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 British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)
Protocol Number	A3921312
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Active Substance	L04AA29 Tofacitinib
Medicinal Product	Xeljanz® (tofacitinib)
Product Reference	EU/1/17/1178/001-004
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Marketing Authorisation Holder (MAH)	Pfizer Europe
Joint PASS	No
Research Question and Objectives	**Research Question**: What are the rates of safety events of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies? **Objectives**: To evaluate the rates of serious infections,

	malignancy, cardiovascular, and other specified outcomes among patients with RA in United Kingdom (UK)-based register who initiate tofacitinib. Rates will also be estimated among RA patients who initiate tumour necrosis factor inhibitor (TNFi) drugs (ie, patients receiving Humira (adalimumab) (ADA), Enbrel (etanercept) (ETA), or Remicade (infliximab) (INF)) to provide context for rates observed on tofacitinib. 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.
Country(-ies) of study	United Kingdom
Author	Ann M. Madsen, PhD Pfizer, Inc. 235 East 42nd Street, 219/09/01 New York, New York 10017 USA

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Europe Boulevard de la Plaine 17 1050 Bruxelles Belgium
MAH Contact Person	Ann M. Madsen, PhD 235 E 42nd Street, Mail Stop 219/9/01 New York, NY 10017 USA

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	adalimumab (Humira)
AE	adverse event
bDMARD	biologic disease modifying antirheumatic drug
BID	bis in die (Twice a day)
BP	blood pressure
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
BSRBR-RA	British Society for Rheumatology Biologics Register-Rheumatoid Arthritis
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DAS	Disease activity score
DMARD	disease modifying antirheumatic drug
DMEC	Data Monitoring and Ethics Committee
EBV	Epstein Barr Virus
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQol Five Dimensions Questionnaire
ESR	erythrocyte sedimentation rate
ETA	etanercept (Enbrel)
EU	European Union
GI	gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HAQ	health assessment questionnaire
IEC	independent ethics committee
IL	interleukin
INF	infliximab (Remicade)
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
JAK	Janus kinase
LTE	long term extension
MACE	major adverse cardiovascular events
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mg	milligram
MTX	Methotrexate
NDA	New Drug Application
NHL	non-Hodgkin's lymphoma
NI	non-interventional
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	Post-authorization study
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PML	progressive multifocal leukoencephalopathy
PV	pharmacovigilance
PY	person-years
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance and Epidemiology End Results
SIR	standardised incidence ratio
SOP	standard operating procedure
TB	tuberculosis
TBD	to be determined
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
UK	United Kingdom

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Ann M. Madsen, PhD	Epidemiologist	Pfizer, Inc.	235 East 42nd Street, 219/09/01 New York, New York 10017 USA
Kimme Hyrich, MD, PhD, FRCPC	Professor of Epidemiology and Consultant Rheumatologist	The University of Manchester	Arthritis Research UK Centre for Epidemiology, 2nd Floor Stopford Bldg, Oxford Road, Manchester M13 9PL United Kingdom

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

Version: Final Protocol (v1.0).

Date: 13 June 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 BSRBR-RA.

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

Objectives: To evaluate the rates of serious infections, malignancy, cardiovascular, and other specified outcomes among patients with RA in a United Kingdom (UK)-based register who initiate tofacitinib. Rates will also be estimated among RA patients who initiate other tumour necrosis factor (TNF) inhibitor (TNFi) drugs (ie, patients receiving Humira (adalimumab) (ADA), Enbrel (etanercept) (ETA), or Remicade (infliximab) (INF)) to provide context for rates observed on tofacitinib.

Study design: This active surveillance study uses data from the existing BSRBR-RA, an ongoing, prospective, observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use.

Population: The study population will comprise all patients with RA enrolled within BSRBR-RA who receive tofacitinib following EU approval and marketing, through the end of the study period. Two comparator cohorts of patients within BSRBR with active RA at cohort entry will be used for risk characterization purposes. The first comparator cohort consists of RA patients who are biologic-naïve at recruitment receiving conventional synthetic DMARDS (csDMARD)s, the second consists of RA patients initiating TNFi per national guidelines (Disease activity score (DAS) >5.1).

