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)
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Research Question and Objectives	**Research Question:** What are the rates of adverse outcomes of special 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?

	Objectives: To evaluate the rates of serious infections, malignancy, CV, and other specified outcomes 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. Pending feasibility, rates of malignancy, serious infection, CV and other event rates 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
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABT	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
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
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
JAK	Janus kinase
MACE	major adverse cardiovascular events

Abbreviation	Definition
MAH	market authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MTX	methotrexate
nbDMARD	non-biologic DMARD
NDA	New Drug Application
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
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
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

3. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

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

Version: Final Protocol (v1.0).

Date: 21 August 2019.

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 adverse outcomes of special interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data in the RABBIT registry.

Research Question: What are the rates of adverse outcomes of special interest in RA patients treated with tofacitinib in relation to those treated with biologic DMARDs (bDMARD) and non-biologic DMARDs (nbDMARD)?

Objectives: To evaluate the rates of serious infections, malignancy, CV, and other specified outcomes 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.

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.

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, and heart disease.

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. The final analysis of endpoints will provide the rates of events overall and in subgroups defined by baseline characteristics. Pending feasibility, rates of malignancy, serious infection, CV and other event rates will be compared between tofacitinib-treated RA patients and the comparator cohorts using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders.

Milestones: Updates of patient characteristics and event rates will be provided every six months to Pfizer. Interim reports will compile the results of the semi-annual reports at 2, 4 and 6 years of the study period. A final report, including linked data, will include 7 years of data after start of data collection.

5. AMENDMENTS AND UPDATES

None.

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

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 lymphoproliferative malignancy.

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 adverse events (AEs) 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 lymphoproliferative malignancy 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. 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 adverse outcomes of special interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed patients using actively collected prospective data 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.

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.

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.

Other Safety Events of Interest

RABBIT collects data other safety events of interest in the RA population including central nervous system (CNS) events, 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 adverse outcomes of special interest in RA patients treated with tofacitinib in relation to those treated with bDMARD and nbDMARD.

Objectives:

To evaluate the rates of serious infections, malignancy, CV, and other specified outcomes 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, rates of malignancy, serious infection, CV and other event rates will be compared 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, and other potential confounders.

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 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, AEs and serious AEs (SAEs) 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 13,000 patients enrolled 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:

9.2.1.1. Tofacitinib Exposed Cohort Inclusion Criteria

1. Included in RABBIT.
2. Initiation of tofacitinib.

9.2.1.2. nbDMARD Cohort Inclusion Criteria

1. Included in RABBIT.
2. Enrolled after 1 January 2009.
3. failure of at least one DMARD and initiation of a new DMARD.
4. No previous exposure to bDMARD or targeted synthetic bDMARD (tsDMARD).

9.2.1.3. bDMARD Exposed Cohort Inclusion Criteria

1. Included in RABBIT.
2. Enrolled after 1 January 2009.
3. Initiation of bDMARD therapy.
4. No prior exposure to tsDMARD.

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. 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.

9.4. Risk Window

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

Some outcomes of interest in this study are thought to potentially occur at a higher rate while on drug, but that increased risk subsides after the drug is discontinued (ie, serious infections, herpes zoster, CV events, gastrointestinal (GI) perforation, progressive multifocal leukoencephalopathy (PML).[1] Those events will be evaluated over a risk window that includes time from drug initiation until 90 days after end of treatment. When a patient initiates a new therapy within the 90-day extension, the time and events during the overlapping period will be assigned to both treatments. The 90-day extension period is implemented in part to accommodate ongoing exposure to treatments with longer half-lives, and in part to ensure that any subclinical or undiagnosed illness at time of end of treatment is captured.

