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
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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?

	Objectives: To estimate the rates of serious infections, malignancy (overall, excluding non-melanoma skin cancer [NMSC]), lung cancer, subtypes of lymphoma, CV events, MACE, MI, VTE (DVT and PE, and other specified outcomes, including fractures, 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. Further, event rates will be estimated in elderly patients aged 65 years and older. Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, MI, VTE, and other event rates, including fractures, will be compared between tofacitinib treated RA patients and other comparator cohorts using methods to adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities and other potential confounders.
Country(-ies) of Study	Spain
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2. 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
DVT	deep venous thrombosis
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPITT	European Pharmacovigilance Issues Tracking Tool
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	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mg	milligram
MTX	methotrexate
NDA	New Drug Application
NHL	Non-Hodgkin's lymphoma
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
OI	opportunistic infection
PAS	post authorization study
PASS	Post-Authorization Safety Study
PE	pulmonary embolism
PML	progressive multifocal leukoencephalitis
PRAC	Pharmacovigilance Risk Assessment Committee
PY	person-years
RA	rheumatoid arthritis
RMP	risk management plan

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SER	Spanish Society of Rheumatology
SIR	standardized incidence ratio
SmPC	Summary of Product Characteristics
TB	tuberculosis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
VTE	venus thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

Title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER).

Version: Final Protocol (V3.0)

Date: 14 February 2022

Rationale and background: Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome. Tofacitinib was approved in the European Union (EU) in March 2017 at a dose of 5 mg administered twice daily (BID) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). To enable assessment of safety outcomes of 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 enable assessment of safety events 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. Further, the study will estimate the rates of serious infections, malignancy (overall, excluding NMSC), lung cancer, subtypes of, CV events, major adverse cardiovascular events (MACE), myocardial infarction (MI), venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]) and other specified outcomes, including fractures, among patients with RA in a 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. Pending feasibility, rates of malignancy (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, MI, VTE, and other event rates, including fractures, will be compared between tofacitinib-treated RA patients and the comparator cohort using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and MACE have been added as study endpoints (MI and lymphoma (overall) were already included as a study endpoints). Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

Study design: This active surveillance study 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, including identifying and estimating the risk of safety events.

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 (overall), lymphoma (overall and by subtype), lung cancer, cardiovascular events (including MACE) and VTE (DVT and PE).

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

Milestones: Interim reports will be provided at 2, 4, 6 years after the start of data collection. A final study report will include approximately 7 years after the date of the first tofacitinib patient enrollment in the study.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	September 2021	Title Page	Updated to replace old Pfizer logo with new one. Updated to include EU PAS register number. Updated objectives to align with updates in protocol. Updated contact information for a protocol author Updated contact information for the MAH Contact Person	Editorial change Editorial change Editorial change Study transition for the Marketing Authorisation Holder's (MAH) Protocol Author Study staff transition for the MAH's vendor
	September 2021	Section 2	Updated to include new abbreviations	Editorial Change
	September 2021	Section 3	Updated contact information for a Principal Investigator of the protocol Edits to Abstract	Study transition for MAH's Principle Investigator Editorial change.
	September 2021	Section 4	Revised version and date. Updated Objective, Variables, and Data Analysis to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated Variables to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes. Updated Study Design.	PRAC request and clarification. Editorial change
	September 2021	Section 7	Updated to include information on changes to protocol resulting from 2021 signal evaluation procedures Updated to include fractures as an additional safety event of interest	Editorial changes Based on available data, Pfizer has identified fractures as a potential risk factor
	September 2021	Section 7.2	Updated to include information on changes to protocol resulting from 2021 signal evaluation procedures	Editorial changes
	September 2021	Section 7.3	Updated to include information on changes to protocol resulting from 2021 signal evaluation procedures	Editorial changes

