NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	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
Protocol number	A3921371
Protocol version identifier	Version 3.0
Date	29 July 2022
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	**Research Question:** What are the rates of safety events of interest among polyarticular course juvenile idiopathic arthritis (pcJIA) patients treated with tofacitinib and among pcJIA patients treated with biologic disease modifying antirheumatic drugs (bDMARDs) in the post-approval setting? **Objective:** **1)** The primary objective is to estimate the incidence rate of thrombosis, infections (including opportunistic infections and

	serious infections), all malignancies combined (excluding nonmelanoma skin cancer [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
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ATE	arterial thromboembolism
bDMARD	biologic disease modifying antirheumatic drug
BID	twice daily
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CFR	Code of Federal Regulations
CI	confidence interval
csDMARD	conventional synthetic disease-modifying antirheumatic drugs
CV	Cardiovascular
DCRI	Duke Clinical Research Institute
DMARD	disease modifying antirheumatic drug
DVT	deep vein thrombosis
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERA	enthesitis-related arthritis
ESI	events of special interest
EU	European Union
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
ILAR	International League of Associations for Rheumatology
IEC	Independent Ethics Committee
IR	immediate release
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus Kinase
JIA	juvenile idiopathic arthritis
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTX	methotrexate
NA	not applicable

Abbreviation	Definition
NMSC	nonmelanoma skin cancer
NSAIDs	nonsteroidal anti-inflammatory drugs
PAS	post authorization study
PASS	post-authorization safety study
pcJIA	polyarticular course juvenile idiopathic arthritis
PE	pulmonary embolism
PsA	psoriatic arthritis
PY	person years
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus
TNFi	tumor necrosis factor-alpha inhibitor
UC	ulcerative colitis
US	United States
USPI	United States Prescribing Information
VTE	venous thromboembolism

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: 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 within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry in the United States

Version: 3.0

Date: 29 July 2022

Primary Author: Sampada Gandhi, Pfizer, Inc

Rationale and background: 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 non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the Food and Drug Administration (FDA).

Research question and objectives: What are the rates of safety events of interest among pcJIA patients treated with tofacitinib and among pcJIA patients treated with biologic disease modifying antirheumatic drugs (bDMARDs) in the post-approval setting?

1) The primary objective is to estimate the incidence rate of thrombosis, infections (including opportunistic infections and serious infections), all malignancies combined (excluding nonmelanoma skin cancer [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 (CV) events and vaccine preventable infections among pcJIA patients who initiate tofacitinib post-approval as well as pcJIA patients who initiate approved bDMARDs.

Study Design: This is an active surveillance, cohort study using prospectively collected data from the existing Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry during the study period (from US approval in September 2020 through December 2029).

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.

Variables: The study variables include baseline patient characteristics (i.e., demographic and clinical characteristics, comorbidities and current and past therapies). The study will evaluate a range of safety events related to the primary and secondary study objectives and include the following:

Primary

- Overall thrombosis (venous thromboembolism [VTE] and arterial thromboembolism [ATE])
    - VTE (which includes deep vein thrombosis [DVT] and pulmonary embolism [PE)
    - ATE
- Infections
    - Opportunistic infections
    - Tuberculosis
    - Herpes zoster
    - 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 intravenous (IV) antimicrobials.
- All malignancies combined (excluding NMSC)
- NMSC
- Lymphoma
- Lung cancer
- Growth effects
    - Height velocity z-score
- Fractures

Secondary

- Vaccine preventable infections (e.g., treated with IV antimicrobial or opportunistic infection)
- Major adverse cardiovascular events (which includes stroke, MI, and cardiovascular death)

Data sources: This is an observational cohort study of tofacitinib-exposed and approved bDMARD-exposed pcJIA patients using data collected prospectively as part of the CARRA

Registry. The CARRA registry began collecting data in the US and Canada in July 2015 with the primary aim of studying the safety of new therapies for pcJIA during routine clinical use. The Registry has currently enrolled over 10,000 participants with JIA from approximately 70 geographically diverse pediatric rheumatology centers. Data are collected every 6 months 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.

Study size: All eligible pcJIA patients who initiate tofacitinib or an approved bDMARD following US approval in September 2020 to one year prior to the end of the study period (December 2028) will be included in this active surveillance study, and no upper limit will be placed on the sample size.

Data analysis: The interim and final reports will include descriptive summaries of baseline variables and crude rates of safety events of interest. The final analysis of outcomes will provide the rates of events overall and in subgroups defined by baseline characteristics (e.g., sex and age). Pending feasibility, comparative analyses that control for sex, age, year of treatment, treatment history, disease severity, comorbidities and other potential confounders will be performed for the final report.

Milestones: The estimated start and end of data collection is January 2026 and February 2030, respectively. An interim drug utilization data analysis will be completed in July 2024. An interim report is planned for July 2026 and final report is planned for September 2030.

