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

Study ID

49437

DARWIN EU® study

No

Study countries

Spain

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.

Study status

Ongoing

Research institutions and networks

Institutions

Pfizer

First published: 01/02/2024

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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

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 07/08/2018

Actual: 07/08/2018

Study start date
Planned: 01/09/2019

Actual: 01/09/2019

Data analysis start date
Planned: 15/09/2025

Date of interim report, if expected
Planned: 14/03/2021

Actual: 04/03/2021

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

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

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

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

Medicinal product name

XELJANZ

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

TOFACITINIB CITRATE

Anatomical Therapeutic Chemical (ATC) code

(L04AA29) tofacitinib

tofacitinib

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.

Age groups

- **Adult and elderly population (≥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.

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.

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 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 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.

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

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

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

Data sources (types)

Disease registry

Drug dispensing/prescription data

Other

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

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No