	September 2021	Section 8	Updated objectives to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated objective to include estimation of event rates in the elderly aged 65 years and older.	PRAC request and clarifications
	September 2021	Section 9.1	Updated Study Design.	Editorial change.
	September 2021	Section 9.2	Updated Study Population.	Editorial change.
	September 2021	Section 9.2.4	Updated Risk Window to include sensitivity analysis for the 90-extension period. Added additional safety endpoints.	PRAC request and clarification.
	September 2021	Section 9.3.1	Updated to list examples of co-morbidities of interest and to include VTE and CV risk factors.	PRAC request and clarifications
	September 2021	Section 9.3.3	Updated to include lymphoproliferative malignancy subtypes, lung cancer and MACE as additional safety endpoints. Updated to include statement that safety endpoints will be analyzed in elderly patients aged 65 years and older. Updated to include fracture as additional safety endpoint. Updated to include all-cause mortality as a safety endpoint.	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk Editorial Change.
	September 2021	Section 9.7	Updated analysis to specify subgroup analyses for MI and MACE as well as lymphoproliferative malignancy subtypes. Updated to specify ‘elderly’ as aged 65 years and older. Updated to include stratified analyses among patients with malignancy and VTE and CV risk factors.	PRAC request and clarifications
	September 2021	Annex 2	Signature and signature date updated	Editorial change
	September 2021	Appendix 1	Updated to include definitions for additional endpoints.	PRAC request and clarifications

2.0	February 2022	Title Page	Updated Research Questions and Objectives to include change in terminology from 'lymphoproliferative malignancy' to 'lymphoma' and to include VTE as an outcome of interest (VTE was already included as an outcome in the previous version of protocol. Included VTE in this section for consistency with the rest of protocol).	PRAC request and clarification
	February 2022	Section 2	Updated to include new abbreviations	Editorial change
	February 2022	Section 4	Revised version and date. Updated Objective and Variables to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added VTE as an outcome of interest for consistency with other sections of the protocol (VTE was an outcome of interest in the previous version of the protocol). Updated Data Analysis to include stratified analysis for VTE incidence rates by ⩾1 VTE risk factors versus no VTE risk factors. Removed 6-monthly reports from the Milestones.	Editorial change PRAC request and clarification PRAC request and clarification
	February 2022	Section 7.3	Updated the Cardiovascular Disease section to remove MACE as an "important identified risk".	PRAC request and clarification
	February 2022	Section 8	Updated Objective to replace the term 'lymphoproliferative malignancy' with 'lymphoma' and added VTE (DVT and PE) as an outcome of interest for consistency with other sections of the protocol (VTE was an outcome of interest in the previous version of the protocol).	PRAC request and clarification
	February 2022	Section 9.3.1	Updated to include chronic kidney disease and hypercholesterolemia.	PRAC request and clarification
	February 2022	Section 9.3.3	Updated the Endpoints to replace the term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
	February 2022	Section 9.7	Updated Data Analysis to include stratified analysis for VTE incidence rates by ⩾1 VTE risk factors versus no VTE risk factors. For consistency, updated to include statement that safety endpoints will be analyzed in elderly patients aged 65 years and older.	PRAC request and clarification Editorial change

	February 2022	Section 9.9	The limitations of the study methods were updated to include additional limitations to methods that were amended in the previous protocol amendment (e.g. missingness of certain patient characteristics)	PRAC request and clarification
	February 2022	Section 12	Removed reference to the reports provide to MAH every 6 months.	PRAC request and clarification.
	February 2022	All sections where applicable	Replaced term 'lymphoproliferative malignancy' with 'lymphoma'.	PRAC request and clarification
	February 2022	Annex 2	Signature date updated	Editorial change

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 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 lymphoma.

It therefore follows that for all new biologic and other targeted therapies there is a need for active surveillance to identify higher than expected rates of such safety events overall and within strata of disease severity, treatment history, and other concomitant therapy. Long term morbidity and mortality event-tracking of these cohorts over 7 years is an appropriate method for evaluating the risk associated with these treatments.

