, always at risk"):** Time at risk will be calculated from the day six months after drug initiation until the first occurrence of the event of interest, the occurrence of death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. A patient is considered as once exposed, always at risk, despite stop of the respective drug treatment or switching to another drug. The latency period of 6 months after treatment initiation is respected to take into account the delayed onset of malignancy outcomes and to prevent reverse causation. This approach will be applied as primary analysis to outcomes 17 and 18 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy (no additional risk window is added after the end of pregnancy) and

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one month before conception for women, and for men two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

nbDMARD cohort:[5]

- For the nbDMARD cohort, only the **on-drug approach** is used. For patients on a nbDMARD treatment as mono- or combination therapy (i.e., a therapy involving more than one nbDMARD) but not in combination with a bDMARD or a tsDMARD, the time at risk will be calculated as current exposure starting from drug initiation until the first occurrence of the event of interest, the initiation of a bDMARD or tsDMARD, death, loss to follow-up, end of study, or 7 years of follow-up, whichever occurs first. Time at risk will continue if patients stop nbDMARDs and remain without any DMARD therapy. This approach will be applied to outcomes 1 to 19 listed in section 4.3.2.
- **Exposure during pregnancy:** Time at risk will be calculated if the patient was exposed during pregnancy (no additional risk window is added after the end of pregnancy) and one month before conception for women, and for men two months before conception. This approach will be applied to outcome 20 listed in section 4.3.2.

4.7.2. Risk window definitions

4.7.2.1. Interim reports

Tofacitinib cohort (main cohort):

A 90-day risk window will be applied to the on-drug approach. Starting with the first month after discontinuation, an additional three months of exposure (90-day risk window) will be added when using the on-drug approach.

nbDMARD cohorts:

The duration of follow up within the nbDMARD cohort does not rely on a 90-day risk window or the once-exposed at-risk paradigm.

4.7.2.2. Final report

Tofacitinib cohort (main cohort):

A 90-day risk window will be applied to the on-drug approach. Starting with the first month after discontinuation, an additional three months of exposure (90-day risk window) will be added when using the on-drug approach. For the ever exposed and ever exposed plus latency period approaches, an additional risk window after exposure is not applicable since exposure extends until end of follow-up (see section 4.7.1.2). For the exposed during pregnancy approach, no risk window is added after the end of pregnancy.

bDMARD cohort:

A 90-day risk window will be applied to the on-drug approach. Starting with the first month after discontinuation, an additional three months of exposure (risk window) will be added. For medications containing rituximab, a risk window of nine months will be added due to its

[5] The nbDMARD cohort is designed hierarchically as the complement to b/tsDMARD treatment, i.e., patients contribute to the nDMARD cohort only when they are not exposed to b/tsDMARD treatment at the same time. Since with an ever exposed approach the prolonged nbDMARD exposure overlaps with the following bDMARD or tofacitinib treatment, no ever exposed approach is implemented for this cohort.

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pharmacologic properties (depletion of B-cells) when using the on-drug approach. For the ever exposed and ever exposed plus latency period approaches, an additional risk window after exposure is not applicable since exposure extends until end of follow-up (see section 4.7.1.2). For the exposed during pregnancy approach, no risk window is added after the end of pregnancy.

nbDMARD cohort:

The duration of follow up within the nbDMARD cohort does not rely on any risk window or the once-exposed at-risk paradigm.

Tofacitinib and bDMARD cohorts:

The on drug approach will be implemented applying the censor at switch principle: 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 only events prior to the new medication start will be assigned to the discontinued medication. For regression models, as a sensitivity analysis, initiation of the new medication will not stop the 90-day risk window, and follow-up time and events occurring after the switch will be attributed to prior therapy and not current therapy.

Under the once exposed always at risk approach, events will be double-counted for incidence rates 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 PY since index date to the respective cohorts. For regression analyses, under the once exposed always at risk approach events will only be assigned to the first considered treatment episode of a patient.

Unless noted otherwise, assignment of exposure time and events to treatments will be handled as described for both incidence rates and Cox regression models.

4.7.3. Primary analyses

4.7.3.1. Interim reports

Patient descriptive characteristics – Baseline characteristics (see **Appendix Table 1A**)

The following summary measures will be calculated for all cohorts:

- mean with standard deviation or median with interquartile range for continuous variables or
- counts and their respective proportion for categorical variables

All treatment exposure cohorts will be described at the time of enrolment into the study (every patient counts only once).

Event rates (see **Appendix Table 2A**)

Event rates will include all events (ie, patients who experience the event of interest will not be censored at the first event per patient group). Crude event rates, which can include multiple safety events of interest per patient, and corresponding 95% confidence intervals

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(CIs) per 1000 PY will be estimated. ERs for all safety endpoints except for pregnancies and adverse pregnancy outcomes will be presented as

- cumulative number of events during the time at risk,
- percentage of patients at risk with events,
- total PY,
- female PY,
- male PY,
- ER per 1,000 PY and
- 95% confidence interval for the ER.

The calculation of PY is based on the sum of the months at risk per patient and exposure cohort divided by twelve. For estimating ERs, patients who experience the event of interest will not be censored at the first event per patient per exposure cohort. To estimate corresponding confidence intervals, a Poisson distribution will be assumed.

Pregnancy outcomes (see **Appendix Table 3**)

Pregnancy and events associated with pregnancies will be investigated descriptively and given as frequencies.

Pregnancies will be assigned to the treatment at time of conception and/or one month prior to conception. Number of pregnancies reported for pregnant patient with RA, and also pregnancies of partners will be shown.

Events associated with pregnancies will be described only for pregnant patients.

For all study cohorts, the following variables will be estimated:

- For pregnancies where the pregnant patient is exposed: number of total pregnancies, twin pregnancies, pregnancy outcomes (live births; abortion, fetal death, stillbirth; unknown outcome), pregnancy-related events (serious and non-serious pregnancy events (e.g., gestational diabetes, preeclampsia), serious and non-serious neonatal events);
- For pregnancies with partner exposure: total number of pregnancies, twin pregnancies, pregnancy outcomes (live births; abortion, fetal death, stillbirth; unknown outcome).

4.7.3.2. Final report

Patient descriptive characteristics – Baseline characteristics (see **Appendix Table 1Ba – 1Bd**)

The following summary measures will be calculated for all cohorts:

- median with interquartile range or mean with standard deviation for continuous variables or
- counts and their respective proportion for categorical variables
- missing (n, (%)) (for both continuous and categorical variables)

All treatment exposure cohorts will be described

(I) at the time of enrolment into the study (every patient counts only once) and

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(II) at the time of the start of a new treatment either at enrolment or during follow-up observation. In the latter case, every new treatment start will be considered as baseline. This implies that patients can contribute to several exposure cohorts during the time of observation, and also several times to one exposure cohort.

Baseline characteristics will presented overall and stratified by

a. The number of previous b/tsDMARD (0, 1, >=2)

b. Prior use of non-tofacitinib JAK-inhibitor therapy (0, >0)

c. Mono vs. combo therapy with csDMARDs, specifically MTX

Incidence rates (see **Appendix Table 2B**)

Incidence rates will be restricted to the first event per patient per exposure group (ie, patients who experience the event of interest within one exposure cohort will be censored at the first event, however, further events after switch to another exposure cohort will be counted). Crude incidence rates (IR) per 1000 PY and corresponding 95% CIs will be estimated. The cumulative number of incident events will also be tabulated for each cohort and safety event of interest. IRs for all safety endpoints except for pregnancies and adverse pregnancy outcomes will be presented as:

- cumulative number of incident events during the time of observation,
- total PY,
- female PY,
- male PY,
- total mean follow-up time (in years),
- crude IR per 1,000 PY,
- 95% confidence interval for the IR,
- Age-sex standardized IR per 1,000 PY and
- 95% confidence interval for the IR.

