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 Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER)
Protocol Number	A3921316
Protocol Version Identifier	v 1.0
Date	21 August 2019
EU Post Authorisation Study (PAS) Register Number	To be determined
Active Substance	L04AA29 Tofacitinib
Medicinal Product	Xeljanz® (tofacitinib)
Product Reference	EU/1/17/1178/001-004
Procedure Number	EMEA/H/C/0004214
Marketing Authorisation Holder (MAH)	Pfizer Europe
Joint PASS	No
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 other new advanced targeted therapies?

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	Objectives: To estimate the rates of serious infections, malignancy, CV, and other specified outcomes among patients with RA in a Spain-based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients initiating other biologic disease modifying antirheumatic drug (bDMARD) therapies 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	Spain
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
AEMPS	Spanish Agency for Medicines and Sanitary Products
bDMARD	biologic disease modifying antirheumatic drug
BID	bis in die (Twice daily)
BIOBADASER	Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases
CNS	central nervous system
csDMARD	conventional synthetic disease modifying antirheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DMARD	disease modifying antirheumatic drug
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	erythrocyte sedimentation rate
EU	European Union
GI	gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HZ	herpes zoster
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
JAK	janus kinase
LTE	long term extension
MACE	major adverse cardiac events
MAH	market authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MTX	methotrexate
NDA	New Drug Application
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	post authorization study
PASS	Post-Authorization Safety Study
PML	progressive multifocal leukoencephalitis
PY	person-years
RA	rheumatoid arthritis
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SER	Spanish Society of Rheumatology
SIR	standardized incidence ratio
TB	tuberculosis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor

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2. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable.

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3. 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 Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER).

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 BIOBADASER.

Research Question: What are the rates of adverse outcomes of special interest in RA patients treated with tofacitinib in relation to other new advanced targeted therapies (eg, biologic DMARDS (bDMARDS)?

Objectives: To estimate the rates of serious infections, malignancy, CV, and other specified outcomes among patients with RA in a Spanish register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients initiating bDMARDS to provide context for rates observed on tofacitinib.

Study design: This active surveillance study is using existing data from BIOBADASER, an ongoing, prospective observational cohort study conducted to monitor the safety of biological drugs in a real-world setting, to identify adverse events (AE)s, and to estimate the risk of AEs.

Population: The study population will comprise all patients with RA enrolled within the BIOBADASER who receive tofacitinib following European Medicines Agency (EMA) approval and Spanish launch. For contextualization purposes, the study population will also include BIOBADASER patients meeting the inclusion/exclusion criteria who are treated with bDMARDs.

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 not restricted to, the following: serious infections, malignancies, and cardiovascular events.

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Data sources: BIOBADASER collects core baseline data, including patient demographics and disease characteristics, from the recruiting clinician using a standardised form. In addition, some personal and medical information are obtained directly from each patient recruited (eg, smoking history, alcohol consumption, and work status). Recruiting physicians provide information on treatment changes and endpoints of interest in conjunction with clinic visits or at least every 12 months.

Study size: This is a descriptive study without pre-specified hypotheses therefore there is no minimum sample size requirement.

Data analysis: Descriptive statistics for baseline variables and survival curves for AEs and discontinuation will be reported annually.

Milestones: Annual summary reports of patient characteristics and adverse event rates will be provided 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 study report will include approximately 7 years after the date of the first tofacitinib patient enrollment in the study.

4. AMENDMENTS AND UPDATES

None.

5. 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

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6. 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.[13,27] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA.[14] Unlike biological therapies, such as tumor 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 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.[18] 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

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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 BIOBADASER, is designated as a PASS and is conducted by Pfizer as a Category 3 commitment to the European Medicines Agency (EMA).

