

An active surveillance, post-authorization safety study of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with tofacitinib for moderately to severely active rheumatoid arthritis within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER) (Safety of tofacitinib in BIOBADASER)

**First published:** 05/09/2019

**Last updated:** 03/12/2024

Study

Ongoing

## Administrative details

### EU PAS number

EUPAS31129

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### Study ID

49437

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## **DARWIN EU® study**

No

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### **Study countries**

☐ Spain

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### **Study description**

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 in March 2017 at a dose of 5 mg administered twice daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have responded inadequately to, or who are intolerant to, one or more disease modifying antirheumatic drugs (DMARDs). To enable assessment of adverse outcomes of special interest including rare events and endpoints with long latency periods, Pfizer will implement a post-approval active surveillance study of tofacitinib-exposed patients using actively collected prospective data in BIOBADASER. Objective is to estimate the rates of serious infections, malignancy, CV and other specified outcomes among patients with RA in a Spanish register who initiate tofacitinib. Rates will also be estimated among cohorts of patients initiating biologic DMARDS to provide context for rates observed on tofacitinib.

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### **Study status**

Ongoing

## **Research institutions and networks**

### **Institutions**

Pfizer

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution

## Networks

Registro Español de Acontecimientos Adversos de Terapias Biológicas en Pacientes Reumáticos (BIOBADASER)

☐ Spain

**First published:** 06/07/2010

**Last updated:** 20/08/2024

Network

## Contact details

### Study institution contact

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Study contact

[andrea.leapley@pfizer.com](mailto:andrea.leapley@pfizer.com)

### Primary lead investigator

Michelle Iannacone

Primary lead investigator

## Study timelines

### Date when funding contract was signed

Planned: 07/08/2018

Actual: 07/08/2018

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### Study start date

Planned: 01/09/2019

Actual: 01/09/2019

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### Data analysis start date

Planned: 15/09/2025

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### Date of interim report, if expected

Planned: 14/03/2021

Actual: 04/03/2021

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### Date of final study report

Planned: 14/08/2026

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Pfizer 100%

## Study protocol

[A3921316 NIS PROTOCOL\\_21AUG2019 w-approval record.doc.pdf](#)(1.12 MB)

[A3921316\\_PROTOCOL VERSION 3.0\\_CLEAN\\_14Feb2022.pdf](#)(560.88 KB)

## Regulatory

**Was the study required by a regulatory body?**

Yes

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**Is the study required by a Risk Management Plan (RMP)?**

EU RMP category 3 (required)

## Other study registration identification numbers and links

A3921316

## Methodological aspects

### Study type

### Study type list

**Study topic:**

Human medicinal product

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**Study type:**

**Scope of the study:**

Safety study (incl. comparative)

**Data collection methods:**

Secondary use of data

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**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.

**Main study objective:**

To estimate the rates of serious infections, malignancy, cardiovascular (CV), and other specified outcomes among tofacitinib-exposed patients using actively collected prospective data in BIOBADASER. Rates will also be estimated among existing cohorts of patients initiating bDMARDS to provide context for rates observed on tofacitinib.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

**Name of medicine**

XELJANZ

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**Study drug International non-proprietary name (INN) or common name**

TOFACITINIB CITRATE

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**Anatomical Therapeutic Chemical (ATC) code**

(L04AA29) tofacitinib

tofacitinib

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**Medical condition to be studied**

Rheumatoid arthritis

## Population studied

**Short description of the study population**

The active surveillance population includes rheumatoid arthritis (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 in October 2017). For contextualisation purposes, two cohorts of BIOBADASER patients meeting the inclusion/exclusion criteria who are treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) will be included in the study. Patients switching therapies are eligible to move between cohorts if inclusion/exclusion criteria are met.

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**Age groups**

Adult and elderly population ( $\geq 18$  years)

## Study design details

## **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). A historical cohort (2000-2016) (BIOBADASER 2.0) includes patients with a diagnosis of RA. All participants agreed to prospective data collection and provided informed consent, and new user of an approved bDMARD.

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## **Comparators**

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.

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## **Outcomes**

1. Serious infections (excluding tuberculosis): pneumonia, other infections of the respiratory system, infections of the CNS, sepsis, bone or joint infections, OI, other infections.
2. Tuberculosis (TB).
3. Herpes zoster (HZ).
4. Fractures.
5. Cardiac disorders: heart failure, coronary artery disease, myocardial infarction, major adverse cardiovascular events (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 central nervous system (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 surgery and other joint therapeutic procedures, other operations and (major) therapeutic procedures that lead to hospitalization.
15. Other serious diagnoses, symptoms, and syndromes.

16. NMSC.
  17. Malignancies (overall, excluding non-melanoma skin cancer).
  18. Lymphoma (overall and independently by subtype, including non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukemia).
  19. Lung Cancer.
  20. All-cause Mortality.
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### **Data analysis plan**

Descriptive statistics for baseline variables and survival curves for AEs and discontinuation will be reported. 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.

## Data management

### Data sources

#### **Data source(s), other**

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

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#### **Data sources (types)**

[Disease registry](#)

[Drug dispensing/prescription data](#)

**Data sources (types), other**

Prospective patient-based data collection

## Use of a Common Data Model (CDM)

**CDM mapping**

No

## Data quality specifications

**Check conformance**

Unknown

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**Check completeness**

Unknown

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**Check stability**

Unknown

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**Check logical consistency**

Unknown

## Data characterisation

**Data characterisation conducted**

No