5. AMENDMENTS AND UPDATES

Version number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	28 July 2021	7	Revised to add a justification for inclusion of pcJIA subtypes.	FDA requested these revisions in a correspondence that provides advice/comments dated 02 July 2021.
		9.2	Revised to clarify which data elements are provided directly by physicians and which are extracted from the medical record in sites and variability in data collection.	
		9.2.2	Text stating that patients initiating treatment with tofacitinib will be included in the tofacitinib cohort irrespective of prior bDMARD use was added.	
		9.3.1	Revised to include a definition of baseline period for capturing baseline covariates.	
		9.3.3	Clarifying text was added as follows: patients cannot switch from contributing observation time in the tofacitinib cohort to the bDMARD cohort, because prior use of tofacitinib is an exclusion criterion for the bDMARD cohort.	
		Abstract, 9.3.4	Revised to include a definition of serious infection.	
		9.3.4	Revised to include details on estimation of height velocity z-score.	
		Abstract, 8, 9.3.4	Revised to clarify fractures as a separate outcome.	
		Abstract, 8, 9.3.4, 9.7	The outcome ‘malignancies excluding NMSC’ revised as follows: ‘all malignancies combined (excluding NMSC)’.	
		Abstract, 8, 9.3.4, 9.7	Revised to include lymphoma and lung cancer as separate outcomes.	
		9.7	• Revised to include a justification for 90-day extension risk window and a 28-day extension risk window was added as a sensitivity analysis. • Revised to clarify that double counting of events will not be performed. • Revised to include a lag time of 6 months in a primary analysis and 3	

			months in a sensitivity analysis for all analyses of malignancies.	
		9.9	Text related to one of the limitations of the register was removed.	
		13	4 references, i.e., Walker et al (2005), Michaud et al (2007), Strangfeld et al (2011) and Mercer et al (2017) were removed as these were incorrect references. Haynes et al (2013) was added as the correct reference for the indefinite risk paradigm approach.	
2	23 February 2022	6	Start of data collection date was revised from 31 August 2021 to 31 January 2026.	As per the Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3), the start of data collection corresponds to the date of start of data extraction for the purposes of the primary analysis; therefore, this date was revised to reflect this correctly.
		9.7.1	• Revised to include the 28-day extension window in the primary analysis and the 90-day extension window in a sensitivity analysis of the non-malignancy outcomes. • Figure 1 and Figure 2 were added to depict the 28-Day On-Treatment and the 90-Day On-Treatment Risk periods.	FDA requested these revisions in a correspondence that provides advice/comments dated 20 December 2021.
		9.7, 9.7.4	Interim drug utilization data analysis was added to interim report analysis.	
		Abstract-Milestones, 6, 9.7, 9.7.3	Summarization of interim drug utilization data was added.	
		9.7	• The indefinite risk paradigm approach was removed. • Section 9.7 Data Analysis was reorganized under two sub-headings 9.7.1 Non-malignancy outcomes and 9.7.2 Malignancy Outcomes. • Figure 3 was added to depict the most recent exposure approach risk period.	
3	29 July 2022	Throughout the protocol	'Endpoints' was revised to 'Outcomes' throughout the protocol.	FDA requested these revisions in a correspondence that provides

		9.7, 9.7.3, 9.7.4	Revised to clarify that all tofacitinib treatment patterns, including switching patterns from tofacitinib to any other biologic agent including tumor necrosis factor-alpha inhibitor (TNFi) or nonbiologic agent used in the treatment of pcJIA and vice versa will be summarized.	advice/comments dated 18 July 2022.
		9.7.1	A 28-Day On-Treatment Risk Period with Censoring at Treatment Switch was added.	
		9.7.2	The lag time was extended to 1 year in primary analysis and to 18 months in sensitivity analysis for malignancy outcomes.	

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	pending (prior to start of data collection)
Interim drug utilization data	31 July 2024
Start of data collection	31 January 2026
Interim report	31 July 2026
End of data collection	28 February 2030
Final study report	30 September 2030

7. RATIONALE AND BACKGROUND

Juvenile idiopathic arthritis (JIA) is a heterogenous group of conditions, defined as arthritis persisting for 6 weeks or longer with no other identifiable cause and onset prior to age 16. The International League of Associations for Rheumatology (ILAR) has classified JIA into 7 distinguishable subtypes (rheumatoid factor (RF)+ polyarthritis, RF- polyarthritis, oligoarthritis, systemic JIA (sJIA), juvenile psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis).[1] JIA is the most common pediatric rheumatic illness, with an annual incidence in developed countries of 2 to 20 per 100,000 children and a prevalence of 16 to 150 per 100,000 children.[2]

Polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6-month period and includes RF+ polyarthritis and RF- polyarthritis according to ILAR classification. Patients with other subtypes of JIA who later develop arthritis in multiple joints can also have polyarticular disease, however they are excluded from the ILAR polyarticular JIA subgroup.[3] These patients, along with those with polyarticular JIA, are grouped together under the heading of polyarticular course JIA (pcJIA).For the purposes of this study pcJIA specifically includes those patients with RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and systemic JIA without active system features, consistent with those included in the polyarticular course JIA indication in the Xeljanz US Prescribing Information (USPI).