6.1. Serious Infections

The risk of infections among RA patients depends on the environmental distribution of the organism of interest, inherent patient characteristics and treatment for RA. Persons with RA ≥65 years of age are found to be at increased risk of serious infections relative to those <65 years of age in both clinical trial and observational data.[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,[4,7,9,21] however studies looking at TNFi-treated cohorts over time have shown that rates of serious infection decline over time.[3,24] 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.[24]

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 (HZ) in RA and general population cohorts have been inconsistent, with some showing no increased risk and some showing modestly elevated risk.[11,23,25,29]

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

6.2. Malignancies

Certain types of cancers may occur in higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer.[19,23] 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

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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.[15]

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

6.3. Cardiovascular Disease

Patients with RA have higher rates of CVD than the general population.[20] 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.

6.4. Other Safety Events of Interest

BIOBADASER collects data about 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.

7. 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 other advanced targeted therapies (eg, Biologic DMARDs) in real-world clinical practice?

Objectives:

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 BIOBADASER. To estimate the rates of serious infections, malignancy, CV, and other specified outcomes among patients with RA in a Spain-based register who initiate tofacitinib. Rates will also be estimated among existing cohorts of patients initiating bDMARDS to provide context for rates observed on tofacitinib. No a priori hypotheses will be tested. Pending feasibility, rates of malignancy, serious infection, CV and other event rates will be compared between tofacitinib-treated RA patients and the comparator cohort using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders.

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8. RESEARCH METHODS

8.1. Study Design

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

This study, will estimate the incidence rates of safety events of interest among patients starting tofacitinib for RA treatmentto monitor the safety of biological drugs in a real-world setting, to identify adverse events (AE)s, and to estimate the risk of AEs. Rates will also be estimated among other cohorts within BIOBADASER (1) a contemporaneous cohort of RA patients starting recently approved biological therapies other than biosimilars and (2) a historical cohort of RA patients who initiated treatment with an approved bDMARD between 2000 and 2016. Data capture and follow-up methods are the same for all cohorts within the BIOBADASER. 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).

8.2. Setting

BIOBADASER has been active since being created by the Spanish Society of Rheumatology (SER) and the Spanish Agency for Medicines and Sanitary Products (AEMPS) in 2000. The register is currently in its third phase, BIOBADASER, 3.0. Phase 3 began in December 2015 across 35 centers, and after the first year a maximum of 20 centers meeting quality standards were retained in the register to ensure adequate resources for annual site monitoring. The registry initially included patients treated with biological drugs or biosimilars for any rheumatologic disease treated in participating Rheumatology Services centers. Beginning in September, 2017, tofacitinib-treated patients were added to the register. Approximately 50% of patients entering the registry have a diagnosis of RA. Patients entering the registry will be evaluated at least once each year, or when treatment changes (whether suspension, drug or dose changes) or by the occurrence of AEs. Enrolled patients must have a diagnosis of RA, agree to prospective data collection and provided informed consent, initiated treatment with tofacitinib, or a biological therapy other than infliximab, etanercept and adalimumab, or a biosimilar in the participating centers, or continued ongoing treatment with other biological therapies or restart following treatment suspension for any reason, provided that no more than one year has elapsed since the last treatment was taken and all the data necessary to the registry are available (of the patient, of the treatment and of the AEs). An historical cohort (2000-2016) (BIOBADASER 2.0) includes patients with a diagnosis of RA. All participants agreed to prospective data collection and provided informed consent, and new user of an approved bDMARD.

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Study Population

The active surveillance population includes BIOBADASER patients meeting the inclusion/exclusion criteria who are treated with tofacitinib post-EMA approval and Spanish launch (product fully available October 2017). For contextualization purposes, two cohorts of BIOBADASER patients meeting the inclusion/exclusion criteria who are treated with bDMARDs will be included in the study. The first comparator population consists of a contemporaneous cohort of patients prescribed newer biologics after December 2015 (BIOBADASER 3.0). The second comparator population consists of a historic cohort of patients prescribed bDMARDS between 2000 and 2015 (BIOBADASER, 2.0). Patients switching therapies are eligible to move between cohorts if inclusion/exclusion criteria are met.