There is an increased risk of premature mortality, serious infection and lymphoma in patients with RA and other connective tissue diseases, independent of the treatment they have received.[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. Additionally, following the result of the June 2021 signal evaluation procedure

(European Pharmacovigilance Issues Tracking Tool (EPITT) Number 19382) to assess the increased incidence rate of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients treated with tofacitinib for rheumatoid arthritis (RA), lung cancer has been added as a study endpoint to this protocol (myocardial infarction (MI) and lymphoma (overall) were already included as study endpoints prior to the signal evaluation). It is therefore fundamentally important to describe the occurrence of these events among patients treated with newly approved therapies and among patients who remained on "conventional" therapy or received a different targeted agent.

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).

7.1. 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.

7.2. 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 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. As part of the June 2021 signal procedure (EPITT No. 19832), lung cancer and lymphoma were categorized as important identified risks for tofacitinib.

7.3. 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. In 2019, venous thromboembolism (VTE) was determined to be an important identified risk for tofacitinib. In January 2020, as a result of a reassessment of the benefit-risk of tofacitinib, the European Commission (EC) approved several revisions to the Summary of Product Characteristics (SmPC), including addition of VTE as an important identified risk associated with the use of tofacitinib. As part of the June 2021 signal procedure (EPITT No. 19382), MI was categorized as an important identified risk for tofacitinib.

7.4. Other Safety Events of Interest

BIOBADASER collects data about other safety events of interest in the RA population including central nervous system (CNS) events, fractures, pregnancy and mortality. Rates of these events will also be estimated to potentially identify new safety signals.

8. RESEARCH QUESTION AND OBJECTIVES

This study asks what are the rates of 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 (overall, excluding NMSC), lung cancer, lymphoma (overall and by subtype), CV events, MACE, MI, VTE (DVT and PE), and other specified outcomes, including fractures, 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 (overall, excluding NMSC), lung cancer, subtypes of lymphoma, serious infection, CV events, MACE, MI, VTE, and other event rates, including fractures, will be compared between tofacitinib-treated RA patients and the comparator cohort using methods that adjust for sex, age, year of treatment start, treatment history, disease severity, comorbidities, and other potential confounders. In response to the June 2021 signal evaluation procedure, subtypes of lymphoma, lung cancer, and major adverse cardiovascular events (MACE) have been added as study endpoints (MI and lymphoma (overall) were already included as study endpoints). Further, rates of events, including serious infections, MACE, MI, VTE, and malignancies excluding NMSC, will be estimated in elderly patients aged 65 years and older.

9. RESEARCH METHODS

9.1. 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 treatment to monitor the safety of biological drugs in a real-world setting, including identifying and estimating the risk of safety events. 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).

9.2. 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.

Study Population

The active surveillance population includes RA patients already enrolled in BIOBADASER 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.

9.2.1. Inclusion Criteria

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

9.2.1.1. Tofacitinib-Exposed Cohort Inclusion Criteria

1. Included in BIOBADASER.
2. Initiated tofacitinib.

9.2.1.2. Contemporaneous bDMARD-Exposed Cohort Inclusion Criteria

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

9.2.1.3. Historical bDMARD-exposed Cohort Inclusion Criteria

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

9.2.2. 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.

9.2.3. 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.

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, 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. As an additional sensitivity analysis for MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events with a 90-day extension period applied after treatment discontinuation, if a new medication is started during the 90-day window after discontinuation of a previous medication, initiation of the new medication will stop the 90-day risk window, and any event prior to the new medication start will be assigned to the discontinued medication. Similarly, as part of the primary analysis, for malignancy and all-cause mortality events, a 90-day risk window will be applied to the censoring at switch approach (ie, if a malignancy or death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy).

For non-melanoma skin cancer (NMSC), lung cancer, lymphoma and malignancies excluding NMSC, and all-cause mortality, the manifestation of which is expected to be delayed relative to the time of exposure, the 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.

[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.

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. 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]

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.

9.3. Variables

The study variables include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies) and safety events of interest including, but not restricted to, the following: serious infections, malignancies (overall),

lymphoma (overall and by subtype), lung cancer, cardiovascular events (including MACE) and VTE (DVT and PE).

9.3.1. 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).