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 cardiovascular events.

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

Study size: This is an active surveillance descriptive study without pre-specified statistical hypotheses therefore there is no minimum sample size requirement. The targeted sample size for tofacitinib-treated patients is 500, though enrolment will not be capped and continue throughout the study period. Over 3800 biologic-naïve and 2100 biologic-exposed patients are currently enrolled in the register.

Data analysis: The initial analyses will consist of descriptive comparisons of baseline status and crude event rates between the different cohorts. The final analysis of endpoints will provide the rates of events overall and in subgroups defined by baseline characteristics. Pending feasibility, rates of malignancy, 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: Patient characteristics and rates of events of special interest will be provided to Pfizer every six months. Interim reports will compile the results of the semi-annual reports at 2, 4 and 6 years of the study period. A final study 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	01 September 2019
Start of data collection	15 September 2019
Interim report	14 March 2021
Interim report	14 March 2023
Interim report	14 March 2025
End of data collection	14 September 2025
Final Study Report	14 August 2026

7. RATIONALE AND BACKGROUND

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

Tofacitinib is the first oral JAK inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[16,31] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA).[17] Unlike biological therapies, such as tumour necrosis factor (TNF) inhibitor (TNFi) and anti-interleukin (IL)-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome.

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

Careful observation of large cohorts of patients is needed to detect any increase in risk either of malignancy or infection, possibly due to tofacitinib treatment. Furthermore, it is important that surveillance also examines the occurrence of other 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. 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 BSRBR-RA. Long term morbidity and mortality event-tracking of these cohorts over 7 years is an appropriate method for evaluating the risk associated with these treatments.

There is an increased risk of premature mortality, serious infection and lymphoproliferative malignancy in patients with RA and other connective tissue diseases, independent of the treatment they have received.[21] Thus, the patients on newly approved therapies without a well-established record of safety are already at increased background risk of premature mortality, infection and malignancy. It is therefore fundamentally important to describe the

occurrence of these events among patients treated with newly approved therapies and among patients who remained on "conventional" therapy or received a different targeted agent.

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

Serious Infections

The risk of infections among RA patients depends on the environmental distribution of the organism of interest, inherent patient characteristics and treatment for RA. Persons with RA ≥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.[5,10] The mechanism by which infection risk is increased in RA patients is likely to be multifactorial. In addition to the underlying disease (RA), therapies used to treat the disease have suppressive effects on the immune system. For example, TNFi may affect host defense against infection since TNF mediates inflammation and modulates cellular immune response. Tofacitinib inhibits cytokines that are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

Risk of infections is reportedly higher among TNFi-treated patients than those on DMARDs,[4,8,10,24] however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.[3,28] The decline may reflect a change in the risk profile of the population as a result of at-risk patients switching therapies, reduced co-administration of corticosteroids, in addition to any impact of TNFi therapy on overall health.[28]

Tuberculosis (TB) is the most common opportunistic infection (OI) in the RA population, with risks approximating 10-20 times that of the general population, likely due in part to RA therapy.[2,6,7]

Studies comparing the background risk of herpes zoster in RA and general population cohorts have been inconsistent, with some showing no increased risk and some showing modestly elevated risk.[15,27,30,33]

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

Malignancies

Certain types of cancers may occur in higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer.[22,27] In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

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

Malignancy is an important potential risk for patients taking tofacitinib for the treatment of rheumatoid arthritis.

Cardiovascular Disease

Patients with RA have higher rates of CVD than the general population.[23] The body of published evidence for increased risk of serious CV events among RA patients is more extensive than the published information on lipid patterns; the extent to which adverse lipid profiles contribute to increased CV risk in patients with RA is unclear.

CV risk is an important potential risk for patients taking tofacitinib for the treatment of rheumatoid arthritis.

Other Safety Events of Interest

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

8. RESEARCH QUESTION AND OBJECTIVES

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

Objectives:

To evaluate the rates of serious infections, malignancy, CV, and other specified outcomes among patients with RA in an existing UK-based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients treated with TNFi therapies to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested in this descriptive study. Pending feasibility, rates of malignancy, 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.