Epidemiologic studies with incidence and prevalence estimates for pcJIA are not available, however, regional estimates for the individual JIA subtypes included under the pcJIA category have been reported:

- RF+ polyarthritis: Estimated to consist of 5 to 10% of all JIA. Incidence rates range from 0.10 to 0.90 per 100,000; Prevalence rates range from 0.28 to 10.3 per 100,000.[3,4]
- RF- polyarthritis: Estimated to consist of 10 to 30% of all JIA. Incidence rates range from 0.28 to 6.50 per 100,000. Prevalence rates range from is 1.64 to 33.4 per 100,000.[3,4]
- Oligoarthritis: 30 to 60% of all JIA and of these 50% in persistent and 50% extended oligoarthritis.[4] 27-56% of all JIA. Overall incidence of 4.5 per 100,000.[5]
- Systemic JIA (overall): 4 to 17% of all JIA. 0.5 per 100,000 for all sJIA.[5,6] Incidence and prevalence data are not available for rates of systemic JIA without active features.

Tofacitinib (Xeljanz®) is an oral Janus Kinase (JAK) inhibitor approved in the US for the treatment of moderate to severe rheumatoid arthritis (RA), active psoriatic arthritis (PsA), moderate to severe ulcerative colitis (UC) and polyarticular course JIA (pcJIA) (approved in September 2020 for pcJIA). Treatments are available to control and delay the progression of symptoms of pcJIA, as well as prevent joint damage over the long term. However, additional therapy options are still needed as up to 30% of children with pcJIA continue to have active disease despite treatment with methotrexate (MTX) or biological agents.[7,8] For children who have failed currently available biological disease modifying antirheumatic drugs

(bDMARDs), additional therapies with novel mechanisms may be required to control their disease. The effective treatment of many rheumatic diseases requires parenteral administration of medications. In a recent review of subject preference studies in rheumatology, the route of administration of a drug was found to be one of the most important factors in treatment decisions for people with moderate to severe RA.[9] These findings in adults with RA are even more pronounced in children with pcJIA. There are significant barriers to injections with most children having a fear of injection needles; oral route is the preferred and considered the most appropriate route of administration to pediatric subjects.

Tofacitinib directly addresses current unmet needs by offering both an alternative to injections and an option for subjects' refractory to current treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (corticosteroids), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and bDMARDs (etanercept, adalimumab, golimumab, abatacept, and tocilizumab).

The safety of tofacitinib 5 mg immediate release (IR) tablet and 1mg/mL weight-based equivalent oral solution dosed twice daily (BID) has been evaluated in an integrated population of 251 JIA patients aged 2 to <18 years and was shown to have an acceptable safety profile and was well-tolerated. The understanding of the safety profile of tofacitinib 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 JIA clinical program was consistent with that for the adult RA clinical program, and no new safety risks were identified.

The safety events of interest include selected events from the USPI as well as other events: thrombosis, serious infections, including opportunistic infections, malignancy and effects on growth.
When planning a study of the safety profile of newly approved therapies for pcJIA, it is important to evaluate the safety profile in the context of the experience of pcJIA patients treated with other advanced therapies. This protocol describes a non-interventional, post-approval active safety surveillance study of tofacitinib-exposed and approved bDMARD-exposed pcJIA patients using actively collected prospective data in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

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

8. RESEARCH QUESTION AND OBJECTIVES

Research Question: What are the rates of safety events of interest among pcJIA patients treated with tofacitinib and among pcJIA patients treated with bDMARDs in the post-approval setting?

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.

9. RESEARCH METHODS

9.1. Study design

This is an active surveillance, cohort study using prospectively collected data from the existing Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. The CARRA Registry captures patient enrollment and follow-up data as part of routine medical practice. All patients receive standard of care treatments prescribed by their treating physician/rheumatologist. Data capture and follow-up methods are the same for all patients within the CARRA Registry.

Enrollment in the CARRA Registry is voluntary and eligibility is based on meeting standard clinical definitions for rheumatic disease diagnoses irrespective of current or prior treatment.[10] To maximize the number of tofacitinib-exposed patients, the study will include pcJIA patients enrolled up to one year prior (31 December 2028) to the data lock point (31 December 2029). This will allow a minimum of one year of follow-up (from the start of January 2029 through the end of December 2029) and a maximum of 9 years and two months of follow-up (from October 2020 through December 2029).

9.2. 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.[10] 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.[10] The Registry follows all patients for a minimum of 10 years each with no cap to the upper age of follow-up. The upper age limit for enrollment in the Registry is 19 years old (diagnosis of JIA must have occurred prior to age 16 years, as per the ILAR criteria). The transition of care to adult rheumatology is variable but typically occurs between ages 18 and 22.