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

The primary analysis will assume a once exposed always at risk paradigm, as is frequently used in study of malignancy risk due to bDMARDs.[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. 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

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

exposure. That is, the event will be assigned to both the bDMARD and the tofacitinib exposure cohorts as will the corresponding person years since index to the respective cohorts. Because tofacitinib is expected to be used as a later line therapy, switching is expected to be non-random with most tofacitinib patients having been included in the bDMARD cohort prior to initiation of tofacitinib. In such cases, the bDMARD rate will have more associated person-years and thus a relatively lower rate than the corresponding rate in the tofacitinib cohort.

Using this primary analytic approach, if neither tofacitinib nor bDMARDs cause an increased risk of malignancy both exposure cohort rates will reflect the background rates of malignancy from the time of index to the end of the study period and the comparative effect measure will indicate no difference in rates. If tofacitinib does cause an increased rate of malignancy, which is the effect we are most interested in detecting, a relatively higher rate will be observed in the tofacitinib exposed cohort. The once exposed always at risk approach is therefore able to detect an increased rate given the non-random switching expected to occur given use of bDMARDs prior to tofacitinib and is consistent with previous studies evaluating the risk of individual biologics.[26,14,15,24] Additional analyses will be conducted to evaluate potential confounders and the impact of different latency assumptions as will be described in the SAP. Sensitivity analyses will be conducted that restrict the bDMARD comparator cohort to patients who were never exposed to tofacitinib or other non-biologic advanced therapies and compare the characteristics of those bDMARD patients ever and never exposed to tofacitinib.

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

Of note, several studies compared a once-exposed approach to a time on drug and other approaches and found similar rates of malignancy using an on-drug and ever-exposed approach.[26,14,15]

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

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

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

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

b. Patients are ineligible for bDMARD cohort index after tofacitinib index.

Note: if an event does not occur, person time will be allocated to rate denominator as described in table without corresponding event.

9.5. Variables

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, year of diagnosis.

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 interruption.

4. Co-morbidity calculating the Charlson index.

5. All current therapy.

6. Baseline disease activity including Disease Activity Score (DAS)-28, Health Assessment Questionnaire (HAQ); Pain Visual Analog Scale (VAS), Global Health VAS, Tender Joint Count, Swollen joint count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), American College of Rheumatology (ACR) rating scale.

7. Baseline history of disease including tuberculosis, serious infection, malignancy, heart disease.

9.3.2 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: 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). The actual events of interests are: Serious infections, Tuberculosis, Lymphomas, Aplastic Anaemia/Pancytopenia, Demyelinating Diseases, (Congestive) Heart Failure, Gastrointestinal ulcers and perforations, Malignancies, Myocardial infarction, Stroke, Serious hepatic events/hepatic failure, Serious hypersensitivity reactions, Pregnancies, Death.

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.

9.3.3 Endpoints

Endpoints in RABBIT derive from physician reports of the occurrence of any AE or event of special 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. Cardiac disorders: heart failure, coronary artery disease, myocardial infarction, other cardiac disorders.

5. Hematologic disorders: bone marrow depression and hypoplastic anaemia, decreased white blood cells, platelet disorders, other blood dyscrasia.

6. Disorders of the nervous system (excluding infections): stroke, central demyelination, other disorders of the CNS, disorders of the peripheral nervous system, psychiatric disorders.

7. Progressive multifocal leukoencephalopathy.

8. Allergic conditions and hypersensitivity.

9. Hepatic failure.

10. Gastrointestinal (GI) perforations.

11. Pregnancy.

12. Thromboembolic events: deep vein thrombosis (DVT) and pulmonary embolism (PE).

13. Operations and hospitalisations: bone and joint surgery and other joint therapeutic procedures, other operations and (major) therapeutic procedures that lead to hospitalization.

14. Other serious diagnoses, symptoms, and syndromes.

15. NMSC.

16. Malignancies, excluding NMSC.

17. All-cause Mortality.

Rates of these endpoints of interest and their 95% CI will be reported for tofacitinib exposed and comparator cohorts every six months.

9.4 Data Sources

Core baseline and follow up data, including patient demographics, disease characteristics, and treatment will be based on data from the RABBIT.