9. RESEARCH METHODS

9.1. Study Design

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

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

9.2. Setting

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

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

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

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

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

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

Study Population

The active surveillance population includes rheumatoid arthritis patients already enrolled in the register who met the criteria for the cohorts as defined in Section 9.3.2 as well as patients with rheumatoid arthritis, newly treated with tofacitinib following EMA approval and UK launch of the product (fully available January 2018) and registered with the BSRBR-RA. Over 3800 biologic-naïve and 2100 biologic-exposed patients are currently enrolled in the register. Some tofacitinib-exposed patients will be newly enrolled in the register, having been recruited to the BSRBR-RA within 6 months of their first dose. Others will already have been enrolled in the BSRBR-RA as prior biologic disease modifying anthirheumatic drug (bDMARD) initiators, but will switch to tofacitinib during follow up. Key clinical data at time of switch are requested. For patients enrolled during the 6 month period after initiation, the baseline date will be reported as the drug start date rather than the date of

registration. The first post-baseline visit occurs at 6 months after tofacitinib initiation, regardless of date of enrolment.

9.2.1. Inclusion Criteria

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

9.2.1.1. Inclusion Criteria: Tofacitinib-Exposed Cohort

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

9.2.1.2. Inclusion Criteria: bDMARD-Exposed Cohort

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

9.2.1.3. Inclusion Criteria: bDMARD-Naïve Cohort

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

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.2.3. Index Date

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

9.2.4. Risk Window

Within each cohort each patient will be evaluated for safety events of interest and accrue person-time from the cohort index date until the first occurrence of the event of interest, initiation of biologic (comparator cohort 1), discontinuation of biologic (comparator cohort 2), discontinuation of tofacitinib (tofacitinib-exposed cohort), death, loss to follow up, exit

from the register or after 7 years of follow up. Differences in duration of therapy will be examined (similar to censoring patterns). Interim reports will not censor the existing comparison cohorts to match the tofacitinib cohort. The final report will censor all patients at 7 years after the first tofacitinib exposed patient enters the register. Follow-up will be uniquely determined for each safety endpoint of interest.

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

For non-melanoma skin cancers (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.[18,19,31,28] Under this approach, follow up for each cohort continues from the cohort index date until the first of a malignancy event, loss to follow up, death or end of study. Follow up for each exposure cohort continues after switching to a new drug or discontinuation of treatment. This approach maximizes follow up time and the ability to capture long latency events, ie, events that occur or are detected years after exposure. Under this approach, events will be double-counted if a patient indexed to bDMARD switches to tofacitinib and a malignancy occurs subsequent to tofacitinib exposure. That is, the event will be assigned to both the bDMARD and the tofacitinib exposure cohorts as will the corresponding person years since index to the respective cohorts. Because tofacitinib is expected to be used as a later line therapy, switching is expected to be non-random with most tofacitinib patients having been included in the bDMARD cohort prior to initiation of tofacitinib. In such cases, the bDMARD rate will have more associated person-years and thus a relatively lower rate than the corresponding rate in the tofacitinib cohort.

[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.

Using this primary analytic approach, if neither tofacitinib nor bDMARDs cause an increased risk of malignancy both exposure cohort rates will reflect the background rates of malignancy from the time of index to the end of the study period and the comparative effect measure will indicate no difference in rates. If tofacitinib does cause an increased rate of malignancy, which is the effect we are most interested in detecting, a relatively higher rate will be observed in the tofacitinib exposed cohort. The once exposed always at risk approach is therefore able to detect an increased rate given the non-random switching expected to occur given use of bDMARDs prior to tofacitinib and is consistent with previous studies evaluating the risk of individual biologics.[18,19,31,28] Additional analyses will be conducted to evaluate potential confounders and the impact of different latency assumptions as will be described in the SAP. Sensitivity analyses will be conducted that restrict the bDMARD comparator cohort to patients who were never exposed to tofacitinib or other non-biologic advanced therapies and compare the characteristics of those bDMARD patients ever and never exposed to tofacitinib.

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

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

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

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

	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	0/0b	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.