The calculation of PY is based on the sum of the months at risk per patient and exposure cohort divided by twelve. To estimate corresponding confidence intervals, a Poisson distribution will be assumed.

In addition, the final report will include the number of tofacitinib-exposed pregnancies (**Appendix Table 3**). Pregnancy and events associated with pregnancies will be investigated descriptively and given as frequencies. Events associated with pregnancies will be described only for pregnant patient with RA.

4.7.4. Secondary analyses

4.7.4.1. Interim reports

Not applicable.

4.7.4.2. Final report

Pending feasibility, adjusted hazard ratios (HR) will be estimated with Cox proportional hazards regression models with a robust variance estimator (see **Appendix Table 4**). No Cox analyses will be conducted for outcomes of interest with less than five events in the main cohort (tofacitinib).

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For estimating HRs, patients who experience the event of interest will be censored at the first event. For all safety endpoints of interest, when prior medical history for a particular safety endpoint is collected by the registry, the prior documented history of that particular safety endpoint will be included as binary variable (Y/N) in the adjusted analysis for that specific endpoint, but not for other endpoints. At enrollment and then every 2.5 years, RABBIT collects medical history on the following conditions as comorbidity: hypertension, coronary heart disease, heart failure, cerebrovascular diseases (Apoplex/TIA/PRIND), hyperlipoproteinaemia, diabetes, malignant neoplasia, lymphoma/leucosis, chronic kidney diseases, psychological diseases/depression, and latent (inactive) TB. Adverse events are ascertained continuously after enrollment in RABBIT.

For all outcomes propensity scores (PSs) will be estimated and inverse probability of treatment weights (IPTW) as well as inverse probability of censoring weights (IPCW) will be used to control for potential confounding (see Table 10).

The comparisons to be made will be:

- Main cohort (tofacitinib) vs. bDMARD cohort
- Main cohort (tofacitinib) vs. nbDMARD cohort, whereas in the main cohort, patients with prior exposure to b/tsDMARDs will be excluded

Two PSs for each patient will be estimated using two multivariable logistic regression models, in which the outcome are set as a) the treatment received and b) the presence of censoring/dropout judged as informative. PSs will be estimated for each pair of treatment cohorts and for each safety event of interest separately. Variables included in the two PS models are presented in Table 10**.** For time-varying covariates, the measurements closest in time before the switch to the drug under investigation were used (defined as baseline for this drug). This allowed to control for factors that are proximally related to the treatment initiation (index date). Stabilized weights will be used to reduce variability induced by patients with large weights. The stabilized treatment (censoring) weights will be estimated by multiplying the original weights by the proportion of patients in the respective cohort depending on the treatment (censoring) status of the patient. Final weights will be obtained by multiplying the treatment and censoring weights. Additionally, weights below the 1% quantile and above the 99% quantile will be winsorized, i.e., set to the corresponding quantile. Histograms will be produced to visually depict the overlap in PS in the two treatments being compared. Standardized mean differences (SMD) will be used to compare the balance in baseline covariates between treatment exposure cohorts before and after weighting. The cut-off SMD value indicating substantial imbalance will be chosen as ±0.1 (10%). In case of substantial imbalance, the variable(s) in question will be added as covariates to the Cox proportional hazards regression model. Cox models will only be calculated if the amount of overfitting is acceptable. The amount of overfitting is deemed as acceptable if the number of covariables in the model is less than m/5, where m is the number of events for the considered outcome (see Vittinghoff, E., McCulloch, CE (2007), Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression, American Journal of Epidemiology, 165:710-718).

As described in section 4.7.1.2, four analytical approaches will be considered:

- On-drug approach: as primary analysis for non-malignancy and non-mortality outcomes except pregnancy outcomes, and secondary analysis for malignancy outcomes and all-cause mortality
- Ever-exposed approach: as primary analysis for all-cause mortality

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- Ever-exposed approach plus latency period: as primary analysis for all malignancy outcomes
- Exposed during pregnancy approach: for pregnancy outcomes

On-drug approach: The PSs will be estimated at the time of a treatment initiation to model treatment decisions. For treatments started at enrolment, data for covariates of the PSs will be taken from the enrolment visit. For treatments started during follow-up, data for covariates of the PSs will be taken from the visit date occurring most recently prior to the treatment start date. In other words, for time-varying covariates only covariates measured before or at the time of the new treatment start will be included when calculating PSs. This will allow to control for factors that are proximally-related to the treatment switch. Covariates affected by the treatment and assumed to be in the causal path from treatment to the safety event of interest (i.e., intermediate variables) will not be included in the logistic PS models as the total causal effect could not be consistently estimated in that case. A limitation of this approach is that due to censoring triggered by a treatment switch, effects of the discontinued treatment that may need longer time to develop may not be captured. Outcome-specific exclusions of patients will be done prior to calculation of the PS (e.g., exclusion of patients with prior heart failure to investigate incident heart failure). Treatment episodes will be included in the regression analysis by applying an extended Cox model based on adjustment at start of treatment episodes, i.e. a start–stop ('counting-process') data structure (Anderson-Gill) [3,4].

Ever-exposed approaches: The PSs will be estimated using data for the covariables from the time of the first treatment initiation during the inclusion period, which means that intermediate variables will not be included to avoid overadjustment bias. The reason for this decision is that adjustment for post-exposure variables could harm rather than improve the total effect estimate in terms of bias. Using the ever-exposed approach, the duration of treatment and how proximate the treatment was in relation to the safety event of interest are not accounted for (i.e., short-term treatments and treatments that occurred several months prior to an event are included). It is important to note that differences in follow-up time between treatment cohorts may be introduce bias. In the ever-exposed approach, PSs will be estimated per patient (and not per treatment episode as in the on-drug approach, below), and weighted Cox proportional hazard regression analyses will be used.

Unadjusted and adjusted Hazard Ratios (HRs) and 95% CIs will be estimated. Confounders for the Cox regression are given in Table 10. These confounders were selected a priori, in agreement with recommendations from the RABBIT scientific advisory board (and aligned with previous publications from RABBIT).

Three models will be run (Table 10):

Model A: crude/unadjusted,

Model B: age, sex (male vs. female)

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Model C: 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 Table 10.[6]

Table 10. Confounders for the Cox regression analysis for selected outcomes.

	Outcome					
	Infections (outcome 1, 2 and 3 listed in section 4.3.2)	**CV disease** (outcome 6 and 7 listed in section 4.3.2)	**VTE** (outcome 8 listed in section 4.3.2)	**Malignancy** (outcomes 17 and 18 listed in section 4.3.2)	**All-cause mortality** (outcome 19 listed in section 4.3.2)	**All other outcomes** (outcome 4,5,9 to 16, listed in section 4.3.2)
Model A	None (crude/ unadjusted)					
Model B	Age[# +] Sex (male vs. female)					
Model C	*General covariates*					
	Age[# +] Sex (male vs. female) RA disease duration[#] RF/ ACPA (no vs. yes)[$] Year of treatment start (before 30 June 2021, 30 June 2021 and afterwards) DAS28-ESR[#] FFbH[#] Previous b/tsDMARDs[*+] (0,1 vs. ≥ 2) Glucocorticoid dosage (<5 vs. 5-<10 / ≥ 10 mg/d) Smoking(never vs. ever)					
	Outcome-specific covariates					
	COPD (no vs. yes) Chronic renal disease (no vs. yes)	Obesity (no vs. yes) CV risk factors (0 vs. ≥1) [§]	Diabetes (no vs. yes) Prior heart failure (no vs. yes) prior malignancy prior hypertension	Obesity (no vs. yes)	Diabetes (no vs. yes) Chronic renal disease (no vs. yes) Prior heart failure (no vs. yes) Chronic heart disease (no vs. yes)	None

[6] RABBIT does not explicitly ascertain severity of disease. The considered covariates jointly should reflect severity of RA.