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) (eg, history of serious infection, history of opportunistic infection, history of herpes zoster, history of VTE, history of diabetes mellitus, history of MI, history of hypertension, history of fractures, and ever for malignancy events (ie, history of malignancies excluding NMSC, and specifically history of NMSC, history of lymphoma and history of lung cancer), and history of fractures).

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.

To facilitate the evaluation of the primary endpoint of VTE, the following VTE risk factors will be evaluated at baseline and/or, for some risk factors, within specific time periods prior to index date as specified below:

- Age

- Previous VTE

- Undergoing major surgery from date of hospital admission to 1 month after date of discharge

- MI within previous 3 months prior to index date (defined in Section 9.2.3)
- Heart failure
- Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date
- Malignancy
- Diabetes
- Hypertension
- Inherited coagulation disorders
- Inpatient care because of RA (i.e., RA as main diagnostic listing; from date of admission to date after discharge)

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

- Age (patients ≥65 years versus <65 years)
- History of chronic kidney disease (collected in the initial visit as part of the Charlson index (moderate to severe chronic kidney disease))
- History of hypercholesterolaemia
- History of diabetes
- History of hypertension
- History of previous MI
- History of coronary heart disease
- History of stable angina pectoris

9.3.2. 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 safety events through web-based interface.

9.3.3. 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. Fractures.
5. Cardiac disorders: heart failure, coronary artery disease, myocardial infarction, MACE, other cardiac disorders.
6. Hematologic disorders: bone marrow depression and hypoplastic anaemia, decreased white blood cells, platelet disorders, other blood dyscrasia.
7. Disorders of the nervous system (excluding infections): stroke, central demyelination, other disorders of the CNS, disorders of the peripheral nervous system, psychiatric disorders.
8. Peripheral multifocal leukoencephalopathy.
9. Allergic conditions and hypersensitivity.
10. Hepatic failure.
11. Gastrointestinal (GI) perforations.
12. Thromboembolic events: pulmonary embolism, deep vein thrombosis.
13. Pregnancy.
14. Operations and hospitalizations: bone and joint survery and other joint therapeutic procedures, other operations and (major) therapeutic procedures that lead to hospitalization.
15. Other serious diagnoses, symptoms, and syndromes.
16. NMSC.
17. Malignancies (overall, excluding NMSC).

18. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia).

19. Lung Cancer.

20. All-cause Mortality.

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

9.4. 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.

9.5. 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 cardiovascular events (MACE) based on previous analysis with registers (Pfizer, internal data);
- 7-year study period;
- Constant rate of accrual;

- 5% annual loss to follow up among tofacitinib-treated patients.

Additionally, Table 1 assumes a 0% annual rate of switching off tofacitinib, as would be true for a drug with very high persistence or for an analysis following the once exposed always at risk paradigm. Table 2 assumes a 30% annual rate of switching from tofacitinib to a bDMARD over the study period, as previously demonstrated in the EU for bDMARDs in Italy.[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.

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

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

Table 2. The Power To Detect A Two-Fold Difference In Risk Among Tofacitinib Exposed Patients Compared With bDMARD-Treated Register Patients Given Different Assumed Sample Sizes, alpha = 0.05, 5-Year Study With Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, 30% Switch From Tofacitinib to bDMARD Per Year

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

Based on the first 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.

9.6. Data Management

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

9.7. 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 deviation), and in Kaplan-Meier survival curves, in which the censoring variable is treatment

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 rates of safety events of interest, including infections, MACE, MI, and malignancies including NMSC, will also be evaluated within the elderly aged ≥65 years. Descriptive data will be presented in the interim reports. At study completion, all descriptive and comparative data analyses will be presented in the final report.

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 safety events 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). Increased risk of malignancy (excluding NMSC), MACE, MI, serious infection, VTE, herpes zoster, PML, and gastrointestinal perforation events, as well as an increase in mortality, in patients treated with a combination therapy with MTX specifically will be described if sample sizes are sufficient, in the interim and final reports. These and potentially other agreed upon strata will be determined 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, fractures 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.