CARRA Registry sites use electronic case report forms (eCRF) to ensure adequate data collection. For most sites, this information needed to complete the case report forms is primarily documented in the medical record and may be extracted after the visit and entered into the Registry's electronic data capture (EDC) system. A site may choose to collect some CARRA Registry data directly from the treating physician to either expedite data entry or if there are registry data elements that are not routinely captured in the medical record at their site.

CARRA Registry sites are provided instructions for completing the registry's electronic case report forms. While there is no requirement regarding which data elements are obtained directly from a physician versus extracted from the medical record, the instructions include operational definitions for each data element to ensure consistency of interpretation of the eCRFs across sites, irrespective of method of data collection. Given that sites implement all CARRA Registry data collection procedures in the manner that best fits their clinical workflow and that they are provided with ongoing training regarding the eCRFs, variability in data collection methods is not expected to introduce differential bias.

The Registry data coordinating center is the Duke Clinical Research Institute (DCRI).

9.2.1. Inclusion criteria

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

pcJIA Patients Treated with Tofacitinib

1. Enrollment in the CARRA Registry at a US Registry site
2. Patients with a diagnosis of pcJIA which includes:
    - Extended oligoarthritis
    - Polyarthritis (RF+)
    - Polyarthritis (RF-)
    - Systemic JIA with active arthritis but without systemic features
3. Patients younger than 16 years at diagnosis of pcJIA
4. Patients aged 2-17 years at tofacitinib initiation
5. Patients initiating tofacitinib following approval in September 2020 through December 2028.

pcJIA Patients Treated with bDMARD

1. Enrollment in the CARRA Registry at a US Registry site
2. Patients with a diagnosis of pcJIA which includes:
    - Extended oligoarthritis
    - Polyarthritis (RF+)
    - Polyarthritis (RF-)
    - Systemic JIA with active arthritis without systemic features
3. Patients younger than 16 years at diagnosis of pcJIA
4. Patients aged 2-17 years at initiation of any bDMARD approved for pcJIA treatment in the US (e.g., etanercept, adalimumab, abatacept, tocilizumab). This is first use of unique bDMARD, not restricted to first bDMARD use (i.e., not restricted to bDMARD naïve patients).
5. Patients initiating a bDMARD following tofacitinib approval in September 2020 through December 2028.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

Patients with rheumatology diagnoses other than pcJIA (e.g., SLE and Sjogren's) will be excluded. Any patient enrolled in the CARRA Registry who does not meet one or more of the inclusion criteria will be excluded. Additional cohort-specific exclusion criteria are:

pcJIA Patients Treated with Tofacitinib

1. Concurrent use of biologic

It should be noted that patients initiating treatment with tofacitinib will be included in the tofacitinib cohort irrespective of prior bDMARD use (i.e., both bDMARD-naïve or bDMARD-experienced patients will be included).

pcJIA Patients Treated with bDMARD

1. Patients with prior use of tofacitinib

2. Concurrent use of more than 1 biologic

9.3. Variables

9.3.1. Baseline data

The data captured include, but are not restricted to, the following: age, sex, race/ethnicity, disease duration, disease severity, past therapies, comorbidities (eg, history of malignancies), current concomitant medications. Baseline data will be captured as of the index date and will include all information captured up to and including the index date, which is defined in Section 9.3.2.

9.3.2. Index date

The index date for the tofacitinib cohort will be defined as the date of the first tofacitinib prescription during the study period. For the bDMARD cohort, the index date will be defined as the date of the first prescription of a bDMARD during the study period, whichever specific bDMARD medication was prescribed.

9.3.3. Exposure measurement

Medication information is entered into a medication log by the clinical site including medication name, dose, frequency, route, start date, and stop date.

Subjects will be followed from index date until the occurrence of the safety event of interest, with death and withdrawal of consent for participation in the Registry, and end of study period treated as censoring events. For each safety event of interest, occurrence of that event will result in censoring. However, occurrence of another safety event of interest will not

result in censoring. For example, if estimating the rate of malignancy, the occurrence of serious infection will not be a censoring event.

Patients switching therapies are eligible to move between cohorts if inclusion/exclusion criteria are met. It should be noted that patients cannot switch from contributing observation time in the tofacitinib cohort to the bDMARD cohort, because prior use of tofacitinib is an exclusion criterion for the bDMARD cohort.

9.3.4. Outcomes

The safety outcomes of interest captured in the interim and final report are the following:

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.

8) Fractures

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)

Further detail and operational definitions of outcomes will be provided in a statistical analysis plan (SAP). This list may be extended with a reasonable number of additional sub-diagnoses or new health related outcomes as agreed to by CARRA researchers and the Sponsor before the interim and final study reports. These decisions will be made prior to initiation of analyses and documented in an SAP kept on file by the Sponsor.

In addition, the final study report will include the number of tofacitinib-exposed pregnancies.