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Table 10. Confounders for the Cox regression analysis for selected outcomes.

All covariates without further specification of categories are captured as continuous variables.
#Added as continuous variable.
$Either positive for rheumatoid factor and or anti-citrullinated protein antibodies.
*Specific to comparator groups:

- bDMARD cohort: number of previous bDMARDs
- Comparison of tofacitinib patients that had been bionaive before starting tofacitinib with nbDMARD cohort , therefore previous b/tsDMARDs will be excluded from PS

§CV risk factors are defined as age ≥65 years, history of or current diabetes, history of hyperlipidemia, history of or current hypertension, history of or current coronary heart disease, history of chronic renal disease.
+ For some confounders, the RABBIT team may deem it necessary to change the way in which they are considered in the model, particularly for age and previous b/tsDMARDs. For instance, it may be necessary to account for nonlinear effects for age. For previous b/tsDMARDs, the mentioned categories might lead to considerable imbalances due to very different distributions of this confounders for the exposure groups, it might thus be necessary (e.g., to change the category definition).

Abbreviations: ACPA, anti-citrullinated protein antibodies; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DAS28, disease activity score based on 28 joints; FFbH, functional capacity measured by Hannover Functional Status Questionnaire; IPTW, inverse probability weights; PS, propensity score; RF, rheumatoid factor.

To adjust for confounding, only covariates measured before or at the time of the new treatment start were used. For time-varying covariates, the measurements closest in time before the switch to the drug under investigation were used (defined as baseline for this drug). This allowed to control for factors that are proximally related to the treatment initiation (index date).

4.7.5. Sensitivity analyses

4.7.5.1. Interim reports

Not applicable.

4.7.5.2. Final report

4.7.6. Additional analyses

For regression models, as a sensitivity analysis, initiation of the new medication will not stop the 90-day risk window, and follow-up time and events occurring after the switch will be attributed to prior therapy and not current therapy.

4.7.6.1. Interim reports

Patient characteristics and ERs will be stratified by sex (see section 4.2.2.1).

4.7.6.2. Final report

The subgroup analyses from section 4.2.2.2 will be provided in the final report.

Age/sex-standardized incidence rates will be estimated 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 following groups will be defined: women <65 years, women ≥65 years, men <65 years, men ≥65 years. Direct

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standardization is known to become unstable in case of categories with small numbers that may occur for some outcomes. Therefore, if there are less than four events in any of the groups, an indirect standardization approach using the combined cohorts as standard will be used instead.

4.7.7. Post-hoc analyses

4.7.7.1. Interim reports

Not applicable.

4.7.7.2. Final report

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. The details of the meta-analytic methods are beyond the scope of this SAP and will be documented in a separate meta-analysis SAP. The meta-analysis will be handled by a different team in Pfizer, separate from the RABBIT team.

5. REFERENCES

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmunity reviews. 2005;4(3):130-6.
2. Lautenschlager J, Mau W, Kohlmann T, et al. [Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire]. Zeitschrift fur Rheumatologie. 1997;56(3):144-55.
3. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. The Annals of Statistics. 1982;10(4):1100-20.
4. Cheung YB, Xu Y, Tan SH, et al. Estimation of intervention effects using first or multiple episodes in clinical trials: The Andersen-Gill model re-examined. Stat Med. 2010;29(3):328-36.

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6. APPENDICES

Interim reports: Baseline characteristics will be shown overall and stratified by sex

APPENDIX TABLE 1A. Baseline Characteristics of Tofacitinib-Exposed and nbDMARD Cohorts

Baseline characteristics	Tofacitinib-Exposed Cohort			nbDMARD Cohort		
	Females (n=)	Males (n=)	Total (n=)	Females (n=)	Males (n=)	Total (n=)
Age: mean (SD)						
Years since symptoms onset: mean (SD)						
median						
Global Health VAS: mean (SD) (NRS 0 to 10)						
Pain VAS: mean (SD) (NRS 0 to 10)						
FFbH(% of full function by Hanover Functional Status Questionnaire, version polyarthritis and back pain): mean (SD)						
DAS28: mean (SD)						
median						
28 Tender Joint Count: mean (SD)						
28 Swollen Joint Count: mean (SD)						
CRP (mg/liter): number tested						
mean (SD)						
median						
ESR (mm/1h): number tested						
mean (SD)						
median						
Rheumatoid factor positive: N (%)						
Dose of Glucocorticoids, average over 6 months: mean (SD)						
Patients with previous b- and tsDMARDs: N (%)						
Number of previous b- and tsDMARDs: mean (SD)						
Number of previous csDMARDS: mean (SD)						
No comorbidity: N (%)						
One comorbidity: N (%)						
Two comorbidities: N (%)						
Three or more comorbidities: N (%)						

This cohort is composed of patients exposed to tofacitinib at the time of enrolment.
Abbreviations: SD=standard deviation, VAS= visual analog scale, NRS= numbers, FFbH= Hannover Functionality, DAS28= Disease activity score 28, mg= milligram, mm/1h= millimeter / 1 hour, b and tsDMARD = biologic and targeted synthetic disease modifying antirheumatic drugs, csDMARD = conventional synthetic disease modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein

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Final report: Baseline characteristics will be shown overall and stratified by

- the number of previous b/tsDMARDs (0, 1, ≥2) for main cohort and the bDMARD cohort
- by prior use of non-tofacitinib JAK-inhibitor therapy (0; >0) for main cohort and the bDMARD cohort
- monotherapy vs. combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs), specifically MTX.

NOTE: Appendix Table 1Ba, **Appendix Table 1Bb**, **Appendix Table 1Bc** and **Appendix Table 1Bd** will be populated twice each, once for treatment starts at enrolment or during follow-up and once only for treatment starts at enrolment.

Appendix Table 1Ba: Baseline Characteristics overall

	Main cohort	Comparator cohorts	
Status at entry	Tofacitinib (n=)	bDMARD (n=)	nbDMARD (n=)
Demographics			
Age (median (IQR))			
Female sex N (%)			
Disease-related characteristics			
Year of treatment start [before 30 June 2021, 30 June 2021 and afterwards] (N (%))			
Rheumatoid factor positive (N (%))			
Rheumatoid factor positive missing (N (%))			
Number of features listed in 1987 ACR for RA (median (IQR))			
Number of features listed in 1987 ACR criteria for RA missing (N (%))			
Calendar year of recalled RA symptom onset [< 1990, ≥ 1990 and < 2000, ≥ 2000 and < 2007, ≥ 2007 and < 2017, ≥ 2017]			
Calendar year of recalled RA symptom onset missing (N (%))			
Years since symptom onset (i.e., disease duration) (median (IQR))			
Disease duration missing (N (%))			
Disease duration [<5/>=5 years] (N (%))			
DAS28-ESR (median (IQR))			
DAS28-ESR missing (%)			
HAQ (median (IQR))			
HAQ missing N (%)			
Patients with Previous cs/b/tsDMARDS (N (%))			
Patients with Previous cs/b/tsDMARDS missing (N (%))			

