Malignancy and Cardiovascular Risk Assessment Using the Consortium of Rheumatology Researchers of North America Registry (Corrona) as an External Comparator for Tofacitinib-Exposed Patients within the Rheumatoid Arthritis BID Clinical Trial Program: A Comparative Post-Approval Safety Study (Matched Analysis for Xeljanz with Corrona)

First published: 04/04/2018

Last updated: 22/02/2024

Study Finalised

Administrative details

EU PAS number

EUPAS23344

Study ID

41400

DARWIN EU® study

No

Study countries

☐ United States

Study description

Tofacitinib (Xeljanz®) is an oral Janus kinase inhibitor for treatment of RA in patients with inadequate response to methotrexate (MTX-IR). The clinical development program included approximately 4800 patients with 7000 patient-years of exposure at the time of submission to the US Food and Drug Administration in 2011 (Pfizer, 2014). Due to the design of the Phase 3 trials, limited patient numbers and exposure are available for the comparators in these trials. As such, external data sources (ie, published and public-domain literature sources) have been used to provide background rates for qualitative comparison to the clinical program safety events. The proposed study seeks to supplement those data by performing a formal comparison of malignancy and cardiovascular event rates from the tofacitinib clinical trial program with event rates from the Consortium of Rheumatology Researchers of North America (Corrona) registry. The primary analysis will be on a cohort of RA patients within Corrona initiating a biologic that overlap the tofacitinib population characteristics based on prior disease modifying antirheumatic drug use and patient clinical and demographic characteristics. A propensity score will be used to determine patients in the two cohorts with common support (a similar range of scores). Multivariable adjusted hazard ratios will be estimated to compare the risk of malignancy and cardiovascular events in the two populations. A series of secondary Corrona RA cohorts will be compared to the tofacitinib clinical trial population for sensitivity analyses to evaluate the robustness of the estimated effects in the primary analysis. Secondary cohorts include, but are not limited to, direct propensity score matched population, RA initiators

restricted to ‘tofa trial eligible’ biologic initiators, and a comparison to rates in the full RA population. A final report (detailing all statistical analyses and conclusions) will be delivered by Corrona.

Study status

Finalised

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Jagun Oladayo

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 12/11/2014

Study start date

Planned: 15/02/2019

Actual: 20/11/2019

Date of final study report

Planned: 31/07/2020

Actual: 08/04/2021

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Pfizer, Inc.

Study protocol

A3921204_PROTOCOL_Final_9Nov2017.doc.pdf (2.9 MB)

A3921204_PROTOCOL and APPROVAL AMENDMENT 3_18May2020_.pdf (2.69 MB)

Regulatory

Was the study required by a regulatory body?

No

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

Non-EU RMP only

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

The objective of this study is to estimate the incidence rates and corresponding hazard rate ratios of malignancy and cardiovascular endpoints comparing patients from the tofacitinib RA BID clinical program to patients initiating a biologic DMARD and never exposed to tofacitinib (unexposed) in the Corrona registry.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Name of medicine

XELJANZ

Medical condition to be studied

Rheumatoid arthritis

Population studied

Short description of the study population

Patients diagnosed with Rheumatoid arthritis.

Inclusion Criteria

To maximize comparability of the tofacitinib and Corrona patients, Corrona patients must meet the following criteria of tofacitinib studies at the index date:

1. Aged 18 years or older at index date;
2. Diagnosis of RA (per American College of Rheumatology [ACR criteria]);
3. ACR functional class of I, II or III;
4. No Serious infections, defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event, in the past year;
5. No current or past malignancies with the exception of non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ;
6. No current uncontrolled clinically significant hepatic events or liver disorder, gastrointestinal (GI/bowel perforation), pulmonary, cardiac, or neurological disease
(demyelinating disorder/other neurologic); and
7. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Additionally, to ensure completeness of Corrona patient data, Corrona patients must also meet the following criteria:

1. Initiation and follow-up captured in the Corrona registry during anytime between January 1, 2006 – May 10, 2016 for malignancy, and during February 1, 2009 –
May 10, 2016 for CV analyses; and
2. At least 1 follow-up visit after biologic initiation during follow-up in the registry.

Exclusion Criteria
1. Any Corrona patient that does not meet one or more of the inclusion criteria will be excluded.

Age groups

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Special population of interest

Immunocompromised

Estimated number of subjects

21000

Study design details

Outcomes

The proposed study will evaluate incidence rates and corresponding hazard rate ratios of the following outcomes among persons exposed to tofacitinib versus

comparator. All outcomes described in this section are primary: 1. All malignancies (excluding NMSC), 2. Major adverse cardiovascular events (MACE), 3. Non-fatal MI, and 4. Non-fatal stroke.

Data analysis plan

The primary analysis cohort will be a cohort of patients initiating a biologic within Corrona with no prior tofacitinib exposure that overlaps with the tofacitinib population characteristics based on prior DMARD and TNF use, and patient characteristics. Overlap will be defined as the “common support” for the propensity score distribution, i.e. the range of propensity score values that both populations have in common. A propensity score for use of tofacitinib will be derived and only patients with common support (i.e. overlapping propensity distributions between tofacitinib population and Corrona populations, distributions will be trimmed where there is no overlap) will be used in a multivariable analysis. The cohort from which this population will be derived will be active RA patients initiating a bDMARD with at least one follow-up and no prior tofacitinib exposure. The propensity model will include DMARD history, eligibility criteria and other relevant factors.

Documents

Study results

CT24-WI-GL15-RF01 1.0 NI Study Report Abstract 09 March 2021.pdf (1.21 MB)

Study report

CT24-WI-GL15-RF02 2.0 NI Study Report 09 March 2021 (1).pdf (2.95 MB)

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.

Conflicts of interest of investigators

DoI_EUPAS23344.pdf (4.67 MB)

Data sources

Data sources (types)

Disease registry

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