9.4. Data sources

Data are collected at enrollment and subsequent follow-up visits occurring approximately every 6 months as part of routine clinical practice. Follow-up data are also collected at initiation of treatment with tofacitinib, methotrexate or a biologic agent, irrespective of whether this occurs at a routine 6-month follow-up visit. Multiple derived measures, including the American College of Rheumatology (ACR) Pediatric Response and Disease Flare, the Juvenile Arthritis Disease Activity Score (JADAS), and the provisional ACR definition of inactive disease, can all be determined from data collected at each Registry visit.

In addition to the standard clinical measures and history collected at each follow-up, the CARRA Registry systematically collects data about safety events via a process to identify SAEs and events of special interest (ESIs). Reference to SAEs does not mean that safety reporting is required for this protocol. SAEs are defined by the standard criteria used by the FDA and others. ESIs are protocol defined, pre-specified events of particular concern and interest because of a possible association with newer therapeutic agents, but that might not meet the definition of a SAE. Examples of ESIs include optic neuritis and tuberculosis. Data about safety events are reported to DCRI via the Registry interface as soon as they are discovered by CARRA Registry site investigators, irrespective of the time elapsed since the last data entry. Data are entered using a standard form that includes detailed information about the event onset, diagnostic procedures, treatment and outcome, and recent medications. MedDRA codes are assigned to all SAE and ESI centrally at DCRI by clinical coding

specialists. Additional documentation of safety events, such as hospital discharge summaries or pathology reports, are obtained to increase the specificity and accuracy of any rare safety events identified.

CARRA Registry sites enter all data via an internet-based data collection platform in the context of routine clinical care. Data used in this study are in structured format within the CARRA registry database.

9.5. Study size

This active surveillance study is not intended to test a pre-specified statistical hypothesis therefore no minimum sample size is required. All eligible patients during the study period will be included in the study.

While this is an active surveillance study, conducting quantitative, confounding controlled comparisons will depend on having a sufficient sample. Table 1 below describes the minimal detectable difference in event rates between tofacitinib-initiators and bDMARD-initiators assuming the following:

- α=0.05;
- power =80%;
- 2 different bDMARD-treated patient population sizes (reflecting roughly range of bDMARD-treated patient populations enrolled in CARRA, Pfizer internal data): n=1000, n=2000;
- 4 different tofacitinib-treated patient population sizes: n=50, n=100, n=250, n=500;
- Estimated rates on bDMARD of 6/1000 person-years (PY) (eg, serious infections), 1/1000 PY (eg, hospitalized fracture), and 5/10,000 PY (eg, malignancy) based on previous analysis with CARRA (Pfizer, internal data); and
- Constant rate of accrual.

For a safety event with a rate of 6/1000 PY, such as serious infection, 250 tofacitinib-exposed patients and 2,000 bDMARD-exposed patients would have 80% power to detect a hazard ratio of 2.19.

For a safety event with a rate of 1/1000 PY, such as hospitalized fracture, 250 tofacitinib-exposed patients and 2,000 bDMARD-exposed patients would have 80% power to detect a hazard ratio of 4.94.

For a safety event with a rate of 5/10,000 PY, such as malignancy, 250 tofacitinib-exposed patients and 2,000 bDMARD-exposed patients would have 80% power to detect a hazard ratio of 7.66.

Table 1. Detectable Effect Size for Tofacitinib versus bDMARD Comparison, Given Different Rates in bDMARD group and Assumed Sample Sizes in bDMARD or Tofacitinib Cohorts

Sample size in bDMARD treated population (N1)	Sample size in tofacitinib treated population (N2)	Rate in bDMARD group	Power	Hazard Ratio
1000	50	6/1000 PY	0.8	4.39
1000	100	6/1000 PY	0.8	3.13
1000	250	6/1000 PY	0.8	2.26
1000	500	6/1000 PY	0.8	1.92
2000	50	6/1000 PY	0.8	4.35
2000	100	6/1000 PY	0.8	3.08
2000	250	6/1000 PY	0.8	2.19
2000	500	6/1000 PY	0.8	1.83
1000	50	1/1000 PY	0.8	14.85
1000	100	1/1000 PY	0.8	8.9
1000	250	1/1000 PY	0.8	5.13
1000	500	1/1000 PY	0.8	3.78
2000	50	1/1000 PY	0.8	14.75
2000	100	1/1000 PY	0.8	8.77
2000	250	1/1000 PY	0.8	4.94
2000	500	1/1000 PY	0.8	3.54
1000	50	5/10,000 PY	0.8	26.36
1000	100	5/10,000 PY	0.8	15.01
1000	250	5/10,000 PY	0.8	7.94
1000	500	5/10,000 PY	0.8	5.49
2000	50	5/10,000 PY	0.8	26.22
2000	100	5/10,000 PY	0.8	14.82
2000	250	5/10,000 PY	0.8	7.66
2000	500	5/10,000 PY	0.8	5.12

9.6. Data management

The main CARRA Registry data collection platform is an internet-based EDC system compliant with 21 CFR Part 11 standards. EDC system access is managed via secure username/password authentication to protect against unauthorized data entry or modification. DCRI maintains the EDC system and are responsible for implementing any required enhancements and additions as well as performing regular database back-up and storage.