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Appendix Table 1Ba: Baseline Characteristics overall

	Main cohort	Comparator cohorts	
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure N (%)			
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure missing N (%)			
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)			
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)			
Patients with previous bDMARDs (N (%))			
Patients with previous bDMARDs missing N (%)			
Number of previously used bDMARDs (mean (SD))			
Patients with previous tsDMARDs (N (%))			
Patients with previous tsDMARDs missing N (%)			
Number of previously used b/tsDMARDs [0/ 1/ ≥2] (N (%))			
Number of previously used b/tsDMARDs missing N (%)			
Number of previously used csDMARDs (mean (SD))			
Number of previously used csDMARDs missing N (%)			
Concomitant csDMARDs (N (%))			
Concomitant csDMARDs missing N (%)			
Concomitant MTX (N (%))			
Concomitant MTX missing N (%)			
Concomitant oral steroids (N (%))			
Oral steroids missing N (%)			
Dose of concomitant Glucocorticoids [<5, 5-<10, ≥ 10 mg/d] (N (%))			
Dose of concomitant Glucocorticoids missing N (%)			
Concomitant NSAIDs (N (%))			
Concomitant NSAIDs missing N (%)			

Appendix Table 1Ba: Baseline Characteristics overall

	Main cohort	Comparator cohorts	
Global Health (NRS 0 to 10) (mean (SD))			
Global Health missing N (%)			
Pain (NRS 0 to 10) (mean (SD))			
Pain missing N (%)			
FFbH (median (IQR))			
FFbH missing N (%)			
28 Tender Joint Count (median (IQR))			
28 Tender Joint Count missing N (%)			
28 Swollen Joint Count (median (IQR))			
28 Swollen Joint Count missing N (%)			
CRP (mg/liter) (median (IQR))			
CRP missing N (%)			
ESR (mm/1h) (median (IQR))			
ESR missing N (%)			
Smoking			
Current (N (%))			
Previous (N (%))			
Never (N (%))			
Missing N (%)			
Disease history			
Malignancies (N (%))			
Lymphoma (N (%))			
Tuberculosis (N (%))			
Joint replacement surgery (N (%))			
COPD (N (%))			
Diabetes mellitus (N (%))			
Hypertension (N (%))			
CHD (N (%))			
CKD (N (%))			
Heart failure (incl. CHF) (N (%))			
Comorbidities			
Number of comorbidities (mean (SD))			
No comorbidity (N (%))			
One comorbidity (N (%))			
Two comorbidities (N (%))			
Three or more comorbidities (N (%))			

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Appendix Table 1Ba: Baseline Characteristics overall

	Main cohort	Comparator cohorts

Abbreviations: ACR, American College of Rheumatology; F, Female; M, Male; T, Total; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire, DMARDs, disease modifying antirheumatic drugs, NSAIDs, non-steroidal anti-inflammatory drugs; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MTX, methotrexate; SD, standard deviation; NRS, numbers; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; mg, milligram; mm/1h, millimeter / 1 hour; b and tsDMARD, biologic and targeted synthetic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs

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Appendix Table 1Bb: Baseline Characteristics stratified by the number of previous b/tsDMARDS

	No previous b/tsDMARDs		one previous b/tsDMARDs		≥ 2 previous b/tsDMARDs	
Status at entry	Tofacitinib (n=)	bDMARD (n=)	Tofacitinib (n=)	bDMARD (n=)	Tofacitinib (n=)	bDMARD (n=)
Demographics						
Age (median (IQR))						
Female sex N (%)						
Disease-related characteristics						
Year of treatment start [before 30 June 2021, 30 June 2021 and afterwards] (N (%))						
Rheumatoid factor positive (N (%))						
Rheumatoid factor positive missing (N (%))						
Number of features listed in 1987 ACR for RA (median (IQR))						
Number of features listed in 1987 ACR criteria for RA missing (N (%))						
Calendar year of recalled RA symptom onset [< 1990, ≥ 1990 and < 2000, ≥ 2000 and < 2007, ≥ 2007 and < 2017, ≥ 2017]						
Calendar year of recalled RA symptom onset missing (N (%))						
Years since symptom onset (i.e., disease duration) (median (IQR))						
Disease duration missing (N (%))						
Disease duration [<5/>=5 years] (N (%))						
DAS28-ESR (median (IQR))						
DAS28-ESR missing (%)						

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Appendix Table 1Bb: Baseline Characteristics stratified by the number of previous b/tsDMARDS

HAQ (median (IQR))						
HAQ missing N (%)						
Patients with Previous cs/b/tsDMARDS (N (%))						
Patients with Previous cs/b/tsDMARDS missing (N (%))						
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure N (%)						
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure missing N (%)						
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)						
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)						
Patients with previous bDMARDs (N (%))						
Patients with previous bDMARDs missing N (%)						
Number of previously used bDMARDs (mean (SD))						
Patients with previous tsDMARDs (N (%))						
Patients with previous tsDMARDs missing N (%)						
Number of previously used csDMARDs (mean (SD))						

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Appendix Table 1Bb: Baseline Characteristics stratified by the number of previous b/tsDMARDS

Number of previously used csDMARDs missing N (%)						
Concomitant csDMARDs (N (%))						
Concomitant csDMARDs missing N (%)						
Concomitant MTX (N (%))						
Concomitant MTX missing N (%)						
Concomitant csDMARDs (N (%))						
Concomitant csDMARDs missing N (%)						
Concomitant MTX (N (%))						
Concomitant MTX missing N (%)						
Concomitant oral steroids (N (%))						
Oral steroids missing N (%)						
Dose of concomitant Glucocorticoids [<5, 5-<10, ≥ 10 mg/d] (N (%))						
Dose of concomitant Glucocorticoids missing N (%)						
Concomitant NSAIDs (N (%))						
Concomitant NSAIDs missing N (%)						
Global Health (NRS 0 to 10) (mean (SD))						
Global Health missing N (%)						
Pain (NRS 0 to 10) (mean (SD))						
Pain missing N (%)						
FFbH (median (IQR))						
FFbH missing N (%)						
28 Tender Joint Count (median (IQR))						

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Appendix Table 1Bb: Baseline Characteristics stratified by the number of previous b/tsDMARDS

28 Tender Joint Count missing N (%)						
28 Swollen Joint Count (median (IQR))						
28 Swollen Joint Count missing N (%)						
CRP (mg/liter) (median (IQR))						
CRP missing N (%)						
ESR (mm/1h) (median (IQR))						
ESR missing N (%)						
Smoking						
Current (N (%))						
Previous (N (%))						
Never (N (%))						
Missing N (%)						
Disease history						
Malignancies (N (%))						
Lymphoma (N (%))						
Tuberculosis (N (%))						
Joint replacement surgery (N (%))						
COPD (N (%))						
Diabetes mellitus (N (%))						
Hypertension (N (%))						
CHD (N (%))						
CKD (N (%))						
Heart failure (incl. CHF) (N (%))						
Comorbidities						
Number of comorbidities (mean (SD))						
No comorbidity (N (%))						

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Appendix Table 1Bb: Baseline Characteristics stratified by the number of previous b/tsDMARDS

One comorbidity (N (%))						
Two comorbidities (N (%))						
Three or more comorbidities (N (%))						

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Abbreviations: ACR, American College of Rheumatology; F, Female; M, Male; T, Total; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire, DMARDs, disease modifying antirheumatic drugs, NSAIDs, non-steroidal anti-inflammatory drugs; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MTX, methotrexate; SD, standard deviation; NRS, numbers; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; mg, milligram; mm/1h, millimeter / 1 hour; b and tsDMARD, biologic and targeted synthetic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs

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Appendix Table 1Bc: Baseline Characteristics stratified by prior use of non-Tofacitinib JAK inhibitor therapy

	No prior use of non-Tofacitinib JAK inhibitor therapy		Prior use of non-Tofacitinib JAK inhibitor therapy	
Status at entry	Tofacitinib (n=)	bDMARD (n=)	Tofacitinib (n=)	bDMARD (n=)
Demographics				
Age (median (IQR))				
Female sex N (%)				
Disease-related characteristics				
Year of treatment start [before 30 June 2021, 30 June 2021 and afterwards] (N (%))				
Rheumatoid factor positive (N (%))				
Rheumatoid factor positive missing (N (%))				
Number of features listed in 1987 ACR for RA (median (IQR))				
Number of features listed in 1987 ACR criteria for RA missing (N (%))				
Calendar year of recalled RA symptom onset [< 1990, ≥ 1990 and < 2000, ≥ 2000 and < 2007, ≥ 2007 and < 2017, ≥ 2017]				
Calendar year of recalled RA symptom onset missing (N (%))				
Years since symptom onset (i.e., disease duration) (median (IQR))				
Disease duration missing (N (%))				
Disease duration [<5/>=5 years] (N (%))				
DAS28-ESR (median (IQR))				
DAS28-ESR missing (%)				
HAQ (median (IQR))				
HAQ missing N (%)				
Patients with Previous cs/b/tsDMARDS (N (%))				

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Appendix Table 1Bc: Baseline Characteristics stratified by prior use of non-Tofacitinib JAK inhibitor therapy

Patients with Previous cs/b/tsDMARDS missing (N (%))				
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure missing N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)				
Patients with previous bDMARDs (N (%))				
Patients with previous bDMARDs missing N (%)				
Number of previously used bDMARDs (mean (SD))				
Patients with previous tsDMARDs (N (%))				
Patients with previous tsDMARDs missing N (%)				
Number of previously used b/tsDMARDs [0/ 1/ ≥2] (N (%))				
Number of previously used b/tsDMARDs missing N (%)				
Number of previously used csDMARDs (mean (SD))				
Number of previously used csDMARDs missing N (%)				
Concomitant csDMARDs (N (%))				
Concomitant csDMARDs missing N (%)				
Concomitant MTX (N (%))				
Concomitant MTX missing N (%)				
Concomitant oral steroids (N (%))				

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Appendix Table 1Bc: Baseline Characteristics stratified by prior use of non-Tofacitinib JAK inhibitor therapy

Oral steroids missing N (%)				
Dose of concomitant Glucocorticoids [<5, 5-<10, ≥ 10 mg/d] (N (%))				
Dose of concomitant Glucocorticoids missing N (%)				
Concomitant NSAIDs (N (%))				
Concomitant NSAIDs missing N (%)				
Global Health (NRS 0 to 10) (mean (SD))				
Global Health missing N (%)				
Pain (NRS 0 to 10) (mean (SD))				
Pain missing N (%)				
FFbH (median (IQR))				
FFbH missing N (%)				
28 Tender Joint Count (median (IQR))				
28 Tender Joint Count missing N (%)				
28 Swollen Joint Count (median (IQR))				
28 Swollen Joint Count missing N (%)				
CRP (mg/liter) (median (IQR))				
CRP missing N (%)				
ESR (mm/1h) (median (IQR))				
ESR missing N (%)				
Smoking				
Current (N (%))				
Previous (N (%))				
Never (N (%))				
Missing N (%)				
Disease history				

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Appendix Table 1Bc: Baseline Characteristics stratified by prior use of non-Tofacitinib JAK inhibitor therapy

Malignancies (N (%))				
Lymphoma (N (%))				
Tuberculosis (N (%))				
Joint replacement surgery (N (%))				
COPD (N (%))				
Diabetes mellitus (N (%))				
Hypertension (N (%))				
CHD (N (%))				
CKD (N (%))				
Heart failure (incl. CHF) (N (%))				
Comorbidities				
Number of comorbidities (mean (SD))				
No comorbidity (N (%))				
One comorbidity (N (%))				
Two comorbidities (N (%))				
Three or more comorbidities (N (%))				

Abbreviations: ACR, American College of Rheumatology; F, Female; M, Male; T, Total; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire, DMARDs, disease modifying antirheumatic drugs, NSAIDs, non-steroidal anti-inflammatory drugs; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MTX, methotrexate; SD, standard deviation; NRS, numbers; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; mg, milligram; mm/1h, millimeter / 1 hour; b and tsDMARD, biologic and targeted synthetic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs

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Appendix Table 1Bd: Baseline Characteristics stratified by monotherapy vs. combination therapy with concomitant csDMARDs

	Monotherapy		Combination Therapy	
Status at entry	Tofacitinib (n=)	bDMARD (n=)	Tofacitinib (n=)	bDMARD (n=)
Demographics				
Age (median (IQR))				
Female sex N (%)				
Disease-related characteristics				
Year of treatment start [before 30 June 2021, 30 June 2021 and afterwards] (N (%))				
Rheumatoid factor positive (N (%))				
Rheumatoid factor positive missing (N (%))				
Number of features listed in 1987 ACR for RA (median (IQR))				
Number of features listed in 1987 ACR criteria for RA missing (N (%))				
Calendar year of recalled RA symptom onset [< 1990, ≥ 1990 and < 2000, ≥ 2000 and < 2007, ≥ 2007 and < 2017, ≥ 2017]				
Calendar year of recalled RA symptom onset missing (N (%))				
Years since symptom onset (i.e., disease duration) (median (IQR))				
Disease duration missing (N (%))				
Disease duration [<5/>=5 years] (N (%))				
DAS28-ESR (median (IQR))				
DAS28-ESR missing (%)				
HAQ (median (IQR))				
HAQ missing N (%)				
Patients with Previous cs/b/tsDMARDS (N (%))				

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Appendix Table 1Bd: Baseline Characteristics stratified by monotherapy vs. combination therapy with concomitant csDMARDs

Patients with Previous cs/b/tsDMARDS missing (N (%))				
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to treatment failure missing N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)				
Treatment stop of last previous cs/b/tsDMARD therapy due to adverse event / intolerance N (%)				
Patients with previous bDMARDs (N (%))				
Patients with previous bDMARDs missing N (%)				
Number of previously used bDMARDs (mean (SD))				
Patients with previous tsDMARDs (N (%))				
Patients with previous tsDMARDs missing N (%)				
Number of previously used b/tsDMARDs [0/ 1/ ≥2] (N (%))				
Number of previously used b/tsDMARDs missing N (%)				
Number of previously used csDMARDs (mean (SD))				
Number of previously used csDMARDs missing N (%)				
Concomitant MTX (N (%))				
Concomitant MTX missing N (%)				
Concomitant oral steroids (N (%))				
Oral steroids missing N (%)				

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Appendix Table 1Bd: Baseline Characteristics stratified by monotherapy vs. combination therapy with concomitant csDMARDs