For lymphoma, incidence rates will be stratified by lymphoma subtypes; not limited but including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphatic leukemia. Similarly, CV event rates will be stratified by type of event (eg, myocardial infarction (MI), MACE, serious congestive heart failure). Further, for the outcomes of MI and MACE, incidence rates of the safety events of interest will be stratified by patients with ≥1 CV risk factors versus no CV risk factors. Likewise, VTE event rates will be stratified by type of

event (DVT and PE). Further, for the outcomes of VTE, incidence rates of the safety events of interest will be stratified by patients with ≥1 VTE risk factors versus no VTE risk factors. The rates of safety events of interest, including infections, MACE, MI, VTE, and malignancies excluding NMSC, will also be evaluated within the elderly aged ≥65 years.

Descriptive data will be presented in the interim reports. At study completion, all descriptive and comparative data analyses will be presented in the final report.

If feasible, stratified analyses to estimate the incidence rates for VTE stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors will also be conducted (ie, time period prior to 31 January 2020 vs. time period after 31 January 2020). Additionally, if feasible, stratification of the incidence rates for malignancy excluding NMSC, lung cancer, lymphoma, MACE and MI by time periods defined by changes in the SmPC for use in patients with malignancy and CV risk factors will be conducted (ie, time period after June 2021).

Meta-analytic methods that attempt to combine the results of this study with results from other participating European registers will be used to summarize the findings across studies. A quantitative meta-analysis would permit an estimate of an average effect across the studies with more statistical power than the individual studies, provided a formal evaluation did not reveal substantial heterogeneity. Meta-analysis may reveal between-study heterogeneity such that a subset of more comparable studies could be included in a single estimate. Heterogeneity may be expected, for example due to differences in local prescribing practices, patient populations, competing risks, and prevalence of comorbidities and risk factors. Such heterogeneity would exist even if the coding for endpoint definitions and reporting could be harmonized across registers. In the presence of such heterogeneity, pooling across the registers is not informative as the generalizability of such an estimate is unknown. Pending feasibility of comparative analysis, meta-analytic methods will be determined a priori and described in an approved SAP.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

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

9.9. 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.

Certain patient characteristics to help define baseline risk are not captured or are subject to high levels of missing and may limit data interpretation; such characteristics include alcohol consumption, history of comorbidities (e.g. serious or opportunistic infections, herpes zoster, fractures), characteristics which may influence VTE outcomes (e.g. previous VTE, previous major surgery, current or recent use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date (likely to be missing in database), inherited coagulation disorders), or characteristics which may influence CV risk (e.g. history of coronary artery procedures).

Additionally, stratified analyses by time periods after January 2020 will be limited to the RA patients receiving tofacitinib as the registry is no longer recruiting new patients receiving TNF and DMARD therapy regimens.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While 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.

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 BIOBADASER, 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; analyses planned utilize data from secondary data sources that do not include patient identifiers.

10.4. 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.

10.5. Ethical Conduct of the Study

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any

individual. Thus, the minimum criteria for reporting an 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, Post-Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Tofacitinib for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Spanish Registry of Adverse Events of Biological Therapies and Biosimilars in Rheumatoid Diseases (BIOBADASER)

EU PAS Register® number: EUPAS31129
Study reference number (if applicable): 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[2]	☒	☐	☐	5
1.1.2 End of data collection[3]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim 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] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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, other design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

No measure of association will be determined in this descriptive study. This is a secondary database study using structured data, no reporting of adverse events is required for this protocol.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	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	☒	☐	☐	8.2
4.2.3 Country of origin	☒	☐	☐	8.2
4.2.4 Disease/indication	☒	☐	☐	8.2
4.2.5 Duration of follow-up	☒	☐	☐	8.3.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.1/8.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.2

Comments:

Exposure is assumed after index until report of discontinuation during risk window for interim reports. Final study SAP will describe methods for accounting for exposure.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7, Appendix 1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

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

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

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)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4,9.7.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	9.4,9.7.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.2.4

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)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8