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

9.3. Variables

9.3.1. Baseline Data

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

1. Diagnosis (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. Ethnicity (patient form);

4. Previous drug history of immunosuppressive csDMARDs and biologics, biosimilar or other new advanced therapy, including duration of therapy recorded as start month/year;

5. Co-morbidity (ie, http://bsrbr.org/hospitals/data-collection/);

6. All current therapy;

7. Findings necessary to calculate the DAS 28;
8. HAQ and EuroQol Five Dimensions Questionnaire (EQ-5D);
9. Height, weight, single blood pressure (BP) measurement at baseline;
10. Oral steroid use (baseline and ever exposure);
11. Smoking history (current, past, never – patient form);
12. Alcohol (weekly consumption - patient form);
13. Current working status (patient form); and
14. Vaccination.

9.3.2. Endpoints

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

The following endpoints of interest will be captured within the six-monthly BSRBR report:

1. Aplastic Anaemia, Pancytopaenia, Serious Neutropenia;
2. Cerebrovascular Accident;
3. Death;
4. Demyelination, Optic Neuritis;
5. Hepatitis B Reactivation;
6. Lymphoproliferative Malignancy;
7. Malignancy;
8. NMSC;
9. Myocardial Infarction/Acute Coronary Syndrome;
10. Pregnancy;
11. Progressive Multifocal Leukoencephalopathy (PML);
12. Pulmonary Embolism;

13. Serious Congestive Heart Failure;
14. Serious Infusion/Immunologic Reaction;
15. Serious Hypersensitivity Reaction;
16. Serious Infection;
17. Herpes Zoster;
18. Serious Hepatic Dysfunction/Failure;
19. Serious Lower Gastrointestinal Ulcer/Bleed/Perforation;
20. Serious Lupus/ Lupus-Like Illness;
21. Serious Skin Reaction (eg, Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis);
22. Serious Haemorrhage;
23. Tuberculoisis;
24. Thromboembolic events (pulmonary embolism and deep vein thrombosis).

Given the age-dependent rate events of interests, analyses may be conducted in a subset of elderly patients.

9.4. Data Sources

Baseline

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

Follow up

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

BSRBR data include reports from patients contacted every 6 months for the first three years of their follow up period and asked to complete a patient diary which includes data about hospital admissions and new hospital referrals. Data collection instruments are distributed by post to patients and their physicians according to schedule. One attempt is made to follow-up non-responders. Non-responders at one follow up point are (unless further follow up is

refused) contacted again at the next follow up point and all follow-up data since the last completed study follow-up is requested. Patients lost to follow up continue to be followed for death and cancer endpoints through the respective registers.

Endpoints

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

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

9.5. Study Size

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

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

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=11100, n=5050, n=1650;
- 4 different tofacitinib-treated patient population sizes: n=100, n=250, n=500, n=1000;
- Estimated rates on bDMARD of 30/1000 person years (PY) (eg, serious infection), 10/1000 PY (eg, malignancy excluding NMSC), and 6/1000 PY (eg, major adverse cardiovascular events (MACE)) based on previous analysis with registers (Pfizer, internal data);

- 7-year study period;
- Constant rate of accrual;
- 5% annual loss to follow up among tofacitinib-treated patients.

Additionally, Table 1 assumes a 0% annual rate of switching off tofacitinib, as would be true for a drug with very high persistence or for an analysis following the once exposed always at risk paradigm (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.[10]

For an event with a rate of 30/1000 PY, such as serious infections, 250 patients would allow sufficient power to detect a 2-fold difference in rates between tofacitinib and bDMARD-exposed patients assuming very high persistence (Table 1), while 500 tofacitinib exposed patients would be nearly sufficient if 30% of tofacitinib treated patients switched off of tofacitinib annually.

For an event with a rate of 10 cases per 1000 PY, such as malignancy excluding NMSC, a sample of 500 patients approaches 80% power in a medium (n=5050) to large (n=11,100) register when patient time continues to accrue after drug discontinuation (Table 1). It will be a challenge to achieve sufficient power in a register with fewer bDMARD exposed patients. Nonetheless, replication of a similar trend in an underpowered sample could be locally informative.