CARRA Registry sites directly enter data onto eCRFs contained in the EDC system according to instructions provided by DCRI. All patients are assigned a unique, coded CARRA Registry identifier that is used as a link data across datasets.

9.7. Data analysis

An interim drug utilization data will consist of a description of all tofacitinib treatment patterns, including switching patterns from tofacitinib to any other biologic agent including

tumor necrosis factor-alpha inhibitor (TNFi) or nonbiologic agent used in the treatment of pcJIA and vice versa and duration of use before switch.

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. 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 here, however any major modifications of primary outcome definitions or their analyses will be reflected in a protocol amendment.

Statistical analyses will be performed using SAS, version 9.4 or higher (SAS Institute Inc., Cary, NC). All analyses will be carried out under the direction of a CARRA principal investigator in collaboration with DCRI, the data coordinating center.

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).

9.7.1. Non-malignancy outcomes

The non-malignancy outcomes will be evaluated over a risk window that includes time from drug initiation until 28 days after end of treatment (ie, 28-Day On-Treatment Risk Period) in the primary analysis. A 28-day risk window minimizes the likelihood that an association between medication exposures and safety events is missed.

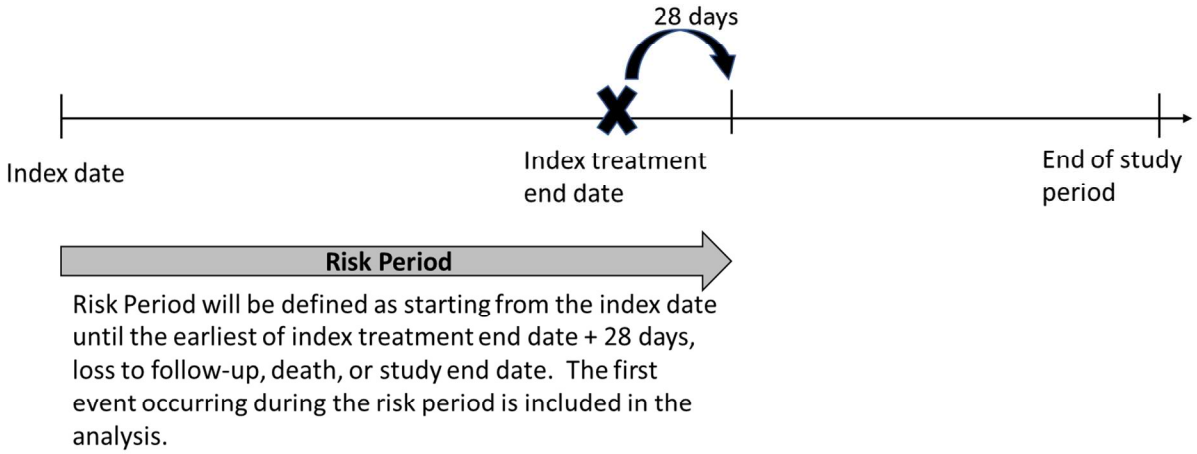
Two sensitivity analyses will be conducted for the non-malignancy outcomes as follows: (1) 28-Day On-Treatment Risk Period with Censoring at Treatment Switch: this risk period will include time from drug initiation until 28 days after end of treatment like the primary approach, but will allow censoring at treatment switch, and (2) 90-day risk window (ie, 90-Day On-Treatment Risk Period): the 90-Day On-Treatment Risk 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.

Explicitly, the three risk periods will be defined as follows:

1. 28-Day On-Treatment Risk Period: the 28-Day On-Treatment Risk Period will be defined as starting from the index date until the earliest of index treatment end date + 28 days, loss to follow-up, death, or study end date (Figure 1).

For patients in the tofacitinib cohort, any safety event that occurs during the 28-day risk period following discontinuation of tofacitinib will be attributed to tofacitinib, irrespective of any new medication initiation during the 28-day risk window, respectively. It should be noted that patients in the tofacitinib cohort cannot subsequently contribute observation time to the bDMARD cohort because prior use of tofacitinib is an exclusion criterion for the bDMARD cohort. For patients in the bDMARD cohort, any safety event that occurs during the 28-day risk period following discontinuation of bDMARD will be attributed to bDMARD, irrespective of any new medication initiation (including tofacitinib) during the 28-day risk period, respectively.

Figure 1. Schematic Diagram of 28-day On-Treatment Risk Period



2. 28-Day On-Treatment Risk Period with Censoring at Treatment Switch: this risk period will be defined as starting from the index date until the earliest of index treatment end date + 28 days, initiation of another pcJIA treatment, loss to follow-up, death, or study end date.