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?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7, 8.5., 8.7

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	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: Michelle Iannacone

Date: 14 February 2022

Signature: 

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

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

CV risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care	See Serious Infections 'Outcome' was defined as any first-ever ACS event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the 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;

		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;

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

			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)
Lung Cancer	Identified through the Cancer Register. ICD-7: 162.1		HLTs: 10038723 Respiratory tract and pleural neoplasms malignant cell type unspecified NEC; 10024973 Lower respiratory tract neoplasms. LLT: 10023292 Kaposi's sarcoma, lung; Exclude PTs: 10043515 throat cancer; 10004280 benign lung neoplasm; 10061002 benign respiratory tract neoplasm, 10052247 bronchial neoplasm benign; 10014654 endobronchial lipoma; 10081106 sclerosing pneumocytoma.
Lymphoma	Identified through the Cancer Register. All non-Hodgkin Lymphoma: ICD-7: 200,202 All Hodgkin Lymphoma: ICD-7: 201	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as	Non-Hodgkin's lymphoma 10029547; Non-Hodgkin's lymphoma metastatic 10071535; Non-Hodgkin's lymphoma recurrent 10029600; Non-Hodgkin's

	Chronic lymphocytic leukemia: ICD-7: 204.1	well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%	lymphoma refractory 10029601; Non-Hodgkin's lymphoma stage I 10029602; Non-Hodgkin's lymphoma stage II 10029603; Non-Hodgkin's lymphoma stage III 10029604; Non-Hodgkin's lymphoma stage IV 10029605; Non-Hodgkin's lymphoma transformed recurrent 10061871; Non-Hodgkin's lymphoma unspecified histology aggressive 10063908; Non-Hodgkin's lymphoma unspecified histology aggressive recurrent 10029609; Non-Hodgkin's lymphoma unspecified histology aggressive refractory 10029610; Non-Hodgkin's lymphoma unspecified histology aggressive stage I 10029611; Non-Hodgkin's lymphoma unspecified histology aggressive stage II 10029612; Non-Hodgkin's lymphoma unspecified histology aggressive stage III 10029613; Non-Hodgkin's lymphoma unspecified histology aggressive stage IV 10029614; Non-Hodgkin's lymphoma unspecified histology indolent 10065856; Non-Hodgkin's lymphoma unspecified histology indolent stage I 10029622; Non-Hodgkin's lymphoma unspecified histology indolent stage II 10029623; Non-Hodgkin's lymphoma unspecified histology indolent stage III 10029624; Non-Hodgkin's lymphoma unspecified histology indolent stage IV 10029625; Hodgkin's disease 10020206; Hodgkin's disease lymphocyte depletion stage I site unspecified 10020208; Hodgkin's disease lymphocyte depletion stage I subdiaphragm 10020209; Hodgkin's disease lymphocyte depletion stage I supradiaphragm 10020210; Hodgkin's disease lymphocyte depletion stage II site unspecified 10020211; Hodgkin's disease lymphocyte depletion stage II subdiaphragm 10020212; Hodgkin's disease lymphocyte depletion stage II supradiaphragm 10020213; Hodgkin's disease lymphocyte depletion type recurrent 10020215; Hodgkin's disease lymphocyte depletion type refractory10020216; Hodgkin's disease lymphocyte depletion type stage III 10020217; Hodgkin's disease lymphocyte depletion type stage IV 10020218; Hodgkin's disease lymphocyte depletion type stage unspecified 10020219; Hodgkin's disease lymphocyte predominance stage I site unspec 10020220; Hodgkin's disease lymphocyte predominance stage I subdiaphragm 10020221; Hodgkin's disease lymphocyte predominance