8.2.1. Inclusion Criteria

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

8.2.1.1. Tofacitinib-Exposed Cohort Inclusion Criteria

1. Included in BIOBADASER.
2. Initiated tofacitinib.

8.2.1.2. Contemporaneous bDMARD-Exposed Cohort Inclusion Criteria

1. Included in BIOBADASER.
2. Initiated bDMARD on or after 01Jan 2016.

8.2.1.3. Historical bDMARD-exposed Cohort Inclusion Criteria

1. Included in BIOBADASER.
2. Initiated bDMARD on or before 31Dec2015.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients not meeting inclusion criteria will be excluded.

Index Date

The index date for the tofacitinib cohort is the date the first tofacitinib dose was taken. Similarly, the index date for bDMARD-initiator cohorts is the date of the initiation of the first bDMARD. Patients who switch to a subsequent therapy are eligible for enrollment as an initiator of the subsequent therapy, and the index date will be the date of initiating the subsequent therapy.

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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, discontinuation of index treatment, death, loss to follow up, exit from the registry or after 7 years of follow up. Differences in duration of therapy will be examined (similar to censoring patterns). Annual 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 encephalopathy (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 from drug initiation until the first event or loss to follow up, reflecting a once-exposed always at risk paradigm. If a patient switches to a new drug, the subsequent observation time will contribute to multiple therapies. PML rates will also be described using this approach.

For 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.[15, 16, 25, 27] 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.

[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.

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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.[15, 16, 25, 27] 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.[15, 16, 27]

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

*: 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	1/6a
*~ ~ ~ ^ - - - ~ ~ ~ X	1/9	1/6	0/3	0/3
^ - - - - ~ ~ ~ X	0/0b	1/7	0/0b	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.

8.3. Variables

8.3.1. Baseline Data

The baseline variables in BIOBADASER are collected from the recruiting patient (or physician where noted) at the index date of first entry to BIOBADASER. Physician information is collected at index and annually thereafter. If a patient switches therapy the most recent data prior to switch will be used as baseline data.

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 (patient).

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3. Ethnicity (patient).

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

5. Co-morbidity calculating the Charlson index (patient).

6. All current therapy.

7. Baseline disease activity (at time of enrollment): number of inflamed and painful joints (28); patient's visual analog scale, and erythrocyte sedimentation rate (ESR).

8. History of TB.

8.3.2. Follow-up

BIOBADASER follow up data derive from routine follow up visits and at least annually query physicians about changes in therapy (switches, interruptions), disease activity, and adverse events through web-based interface.

8.3.3. Endpoints

BIOBADASER endpoint data derive from required reporting by participating physicians on 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. HZ.

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. Peripheral multifocal leukoencephalopathy.

8. Allergic conditions and hypersensitivity.

9. Hepatic failure.

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10. Gastrointestinal (GI) perforations.

11. Thromboembolic events: pulmonary embolism, deep vein thrombosis.

12. Pregnancy.

13. Operations and hospitalizations: bone and joint survery 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.

8.4. Data Sources

This study uses information from existing BIOBADASER register for baseline, follow-up, and endpoint variables. BIOBADASER collects core baseline data, including patient demographics and disease characteristics, from the recruiting clinician using a standardised form. In addition, some personal and medical information are obtained directly from each patient recruited (eg, smoking history, alcohol consumption, and work status). Recruiting physicians provide information on treatment changes and endpoints of interest in conjunction with clinic visits or at least every 12 months.

8.5. 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 Spain.

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

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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.[9].

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.

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Table 1. The Power To Detect A Two-Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD-Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5-Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm

Number of tofacitinib exposed patients	~11100 bDMARD-treated patients	~5050 bDMARD-treated patients	~1650 bDMARD-treated patients
bDMARD rate ~30/1000 PY (eg, serious infections)			
100	0.46	0.45	0.44
250	0.92	0.91	0.88
500	1.00	1.00	0.99
1000	1.00	1.00	1.00
bDMARD rate ~10/1000 PY (eg, malignancy)			
100	0.11	0.12	0.12
250	0.38	0.38	0.36
500	0.75	0.73	0.66
1000	0.98	0.96	0.89
bDMARD rate ~6/1000 PY (eg, MACE)			
100	0.06	0.06	0.06
250	0.20	0.20	0.20
500	0.47	0.46	0.41
1000	0.83	0.79	0.68

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Table 2. The Power To Detect A Two-Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD-Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5-Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, 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 10 months of enrolment of tofacitinib-exposed patients in BIOBADASER, 187 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.