Dose of concomitant Glucocorticoids [<5, 5-<10, ≥ 10 mg/d] (N (%))				
Dose of concomitant Glucocorticoids missing N (%)				
Concomitant NSAIDs (N (%))				
Concomitant NSAIDs missing N (%)				
Global Health (NRS 0 to 10) (mean (SD))				
Global Health missing N (%)				
Pain (NRS 0 to 10) (mean (SD))				
Pain missing N (%)				
FFbH (median (IQR))				
FFbH missing N (%)				
28 Tender Joint Count (median (IQR))				
28 Tender Joint Count missing N (%)				
28 Swollen Joint Count (median (IQR))				
28 Swollen Joint Count missing N (%)				
CRP (mg/liter) (median (IQR))				
CRP missing N (%)				
ESR (mm/1h) (median (IQR))				
ESR missing N (%)				
Smoking				
Current (N (%))				
Previous (N (%))				
Never (N (%))				
Missing N (%)				
Disease history				
Malignancies (N (%))				

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Appendix Table 1Bd: Baseline Characteristics stratified by monotherapy vs. combination therapy with concomitant csDMARDs

Lymphoma (N (%))				
Tuberculosis (N (%))				
Joint replacement surgery (N (%))				
COPD (N (%))				
Diabetes mellitus (N (%))				
Hypertension (N (%))				
CHD (N (%))				
CKD (N (%))				
Heart failure (incl. CHF) (N (%))				
Comorbidities				
Number of comorbidities (mean (SD))				
No comorbidity (N (%))				
One comorbidity (N (%))				
Two comorbidities (N (%))				
Three or more comorbidities (N (%))				

Abbreviations: ACR, American College of Rheumatology; F, Female; M, Male; T, Total; N, Number; IQR, interquartile range; DAS28, disease activity score 28; HAQ, health assessment questionnaire, DMARDs, disease modifying antirheumatic drugs, NSAIDs, non-steroidal anti-inflammatory drugs; CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MTX, methotrexate; SD, standard deviation; NRS, numbers; FFbH, % of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain; mg, milligram; mm/1h, millimeter / 1 hour; b and tsDMARD, biologic and targeted synthetic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs

Interim reports: Event rates will be shown overall and stratified by sex. In the interim reports, there will be separate tables by cohort, but they are presented as one table here for brevity.

APPENDIX TABLE 2A: Total Number of Events and Crude Event Rates (per 1000 Person-Years)

	Cumulative		Event Rate (ER) / 1,000 PYs (95% CI)				
Cohort	**Number of Events**	**Percentage of patients with events**	**Females (PY=)**	**Males (PY=)**	**Total (PY=)**		
Endpoint of interest*							
Tofacitinib							
nbDMARD – b/tsDMARD-naive cohort							
nbDMARD – previously exposed to b/tsDMARDs							

*the endpoints are listed in section 4.3.2 of the SAP
Abbreviations: CI, confidence interval; ER, event rate

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Final report: Incidence rates (IR) will be shown overall and stratified by

- 1) the number of previous b/tsDMARDs (0, 1, ≥2) for main cohort and the bDMARD cohort
- 2) prior use of non-tofacitinib JAK-inhibitor therapy (0; >0) for main cohort and the bDMARD cohort
- 3) monotherapy vs. combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs), specifically MTX, for main cohort and the bDMARD cohort
- 4) age (<65 years and ≥65 years) for all cohorts
- 5) patients with ≥1 VTE risk factors vs. no VTE risk factors for the outcome of VTE and for all cohorts
- 6) time period prior to 31 January 2020 vs. time period after 31 January 2020 if feasible for the outcome of VTE and for all cohorts
- 7) patients with ≥1 CV risk factors vs. no CV risk factors for the outcomes of MACE and MI and for all cohorts
- 8) patients without prior history of malignancy vs. with prior history of malignancy for the outcomes of malignancy and for all cohorts
- Additionally, if feasible:
    - 9) IR for VTE stratified by 31. January 2020;
    - 10) IR for VTE among patients with VTE risk factors stratified by 31 January 2020;
    - 11) IR for malignancy /CV risk stratified by 30 June 2021;
    - 12) IR for malignancy /CV risk among patients with malignancy and CV risk factors stratified by 30 June 2021.

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APPENDIX TABLE 2B: Total Number of Events, Crude and Standardized Incidence Rates (per 1000 Person-Years)

Cohort	Number of Events	Females (PY=)	Males (PY=)	Total follow-up, years	Crude IR per 1000 PY	95% CI	Std. IR per 1000 PY	95% CI
Outcomes of interest*								
Tofacitinib								
bDMARD								
nbDMARD								

*the outcomes are listed in section 4.3.2 of the SAP

Abbreviations: CI, confidence interval; IR, incidence rate; std., standardized by age/sex using a direct[7] approach

[7] If feasible, see 4.7.6.2.

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APPENDIX TABLE 3: **Pregnancies**. Note: in the interim reports, these are presented separately by cohort, but are presented all together here for brevity.

Counts of Pregnancies, pregnancy-related outcomes, and pregnancy-related events			
	Tofacitinib	**bDMARD**	**nbDMARD**
Pregnancies with maternal exposure			
Number of total pregnancies			
Number of patients (mothers)			
Singleton pregnancies			
Twin pregnancies			
Pregnancy outcomes			
Live births (related to patients)			
Abort, fetal death, stillbirth (related to patients)			
Unknown (related to patients)			
Pregnancy related events			
Maternal events, serious and non-serious (related to pregnancies)			
thereof serious			
Neonatal events (related to neonates)			
thereof serious			
Pregnancies after paternal exposure (pregnancies of partners)			
Number of total pregnancies			
Singleton pregnancies			
Pregnancy outcomes			
Live births (related to patients)			

Counts of Pregnancies, pregnancy-related outcomes, and pregnancy-related events			
	Tofacitinib	**bDMARD**	**nbDMARD**
Abort, foetal death, stillbirth (related to patients)			
Unknown (related to patients)			

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; nbDMARD = conventional synthetic disease-modifying anti-rheumatic drug.

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APPENDIX TABLE 4A: Cox regression models for the on drug approach (final report only)

Outcome	Tofacitinib versus	Model A		Model B		Model C	
		HR	95% CI	HR	95% CI	HR	95% CI
Outcomes of interest*	bDMARD						
	nbDMARD						

*the outcomes are listed in section 4.3.2 of the SAP

APPENDIX TABLE 4B: Cox regression models for Tofacitinib vs. bDMARDs in the on drug approach, sensitivity analysis[8] (final report only, model C only)

Outcome	Model C	
	HR	95% CI
Outcomes of interest*		

*the outcomes are listed in section 4.3.2 of the SAP

APPENDIX TABLE 4C: Cox regression models for Tofacitinib vs. bDMARDs in the ever exposed / ever exposed with latency period approach (final report only)

Outcome	Model A		Model B		Model C	
	HR	95% CI	HR	95% CI	HR	95% CI
Outcomes of interest*						

*the outcomes are listed in section 4.3.2 of the SAP

APPENDIX TABLE 5: Histograms of propensity scores of the primary regression analyses – final report only

Outcomes	Tofacitinib vs. bDMARD	Tofacitinib vs nbDMARD
Outcomes of interest		

[8] In this sensitivity analysis, exposure is not censored at switch and the entire risk window is attributed to the previous therapy even when a new therapy is started during the risk window.