9.6. 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 (see Question 8). Table 2 assumes a 30% annual rate of switching from tofacitinib to a bDMARD over the study period, as previously demonstrated in the EU for bDMARDs in Italy (Eposti, 2016).[29]

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
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

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.

9.7. Data Management

All data management activities occur without the overarching RABBIT study.

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).

9.8. Data Analysis

The initial analyses will consist of descriptive comparisons of baseline status and crude event rates between the different cohorts. The final analysis of endpoints will provide the rates of events overall and in subgroups defined by baseline characteristics. Pending feasibility, rates of malignancy, serious infection, CV and other event rates will be compared between tofacitinib-treated RA patients and the comparator cohorts using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders

Semi-Annual Reports: Pfizer will receive three summary reports comprising crude cumulative incidence rates of events of interest and the 95% CI. Pfizer will receive one report on tofacitinib and two control group reports: one of biologics naïve patients and one of SAEs observed in patients under conventional treatment who were previously exposed to biologics. 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 for differences in severity of disease and other confounders will be completed using appropriate multivariate, propensity score matching, or inverse probability weighting methods. For these analyses, the exposure cohorts will be analyzed overall, previous biologics use and monotherapy and combination therapy with concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs). A combination therapy with MTX specifically will be described if sample sizes are sufficient. These and potentially other agreed upon strata will be determined apriori and included in SAP filed with Sponsor. The general analytic approach will be descriptive and include rates of events of interest within stratified treatment cohorts. Data will be presented as number of events, crude and age/sex-standardized incidence rates. Such analyses will be performed by and at the direction of RABBIT. The final report will also evaluate the rates of safety events of interest within the elderly. 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, 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 prior 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.

9.9. Quality Control

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.

9.10. 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 are of concern when comparing event rates. As a new therapy in the EU RA treatment armamentarium, it is possible that patients treated with tofacitinib will represent those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at increased risk for AEs. Biases resulting from channeling may present as increased 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.

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. Several comparators in this study are not contemporaneous to tofacitinib treated patients. Analysis will be unable to identify or control for any changes in rates due to changes in the treatment landscape.

Event misclassification 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.

9.11. Other Aspects

Not applicable.

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 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the 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.

Semi-annual summary reports will be provided to Pfizer every 6 months. Interim reports summarizing the patient characteristics and crude event rates will be submitted to EMA to reflect 2, 4, and 6, years of the study period. A final dataset, to include 7 years of follow up, will be the basis for a final report to be submitted to EMA. The final report will be included

in risk management plan (RMP) updates. Data may be used in regulatory 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 22

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 23

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular and Other Adverse Event Rates among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Sweden (ARTIS) Register

Study reference number: A3921314

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	5

[1] 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.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☒	7
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	7
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.1
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

No measures 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?	☒	☐	☐	8.2

ENCePP Checklist for Study Protocols (Revision 3)

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.3
4.2.2 Age and sex?	☒	☐	☐	8.3
4.2.3 Country of origin?	☒	☐	☐	8.3
4.2.4 Disease/indication?	☒	☐	☐	8.3
4.2.5 Duration of follow-up?	☒	☐	☐	8.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.3

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)	☒	☐	☐	8.5
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 classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

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?	☒	☐	☐	8.4.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.5.1, 8.5.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

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Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.8.2
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	8.8.2
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.10
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.5.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.5.3
9.1.3 Covariates?	☒	☐	☐	8.5.3, 8.5.2
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)	☒	☐	☐	8.4.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.5.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	

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Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.9
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	8.5.3

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.8
10.2 Are descriptive analyses included?	☒	☐	☐	8.8
10.3 Are stratified analyses included?	☒	☐	☐	8.8
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	8.8
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	8.6

Comments:

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)	☒	☐	☐	8.9
11.2 Are methods of quality assurance described?	☒	☐	☐	8.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.4

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?	☒	☐	☐	8.10
12.1.2 Information bias?	☒	☐	☐	8.10
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)	☒	☐	☐	8.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.6

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Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

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?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Ann Madsen

Date: dd/Month/year 04/20/2018

Signature:

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ANNEX 3. ADDITIONAL INFORMATION

See Appendix 1.