8.6. Data Management

In BIOBADASER, each patient is assigned a unique auto-numeric code that stays with the patient even from center to center.

8.7. Data Analysis

Annual Reports: Descriptive reports summarizing the crude rates of occurrence of safety-related endpoints among tofacitinib-treated patients and comparator populations will be created annually, as is the practice of BIOBADASER.

The data collected will be compiled in indices (counts, rates, mean, median, standard devation)), and in Kaplan-Meier survival curves, in which the censoring variable is treatment

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interruption or safety event of interest, depending on the objective. The results will be reported in absolute and relative frequencies and incidence density rates (patients/year). The final report will also evaluate the rates of safety events of interest within the elderly.

The report will also include: Number of participating centers; Number of patients on treatment that have been included and description: sex, age at the beginning of treatment, diagnosis, duration of illness at the start of treatment, biological treatments received, information on treatment interruptions, absolute and relative frequency of interruptions, survival curve until interruption, absolute and relative frequency of interruptions due to ineffectiveness , absolute and relative frequency of interruptions due to safety events of interest, absolute and relative frequency of interruptions for other reasons, Information on safety events of interest: absolute and relative frequency of AEs during treatment: Overall, and by specific event.

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 BIOBADASER. The approved SAP will also describe the a priori determined common set of Medical Dictionary for Regulatory Activities.

(MedDRA) codes and the same MedDRA version to define serious infections, GI perforations, herpes zoster, and CV events (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 bDMARD class rather than individual therapies.

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

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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.

8.8. Quality Control

Data used in this study are secondary use of data collected as part of existing BIOBADASER registry. BIOBADASER incorporates annual quality checks as part of its ongoing processes.

8.9. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing data from BIOBADASER, a well-established Spain-based rheumatology registry. Despite the strengths of the registry, 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. 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. 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 BIOBADASER 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.

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8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. 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 BIOBADASER, therefore patient consent is not applicable.

9.2. 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.

9.3. Patient Withdrawal

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

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

IRB/IEC review was not required per local regulation.

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.

9.5. Ethical Conduct of the Study

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

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10. 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 adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met*.

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, 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) are not available* and AEs are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual reports will be generated and provided to 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 the risk management plan (RMP) updates. Data may be used in regulatory communications external to Spain 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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13. LIST OF TABLES

14. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

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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 Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER)

Study reference number: A3921316

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.

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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:

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)

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.2
4.2.2 Age and sex?	☐	☒	☐	
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)	☒	☐	☐	8.5
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?	☒	☐	☐	8.6
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6/8.7
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)	☐	☐	☒	
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?	☒	☐	☐	8.10
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:

Adjustment methods will be determined in 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)	☒	☐	☐	8.7
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.7
9.1.3 Covariates?	☒	☐	☐	8.7
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?	☐	☒	☐	
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:

Final adjusted analysis methods to be described in SAP

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)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	8.11
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

BIOBADASER is an independent entity and will be conducting the analyses

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.
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.

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Appendix 1. ICD and MedDRA Codes For Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	Operationalization	Validation ICD	Operationalization (Final list TBD based on reported endpoints)
Serious infections	Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1	This algorithm has not been specifically validated in ARTIS, but the register itself is subject to strict quality assurance routines and has been validated several times. Refs: Ludvigsson et al. External Review and Validation of the Swedish National Inpatient Register, BMC Public Health, 2011 (11):450 http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish	Hospitalization and/or use of parenteral antibiotics+ MedDRA Infections and Infestations SOC 10021881

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

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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; 10008076 Cerebral aneurysm ruptured syphilitic;

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		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 artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure;

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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 fistula; 10058381 Oesophageal fistula repair; 10059175

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			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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