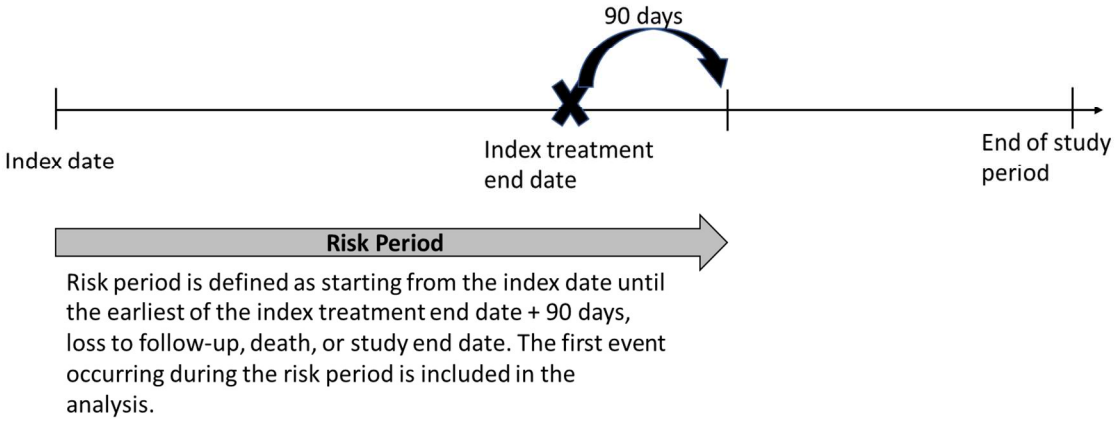
For patients in the tofacitinib cohort, any safety event that occurs during the 28-day risk period following discontinuation of tofacitinib will be attributed to tofacitinib. However, if patients initiate another pcJIA treatment during the 28-day risk window, safety events occurring following the initiation of another pcJIA treatment will not be attributed to tofacitinib treatment. For patients in the bDMARD cohort, any safety event that occurs during the 28-day risk period following discontinuation of bDMARD will be attributed to bDMARD. However, if patients initiate another pcJIA treatment during the 28-day risk window, safety events occurring following the initiation of another pcJIA treatment will not be attributed to bDMARD treatment.

3. 90-Day On-Treatment Risk Period: the 90-Day On-Treatment Risk Period will be defined as starting from the index date until the earliest of the index treatment end date + 90 days, loss to follow-up, death, or study end date (Figure 2).

For patients in the tofacitinib cohort, any safety event that occurs during the 90-day risk period following discontinuation of tofacitinib will be attributed to tofacitinib, irrespective of

any new medication initiation during the 90-day risk window, respectively. It should be noted that patients in the tofacitinib cohort cannot subsequently contribute observation time to the bDMARD cohort because prior use of tofacitinib is an exclusion criterion for the bDMARD cohort. For patients in the bDMARD cohort, any safety event that occurs during the 90-day risk period following discontinuation of bDMARD will be attributed to bDMARD, irrespective of any new medication initiation (including tofacitinib) during the 90-day risk period, respectively.

Figure 2. Schematic Diagram of 90-day On-Treatment Risk Period



The event counting will begin from the index date. Event time and the censoring time will be calculated from the index date until the event date or the end of the risk period. For subjects who do not experience an outcome of interest within the defined risk period or experience the outcome, but outside the defined risk period, the subject will be censored at the end of the risk period.

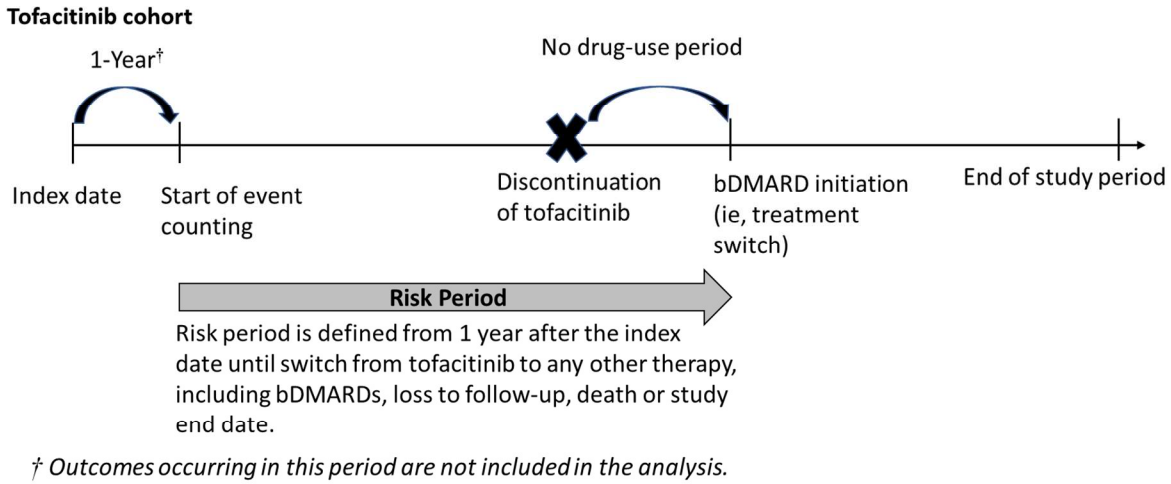
9.7.2. Malignancy outcomes

Malignancy outcomes will be evaluated using a 'Most Recent Exposure Approach'. In this approach, a patient is considered 'at risk' from 1 year after exposure to an index treatment (ie, tofacitinib or bDMARDs) and continues to be 'at risk' until the patient switches to another treatment from the index treatment.