			stage I supradiaphragm 10020222; Hodgkin's disease lymphocyte predominance stage II site unspec 10020223; Hodgkin's disease lymphocyte predominance stage II subdiaphragm 10020224; Hodgkin's disease lymphocyte predominance stage II supradiaphragm 10020225; Hodgkin's disease lymphocyte predominance type recurrent 10020227; Hodgkin's disease lymphocyte predominance type refractory 10020228; Hodgkin's disease lymphocyte predominance type stage III 10020229; Hodgkin's disease lymphocyte predominance type stage IV 10020230; Hodgkin's disease lymphocyte predominance type stage unspecified 10020231; Hodgkin's disease mixed cellularity recurrent 10020233; Hodgkin's disease mixed cellularity refractory 10020234; Hodgkin's disease mixed cellularity stage I site unspecified 10020235; Hodgkin's disease mixed cellularity stage I subdiaphragmatic 10020236; Hodgkin's disease mixed cellularity stage I supradiaphragmatic 10020237; Hodgkin's disease mixed cellularity stage II subdiaphragmatic 10020238; Hodgkin's disease mixed cellularity stage II supradiaphragmatic 10020239; Hodgkin's disease mixed cellularity stage III 10020240; Hodgkin's disease mixed cellularity stage IV 10020241; Hodgkin's disease mixed cellularity stage unspecified 10020242; Hodgkin's disease nodular sclerosis 10020244; Hodgkin's disease nodular sclerosis recurrent 10020245; Hodgkin's disease nodular sclerosis refractory 10020246; Hodgkin's disease nodular sclerosis stage I 10073535; Hodgkin's disease nodular sclerosis stage II 10073534; Hodgkin's disease nodular sclerosis stage III 10020252; Hodgkin's disease nodular sclerosis stage IV 10020253; Hodgkin's disease recurrent 10020266; Hodgkin's disease refractory 10020267; Hodgkin's disease stage I 10020268; Hodgkin's disease stage II 10020269; Hodgkin's disease stage III 10020270; Hodgkin's disease stage IV 10061597; Hodgkin's disease unclassifiable 10020271; Chronic lymphocytic leukaemia 10008958; Chronic lymphocytic leukaemia (in remission) 10008959; Chronic lymphocytic leukaemia recurrent 10008961; Chronic lymphocytic leukaemia refractory 10008962; Chronic lymphocytic leukaemia stage 0 10008963;

			Chronic lymphocytic leukaemia stage 1 10008964; Chronic lymphocytic leukaemia stage 2 10008965; Chronic lymphocytic leukaemia stage 3 10008966; Chronic lymphocytic leukaemia stage 4 10008967; Chronic lymphocytic leukaemia transformation 10058717;
Fractures	Identified in patient register, in- or outpatient component. Skull/face: S02 Neck: S12 Ribs/chest: S22 Lumbar spine/pelvis: S32 Shoulder/humerus: S42 Forearm: S52 Wrist/hand: S62 Femur: S72 Ankle/wrist: S82 Foot: S92 Fractures on multiple body parts: T02 Location of fracture not defined in detail: T08, T10, T12, T14.2.	The PPV for fractures in the Swedish NPR is extremely high: a validation of 647 patient charts the PPV of fracture in Swedish patient records was 1.00. There is high accuracy for both a diagnosis of hip fracture and a fracture of any type in the Swedish Patient Register	HLGT | Bone and joint injuries (Primary Path) • Exclude all PTs within HLT Bone and joint injuries NEC • Exclude the following individual PTs from other HLTs: Bone fissure, Cuboid syndrome, Fractured delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner fracture, Pathological fracture, Pseudoarthrosis, Pseudofracture, Anterior labroligamentous periosteal sleeve avulsion lesion, Bankart lesion, Fracture of clavicle due to birth trauma, Radial head dislocation, Scapulothoracic disassociation, Dislocation of vertebra, Intervertebral disc injury, Spinal fusion fracture, Costal cartilage fracture, Costochondral separation, Dislocation of the sternum. HLGT | Fractures (Primary Path) • Exclude all PTs within HLT Fracture complications • Exclude the following individual PTs from other HLTs: Bone fissure, Metaphyseal corner fracture, Pathological fracture, Pseudofracture, Fracture of clavicle due to birth trauma, Scapulothoracic disassociation, Spinal fusion fracture, Costal cartilage fracture.

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