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APPENDIX TABLE 6: Standardized mean differences of the primary regression analyses – final report only

Outcome	Variable	Tofacitinib vs. bDMARD	Tofacitinib vs nbDMARD
Outcomes of interest	Logit propensity score		
	variables listed in Table 10, Model C		

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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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TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES AND FIGURES 3
1. LIST OF ABBREVIATIONS 4
2. RATIONALE AND BACKGROUND 6
3. RESEARCH QUESTION AND OBJECTIVES 7
4. RESEARCH METHODS 7
4.1. Study Design 7
4.2. Subjects 8
4.3. Variables 8
4.4. Data Sources And Measurement 9
4.5. Study Size 9
4.6. Statistical methods 10
4.6.1. Treatment/Cohort Labels 10
4.6.2. Main Statistical Methods 12
4.6.3. Changes In Planned Meta-Analyses 13
5. RESULTS 13
5.1. Participants 13
5.2. Demographics And Baseline Characteristics 14
5.3. Outcome Data 16
5.4. Main Results 17
5.4.1. All-Cause Mortality 17
5.4.2. Malignancy Endpoints 17
5.4.3. Non-Malignancy Endpoints 18
6. DISCUSSION 31
6.1. Key Results 31
6.2. Limitations 31
7. CONCLUSIONS 31
8. REFERENCES 32

090177e1a6a6094e\Final\Final On: 28-Jul-2026 18:09 (GMT)

LIST OF IN-TEXT TABLES AND FIGURES

Table 1. Registries Contributing Observations 9
Table 2. Comparison of Cohorts in Each Study....11
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) 13
Table 4. Demographics and Baseline Characteristics of RA Patients in Main Cohort and Comparator Cohort in Each Study 15
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....20
Table 6. Pooled Estimates of Crude Incidence Rates (and 95% CIs) of Malignancy Endpoints Among the Tofacitinib and bDMARD Cohorts Using Ever-Exposed Approach 22
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 24
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....26
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 29

Annex 1. List of stand-alone documents

Appendix 1. META ANALYSIS STATISTICAL ANALYSIS PLAN

090177e1a6a6094e\Final\Final On: 28-Jul-2026 18:09 (GMT)

090177e1a6a6094e\Final\Final On: 28-Jul-2026 18:09 (GMT)

1. LIST OF ABBREVIATIONS

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

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

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2. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[1] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of comorbidities.

Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma). These patients are also treated with multiple classes of agents, including nonsteroidal anti -inflammatory drugs (NSAIDs), glucocorticoids, and DMARDs including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral JAK inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[3,6] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[4] Unlike biological therapies, such as tumour necrosis factor (TNF) inhibitor (TNFi) and anti-interleukin (IL) 6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome.

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

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

It therefore follows that for all new biologic and other targeted therapies there is a need for active surveillance to identify higher than expected rates of such safety endpoints overall and within strata of disease severity, treatment history, and other concomitant therapy. Long term morbidity and mortality event tracking of these cohorts over 7 years is an appropriate method for evaluating the risk associated with these treatments.

There is an increased risk of premature mortality, serious infection and lymphoma in patients with RA and other connective tissue diseases, independent of the treatment they have received.[5] Thus, the patients on newly approved therapies without a well-established record of safety are already at increased background risk of premature mortality, infection and malignancy. Additionally, following the result of the June 2021 signal evaluation procedure (EPITT 19382) to assess the increased incidence rate of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients

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treated with tofacitinib for rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma were already included as study endpoints prior to the signal evaluation). It is therefore fundamentally important to describe the occurrence of these events among patients treated with newly approved therapies and among patients who remained on “conventional” therapy or received a different targeted agent.

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

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

Additionally, a meta-analysis integrated country-specific results, providing a more precise and robust evaluation of the risks associated with tofacitinib in the post-approval real-world setting to support safe prescribing practices and regulatory oversight. A quantitative meta-analysis permitted an estimate of an average effect across the studies with more statistical power than the individual studies, provided a formal evaluation did not reveal substantial heterogeneity. Meta-analysis revealed between-study heterogeneity such that a subset of more comparable studies could be included in a single estimate. Heterogeneity was expected, for example, due to differences in local prescribing practices, patient populations, competing risks, and prevalence of comorbidities and risk factors. Such heterogeneity existed even if the coding for endpoint definitions and reporting could be harmonized across registers. In the presence of such heterogeneity, pooling across the registers is not informative as the generalizability of such an estimate was unknown.

3. RESEARCH QUESTION AND OBJECTIVES

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

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

4. RESEARCH METHODS

4.1. Study Design

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

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A3921314 was an active surveillance study of existing nationwide cohorts in Sweden using linkages between drug-based registers, disease-based registers, national death register, cancer register, inpatient register, and outpatient register. All linkages were deterministic based on unique patient identifiers.

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

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

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

4.2. Subjects

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

4.3. Variables

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

The following endpoints were pooled across all four PASS.

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

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

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

4.4. Data Sources And Measurement

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

Table 1. Registries Contributing Observations

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

4.5. Study Size

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

For A3921312, the study enrolment goal was 500 patients in the tofacitinib arm, but success depended largely on use of tofacitinib in UK. Enrolment would not be capped at 500 but continue throughout the study period. Based on the first 12 months of enrolment of tofacitinib exposed patients in BSRBR, 110 patients were projected to be enrolled in the first 24 months, allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remained constant over the period.

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

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

For A3921316, based on the first 10 months of enrolment of tofacitinib exposed patients in BIOBADASER, 187 patients were projected to be enrolled in the first 24 months, allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remained constant over the period.

For A3921317, the targeted sample size for tofacitinib treated patients was 500. Enrolment would not be capped at 500 but continue throughout the study period. Based on the first 16 months of enrolment of tofacitinib exposed patients in RABBIT, 558 patients were projected to be enrolled in the first 24 months, allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remained constant over the period.

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

4.6. Statistical methods

4.6.1. Treatment/Cohort Labels

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

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

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

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

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Table 2. Comparison of Cohorts in Each Study

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

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

4.6.2. Main Statistical Methods

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

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

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

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

1. Censor-at-Switch Approach:

    - For all-cause mortality and malignancy endpoints: if a malignancy or death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy.

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

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

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

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

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

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

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

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

4.6.3. Changes In Planned Meta-Analyses

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

5. RESULTS

5.1. Participants

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

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

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

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

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5.2. Demographics And Baseline Characteristics

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

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

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

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

5.3. Outcome Data

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

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

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

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

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

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

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

The following adjusted HR were included in the pooled estimates:

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

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

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

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

5.4. Main Results

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

5.4.1. All-Cause Mortality

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

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

5.4.2. Malignancy Endpoints

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

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

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

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

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

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

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

5.4.3. Non-Malignancy Endpoints

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

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

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

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

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

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

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

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

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

With Censor-at-Switch approach, if death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy.
With Ever-Exposed Approach, follow up for each cohort continued after switching to a new drug or discontinuation of treatment.
Footnotes:

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

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

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

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

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

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

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

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

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

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

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

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

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

With Censor-at-Switch approach, if a malignancy occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy.
For endpoints with fewer than 5 events in either cohort, event counts in A3921312 were derived using incidence rates and person-years to support the pooled estimation.
[#] A continuity correction was applied to studies with zero events; therefore, pooled incidence rates may be >0 despite no observed events.
Footnotes:

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

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

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

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

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

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

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

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

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

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

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
A3921312									
MACE	-	-	-	-	-	-	-	-	0.99 (0.36, 2.77)
Progressive multifocal leukoencephalopathy (PML)	0	845	-	-	0	5793	-	-	-
A3921314									
Herpes zoster	2	1470	1.36	(0.34, 5.44)	26	48161	0.54	(0.37, 0.79)	-
MACE	20	1445	13.84	(8.93, 21.45)	676	47125	14.34	(13.30, 15.47)	1.05 (0.67, 1.66)
Venous Thromboembolism (VTE (DVT/PE))	11	1455	7.56	(4.19, 13.65)	335	47642	7.03	(6.32, 7.83)	1.00 (0.54, 1.86)
GI perforation	6	1474	4.07	(1.83, 9.06)	101	48050	2.10	(1.73, 2.55)	1.56 (0.66, 3.67)
Progressive multifocal leukoencephalopathy (PML)	0	1532	0	-	3	60811	0.05	(0.02, 0.15)	-
A3921316									
Herpes zoster	18	1199.78	15.0	(9.5, 23.8)	136	17344.49	7.8	(6.6, 9.3)	1.95 (1.17, 3.25)
MACE	6	1264.46	4.7	(2.1, 10.6)	65	17796.74	3.7	(2.9, 4.7)	1.21 (0.48, 3.03)
Deep vein thrombosis (DVT)	2	1272.95	1.6	(0.4, 6.3)	11	17951.67	0.6	(0.3, 1.1)	1.34 (0.17, 10.65)
Pulmonary embolism (PE)	0	1273.65	-	-	5	17988.7	0.3	(0.1, 0.7)	-
Venous Thromboembolism (VTE (DVT/PE))	2	1267.47	1.6	(0.4, 6.3)	17	17922.11	0.9	(0.6, 1.5)	1.01 (0.13, 7.84)
GI perforation	0	1258.11	-	-	30	17916.25	1.7	(1.2, 2.4)	-
Progressive multifocal leukoencephalopathy (PML)	0	1273.65	-	-	0	18005.78	-	-	-
A3921317									
Herpes zoster	49	2258.75	21.69	(16.05, 28.68)	143	17267.16	8.28	(6.98, 9.76)	2.38 (1.65, 3.43)
Fractures	48	2260.7	21.23	(15.66, 28.15)	306	16979.65	18.02	(16.06, 20.16)	1.18 (0.84, 1.66)
MACE	20	2324.69	8.60	(5.26, 13.29)	91	17392.01	5.23	(4.21, 6.42)	1.78 (1.04, 3.06)
Deep vein thrombosis (DVT)	2	2340.85	0.85	(0.10, 3.09)	18	17479.19	1.03	(0.61, 1.63)	-

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

Endpoint of Interest	Tofacitinib Cohort				bDMARD Cohort				Tofacitinib vs. bDMARD
	N[1]	PY[2]	IR[3]	95% CI[4]	N[1]	PY[2]	IR[3]	95% CI[4]	HR (95% CI)[5]
Pulmonary embolism (PE)	6	2338.9	2.57	(0.94, 5.58)	31	17463.67	1.78	(1.21, 2.52)	1.55 (0.58, 4.11)
Venous Thromboembolism (VTE (DVT/PE))	6	2338.9	2.57	(0.94, 5.58)	41	17450.2	2.35	(1.69, 3.19)	1.14 (0.44, 2.96)
GI perforation	5	2340.53	2.14	(0.69, 4.99)	44	17441.75	2.52	(1.83, 3.39)	-
Progressive multifocal leukoencephalopathy (PML)	0	2341.33	0.00	(0.00, 1.58)	1	17506.88	0.06	(0.00, 0.32)	-
Pooled Estimates[6]									
Herpes zoster	69	4928.53	18.18	(14.36, 23.02)	305	82772.65	6.40	(5.72, 7.16)	2.22 (1.65, 3.00)*
MACE	46	5034.15	9.79	(7.33, 13.07)	832	82313.75	11.54	(10.79, 12.36)	1.26 (0.93, 1.72)
Deep vein thrombosis (DVT)	4*	3613.8*	1.16*	(0.43, 3.09)*	29*	35430.86*	0.85*	(0.59, 1.22)*	-
Pulmonary embolism (PE)	6*	3612.55*	2.22*	(1.03, 4.79)*	36*	35452.37*	1.37*	(0.99, 1.90)*	-
Venous Thromboembolism (VTE (DVT/PE))	19	5061.37	4.56	(2.91, 7.14)	393	83014.31	5.75	(5.21, 6.35)	1.04 (0.63, 1.72)
GI perforation	11	5072.64	2.78	(1.56, 4.95)	175	83408	2.12	(1.83, 2.45)	-
Progressive multifocal leukoencephalopathy (PML)	0	5991.98	0.36#	(0.09, 1.43)#	4	102116.7	0.05	(0.02, 0.12)	-

With Censor-at-Switch approach, if a new medication is started during the 90-day window after discontinuation of a previous medication, initiation of the new medication will stop the 90-day risk window, and any event prior to the new medication start will be assigned to the discontinued medication.
* Descriptive result based on two studies; SAP did not pre-specify formal pooling with only two PASS.
# A continuity correction was applied to studies with zero events; therefore, pooled incidence rates may be >0 despite no observed events.
Footnotes:

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

Data source: A3921312 Study Report Table 10 (adjusted HR following sensitivity analysis), A3921314 Study Report Table 17 and Table 18 (HRd), A3921316 Study Report Table 13 and Table 6, A3921317 Study Report Table 10-9 and Table 10-13 (Model C).

6. DISCUSSION

6.1. Key Results

Overall, the pooled results showed that crude incidence rates for all-cause mortality were generally similar between the tofacitinib and bDMARD cohorts in both the censor-at-switch and ever-exposed analyses, and the pooled adjusted HRs were close to 1. For malignancy endpoints, pooled estimates of crude incidence rates for NMSC and lung cancer were higher in the tofacitinib cohort and the corresponding adjusted hazard ratios were greater than 1, with 95% CIs excluding 1. Lymphoma and its subtypes were rare in both cohorts. For non-malignancy endpoints, pooled estimates of crude incidence rates for herpes zoster were higher in the tofacitinib cohort than in the bDMARD cohort and the corresponding adjusted hazard ratios were greater than 1, with 95% CIs excluding 1. Other non-malignancy endpoints showed similar pooled estimates between cohorts. These findings provide an integrated summary of the relative occurrence of the prespecified safety endpoints across the included registries under the analytic approaches specified in the meta-analysis.

6.2. Limitations

This meta-analysis has several limitations that should be considered when interpreting the findings. First, the pooled results were derived from observational registry data collected across multiple countries, and differences in healthcare systems, prescribing patterns, patient characteristics, follow-up practices, and endpoint ascertainment may have contributed to between-study heterogeneity. Second, although efforts were made to define comparable cohorts across studies, the comparator cohorts were not identical across the PASS, and some analyses included only a subset of studies because of study-specific methodological differences, such as the 6-month latency period applied in A3921317 for malignancy analyses or the availability of assign-to-prior analyses for selected non-malignancy endpoints. Third, sample sizes differed substantially between the tofacitinib cohort (N=1,780) and the bDMARD cohort (N=25,140). This imbalance may have limited the precision of estimates for rare outcomes in the smaller tofacitinib cohort and contributed to uncertainty in some comparisons. Fourth, several endpoints were rare, resulting in small numbers of events, wide confidence intervals, and in some cases the absence of pooled hazard ratio estimates. Finally, as with all non-interventional studies, the pooled estimates may be affected by residual confounding, incomplete capture of relevant risk factors, and differences in treatment selection that cannot be fully addressed through study-level adjusted analyses.

7. CONCLUSIONS

In this meta-analysis of four PASS in patients with RA, pooled estimates for all-cause mortality were generally similar between the tofacitinib and bDMARD cohorts, while higher pooled estimates of crude incidence rates were observed for NMSC, lung cancer, and herpes zoster in the tofacitinib cohort, with adjusted hazard ratios and the 95% CIs above 1, indicating higher risks for patients treated with tofacitinib. These events (ie, NMSC, lung cancer and herpes zoster) are identified risks in the EU RMP. These findings should be interpreted in the context of the observational design, between-study heterogeneity, and limited precision for rare endpoints.

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