An Active Safety Surveillance Study to Estimate Incidence Rates of Safety Events of Interest among Patients Treated with Tofacitinib for Polyarticular Course Juvenile Idiopathic Arthritis (pcJIA) within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry in the United States

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Study Planned

Administrative details

EU PAS number

EUPAS103626

Study ID

103627

DARWIN EU® study

No

Study countries

United States

Study description

Tofacitinib (Xeljanz®) is an oral Janus Kinase (JAK) inhibitor approved in the United States (US) in September 2020 for use in patients with polyarticular course juvenile idiopathic arthritis (pcJIA) (5mg immediate release (IR) tablet and 1mg/mL oral solution).

The safety of tofacitinib 5 mg IR tablet and weight-based equivalent oral solution dosed twice daily (BID) has been evaluated in an integrated population of 251 subjects aged 2 to <18 years with juvenile idiopathic arthritis (JIA) and was shown to have an acceptable safety profile and was well-tolerated.

The understanding of the safety profile of tofacitinib in patients with JIA was further informed by comparison to a larger database of RA studies, which includes 24 completed RA clinical studies and 3,969 patients exposed to tofacitinib 5mg IR tablet BID.

The safety profile of tofacitinib in the pJIA clinical program was consistent with that for the adult RA clinical program, and no new safety risks were identified.

To enable long-term assessment of safety outcomes, a post-approval, active surveillance study of tofacitinib-exposed pcJIA patients will be conducted using data collected within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

This noninterventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the Food and Drug Administration (FDA).

Study status

Planned

Research institutions and networks

Institutions

Pfizer

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Institution

Networks

Childhood Arthritis and Rheumatology Research Alliance

Contact details

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Primary lead investigator

Li Wang

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 08/02/2021

Actual: 08/02/2021

Study start date
Planned: 31/01/2026

Date of interim report, if expected
Planned: 31/07/2026

Date of final study report
Planned: 30/09/2030

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Pfizer 100%

Study protocol

A3921371_CARRA PROTOCOL V3.0 _29 JULY 2022.pdf (9.93 MB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Other study registration identification numbers and links

A3921371

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, cohort study using prospectively collected data from the existing CARRA Registry.

Main study objective:

1) The primary objective is to estimate the incidence rate of thrombosis, infections (including opportunistic infections and serious infections), all malignancies combined (excluding NMSC), NMSC, lymphoma, lung cancer, growth effects, and fractures among pcJIA patients who initiate tofacitinib post-approval as well as pcJIA patients who initiate approved bDMARDs.
2) The secondary objective is to estimate the incidence rate of major adverse cardiovascular events (MACE) and vaccine preventable infections among pcJIA patients who initiate tofacitinib post-approval as well as pcJIA patients who initiate approved bDMARDs.

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

(L04AF01) tofacitinib

tofacitinib

Additional medical condition(s)

polyarticular course juvenile idiopathic arthritis

Population studied

Short description of the study population

The study population will include pcJIA patients ≥2 years who receive tofacitinib within the CARRA registry, following US approval, through one year prior to the end of the study period.

The study population will also include a contemporaneous cohort of pcJIA patients ≥2 years who initiate approved bDMARDs on or after the tofacitinib approval date, through one year prior to the end of the study period.

Age groups

- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)

Study design details

Setting

CARRA is a research network of 107 pediatric rheumatology clinical practice sites in the US and internationally, founded in 2002 by pediatric rheumatologists.

The CARRA Registry is an observational registry that collects longitudinal

information on children and adolescents who have pediatric rheumatic diseases at approximately 70 academic pediatric rheumatology centers in the US, Canada, and Israel.

The objectives of the CARRA Registry are to collect and analyze safety data in the context of the natural history of rheumatic disease in children with a focus on robust collection of medication data, serious adverse events (SAEs), and long-term follow-up.

The CARRA Registry began prospectively collecting data in the US and Canada in July 2015 with the primary aim of studying the safety of new therapies for JIA during routine clinical use and has since expanded to include sites outside of North America as well as patients with childhood-onset systemic lupus erythematosus, juvenile dermatomyositis, localized scleroderma. The CARRA Registry is used extensively to conduct safety surveillance and satisfy post-marketing commitments and requirements to regulatory authorities, such as the FDA.

The Registry has currently enrolled over 10,000 participants with JIA from approximately 70 geographically diverse pediatric rheumatology centers in the United States, Canada, and Israel.

Data are collected every 6 months from standard-of-care clinical encounters and include clinical assessments, detailed medication use, and safety events. Patients who stop receiving care at a CARRA registry site continue to contribute data to the registry every six months via a long-term follow-up program. Long-term follow-up data collection is managed by the Registry’s coordinating center and may occur over the phone or via online survey.

The Registry follows all patients for a minimum of 10 years each with no cap to the upper age of

follow-up.

Outcomes

Primary

1) Overall thrombosis (venous thromboembolism [VTE] and arterial thromboembolism [ATE])

a) VTE (which includes deep vein thrombosis [DVT] and pulmonary embolism [PE)

b) ATE

2) Infections

a) Opportunistic infections

b) Tuberculosis

c) Herpes zoster

d) Serious infections: defined as any serious infection event that meets any of the following criteria: death, life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect, important medical event or requiring treatment with IV antimicrobials.

3) All malignancies combined (excluding NMSC)

4) NMSC

5) Lymphoma

6) Lung cancer

7) Growth effects

a) Height velocity z-score: Annual height velocity will be determined for each patient every 12 months after the index date by subtracting the height measured 12 months previously from the current height. The mean and standard deviation of the height velocity in centimeters per year will be determined for both exposure cohorts for each year of the study. Because height velocity is dependent upon age and sex, and these characteristics may differ between the tofacitinib and

bDMARD exposure cohorts, the age- and sex-adjusted standard score (z-score) will be determined for each patient’s annual height velocity using a standard reference. The mean and standard deviation of the age- and sex-adjusted z-score will be determined for both exposure cohorts for each year of the study.
Secondary
9) Vaccine preventable infections (e.g., treated with IV antimicrobial or opportunistic infection)
10) Major adverse CV events (which includes stroke, MI, and CV death)

Data analysis plan

The interim analysis will consist of descriptive comparisons of baseline characteristics, drug utilization data describing all tofacitinib treatment patterns, including switching patterns from tofacitinib to any other biologic agent including TNFi or nonbiologic agent used in the treatment of pcJIA and vice versa and duration of use before switch, and crude event rates by treatment cohorts.
The final analysis of outcomes will provide treatment group-specific rates of events overall and in subgroups defined by baseline characteristics.
Data analysis will include malignancy outcomes defined as all malignancies combined (excluding NMSC), NMSC, lymphoma and lung cancer and non-malignancy outcomes defined as all outcomes of interest other than the malignancy outcomes.
Non-malignancy outcomes 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).

Data management

Data sources

Data source(s), other

Childhood Arthritis and Rheumatology Research Alliance Registry United States

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