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.

	ARTIS		BIOBADASER, BSRBR, RABBIT
HZ reactivation	Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes B00 and B02. If main diagnosis is RA, contributory diagnoses are also considered.	The algorithm used to identify this endpoint in ARTIS has not been validated and is expected to only identify the most severe cases.	10019974 Herpes zoster, 10019983 Herpes zoster ophthalmic, 10030865 Ophthalmic herpes zoster, 10058428 Herpes zoster multi-dermatomal, 10063491 Herpes zoster oticus, 10065038 Herpes zoster disseminated, 10065119 Necrotising herpetic retinopathy, 10072210 Genital herpes zoster, 10074241 Varicella zoster gastritis, 10074245 Herpes zoster pharyngitis, 10074248 Herpes zoster meningoencephalitis, 10074253 Herpes zoster necrotising retinopathy, 10074254 Varicella zoster pneumonia, 10074254 Varicella zoster pneumonia, 10074259 Herpes zoster meningitis, 10074297 Herpes zoster cutaneous disseminated.

	ARTIS		BIOBADASER, BSRBR, RABBIT
CV risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care.	See Serious Infections 'Outcome' was defined as any first-ever ACS event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the underlying cause of death. For discharge diagnoses, the date of admission to hospital was considered the event date. This outcome definition has previously been validated in a Swedish early RA cohort, with a positive predictive value of 95% [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.	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism; Fatal only 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type;;10006145 Brain stem haemorrhage;;10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus; 10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage;

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

	ARTIS		BIOBADASER, BSRBR, RABBIT
			artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure.

	ARTIS		BIOBADASER, BSRBR, RABBIT
GI perforation	Hospitalizations in the Patient Register listing ICD10-codes: K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K31.6, K35.0, K35.1, K57.0, K57.2, K57.4, K57.8, K63.0, K63.1, K63.2.	See Serious Infections; Pharmacoepidemiol Drug Saf. 2011 Nov;20(11):1150-8. doi: 10.1002/pds.2215. Epub 2011 Aug 27. Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients.	10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheo-oesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924 Aorto-duodenal fistula; 10003012 Appendicitis perforated; 10009995 Colonic fistula; 10013536 Diverticular fistula; 10013538 Diverticulitis; 10013541 Diverticulitis intestinal haemorrhagic; 10013828 Duodenal fistula; 10013832 Duodenal perforation; 10013849 Duodenal ulcer perforation; 10013849 Duodenal ulcer perforation; 10013850 Duodenal ulcer perforation, nobstructive; 10017815 Gastric perforation; 10017835 Gastric ulcer perforation; 10017836 Gastric ulcer perforation, obstructive; 10017866 Gastritis haemorrhagic; 10017877 Gastrointestinal fistula; 10017954 Gastrointestinal gangrene; 10017955 Gastrointestinal haemorrhage; 10018001 Gastrointestinal perforation; 10021305 Ileal perforation; 10021310 Ileal ulcer perforation; 10022647 Intestinal fistula; 10022694 Intestinal perforation; 10023174 Jejunal perforation; 10023178 Jejunal ulcer perforation; 10023804 Large intestine perforation; 10030181 Oesophageal perforation; 10034354 Peptic ulcer perforation; 10034358 Peptic ulcer perforation, obstructive; 10034397 Perforated peptic ulcer oversewing; 10034649 Peritoneal abscess; 10034674 Peritonitis; 10038073 Rectal perforation; 10038975 Retroperitoneal abscess; 10041103 Small intestinal perforation; 10046274 Upper gastrointestinal 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

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

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