For an endpoint with an event rate of 6/1000 PY, such as MACE, even assuming high persistence (Table 1) a sample size of 1000 tofacitinib patients within a registry with more than 5000 bDMARD patients would be required to make well-powered comparison. In a scenario with a 30% annual rate of switching off of tofacitinib, 1000 tofacitinib treated patients and 11100 bDMARD patients would only provide 40% power to detect a 2-fold difference (Table 2).

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

Table 1. The Power To Detect A Two-Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD-Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 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

Number of tofacitinib exposed patients	~11100 bDMARD-treated patients	~5050 bDMARD-treated patients	~1650 bDMARD-treated patients
bDMARD rate ~30/1000 PY (eg, serious infections)			
100	0.18	0.18	0.18
250	0.50	0.49	0.46
500	0.84	0.82	0.75
1000	0.99	0.98	0.93
bDMARD rate ~10/1000 PY (eg, malignancy)			
100	0.06	0.06	0.06
250	0.16	0.16	0.15
500	0.33	0.32	0.30
1000	0.64	0.60	0.50
bDMARD rate ~6/1000 PY (eg, MACE)			
100	0.04	0.04	0.04
250	0.09	0.09	0.09
500	0.19	0.19	0.18
1000	0.40	0.38	0.32

Based on the first 12 months of enrolment of tofacitinib-exposed patients in BSRBR, 110 patients are projected to be enrolled in the first 24 months, allowing at least 5 years follow up by the end of the planned study period, assuming the initial rate remains constant over the period.

9.6. Data Management

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

9.7. Data Analysis

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

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

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

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

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 BSRBR. The approved SAP will also describe the a priori determined common set of MedDRA codes and MedDRA version to define serious infections, GI perforations, herpes zoster, and CV events (eg, MACE). The codes will be harmonised with other registers conducting similar analysis. A draft set of MedDRA codes is included in Appendix 1. Any such comparisons will be made with the overall TNFi class rather than individual therapies. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

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

The final report will also evaluate the rates of safety events of interest within the elderly. 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.

9.8. Quality Control

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

9.9. Limitations of the Research Methods

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

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

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

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the BSRBR-RA has an established system to identify and capture endpoint data, it is not feasible in such an observational study to verify all events via source documentation.

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

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

All parties will ensure protection of patient personal data and will not include patient names or any other personal identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

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

10.2. Patient Consent

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

10.3. Patient Withdrawal

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

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

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

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

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Semi-annual reports will be generated by BSRBR and shared with Pfizer. Interim reports summarizing the patient characteristics and crude event rates will be submitted to EMA to reflect 2, 4 and 6 years of the study period. A final dataset, to include 7 years of follow up, will be the basis for a final report to be submitted to EMA. The final report will be included in Risk Management Plan (RMP) updates as appropriate. Data may be used in regulatory communications external to the UK for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for external publication purposes.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

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

Study reference number: A3921312

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] 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**
1.1.4 Interim progress report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Secondary database study

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.

ENCePP Checklist for Study Protocols (Revision 3)

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	8.3
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?	☒	☐	☐	8.5
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)	☒	☐	☐	8.3
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?	☒	☐	☐	8.6
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7
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)	☒	☐	☐	8.11
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?	☒	☐	☐	8.10
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.12
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.12
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

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

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)	☒	☐	☐	8.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6
9.1.3 Covariates?	☒	☐	☐	8.6
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)	☒	☐	☐	8.6
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
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))	☒	☐	☐	8.7
9.3.3 Covariates?	☒	☐	☐	8.7
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 Is the choice of statistical techniques described?	☒	☐	☐	8.10
10.2 Are descriptive analyses included?	☒	☐	☐	8.10
10.3 Are stratified analyses included?	☒	☐	☐	8.10
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

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

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.1
11.2 Are methods of quality assurance described?	☒	☐	☐	8.11
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.10

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?	☒	☐	☐	8.12
12.1.2 Information bias?	☒	☐	☐	8.12
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)	☒	☐	☐	8.12
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.8

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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?	☒	☐	☐	9.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

This study uses secondary deidentified aggregate data.

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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