In this approach, the risk period will be defined as starting from 1 year after the index date until the earliest of the index treatment switch date, loss to follow-up, death, or study end date. As a sensitivity analysis, the risk period will also be defined as starting from 18 months after the index date until the earliest of the index treatment switch date, loss to follow-up, death, or study end date. For tofacitinib cohort, the risk period is defined from 1 year after the index date until switch from tofacitinib to any other therapy, including bDMARDs, loss to follow-up, death or study end date (Figure 3; tofacitinib cohort is used as an example). Similarly, among patients indexed to a bDMARD cohort, the risk period is defined from 1 year after the index date until switch to tofacitinib or non-biologic advanced systemic therapy, loss to follow-up, death, or study end date. If a patient discontinues the index treatment and does not switch to another treatment (ie., no drug-use), the patient will still be

considered 'at risk' for developing an outcome under the most recent exposure approach, allowing for the delayed manifestation of a malignancy outcome relative to the time of exposure.

Figure 3. Schematic Diagram of Most Recent Exposure Approach Risk Period



† Outcomes occurring in this period are not included in the analysis.

The event counting will begin from 1 year after the index date (lag-time) in the primary analysis and from 18 months after the index date as a sensitivity analysis. However, the event time and the censoring time will be calculated from the index treatment date until the event date or the end of the risk period. For subjects who do not experience an outcome of interest within the defined risk period or experience an outcome but outside the defined risk period (excluding the outcomes that occur in the event counting lag-time), the subject will be censored at the end of the risk period.

9.7.3. Summarization of Interim Drug Utilization Data

In July 2024, 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 will be summarized.

9.7.4. Interim analysis

After the first five years of the study period, CARRA will develop an interim report summarizing the number of persons enrolled in the cohorts, baseline characteristics of the cohorts, 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 the crude cumulative incidence rates of events and the 95% CI among pcJIA patients treated with tofacitinib and among pcJIA patients treated with approved bDMARDs.

9.7.5. Final analysis

The final analysis of outcomes will provide the rates of events overall and in subgroups defined by baseline characteristics (e.g., sex and age). Pending feasibility, the final comparative analyses that control for sex, age, year of treatment, treatment history, disease severity, comorbidities and other potential confounders, will be conducted using appropriate multivariate, propensity score matching, or inverse probability weighting methods.

For these analyses, the exposure cohorts will be analyzed overall, by previous biologics use and monotherapy and combination therapy with concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). These and potentially other agreed upon strata will be determined a priori and included in SAP filed with Sponsor. Data will be presented as number of events, crude and adjusted incidence rates, as feasible.

The approved SAP will also describe the a priori determined common set of MedDRA codes and MedDRA version to define serious infections, herpes zoster, and CV events (eg, MACE). Comparisons will be made with the classes rather than individual therapies (e.g., tumor necrosis factor-alpha inhibitor [TNFi] and abatacept/tocilizumab). The SAP may modify the plans outlined in the protocol; any major modifications of analyses would be reflected in a protocol amendment.

9.8. Quality control

This study involves secondary data, collected as part of the existing CARRA Registry, which has established quality control practices.

DCRI personnel have trained all clinical sites on appropriate practices for data collection following standard operating procedures. Data are entered using a web-based interface with programmed validity and consistency checks. If incomplete or inaccurate data are subsequently identified, data clarification requests are sent to the sites until the issues are resolved and all required data are complete. In order to ensure full compliance with FDA regulations for acceptable use of electronic records for clinical trials (i.e., 21 CFR Part 11 compliance), detailed audit trails are maintained for all relevant entries or subsequent revisions of data.

9.9. Limitations of the research methods

This study is designed to assess the safety of tofacitinib in patients with pcJIA within the routine clinical practice setting using data from the CARRA Registry, a well-established US-based pediatric rheumatology registry. Strengths of this approach include an incident new user design and systematic prospective collection of safety event data for all participants irrespective of medication exposure.

The CARRA Registry represents a convenience sample of patients from selected pediatric rheumatology centers, and participants are not systematically enrolled. While the CARRA Registry is subject to selected participation, enrolled patients are likely representative of the larger pcJIA patient population in the US (especially those treated with biologics and

targeted small molecules), given the size and geographic distribution of sites and registry patients. CARRA estimates approximately 10-12% of children in the US with JIA are captured in the 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, outcome misclassification, residual confounding and generalizability are of concern when comparing event rates. As a new therapy in the US pcJIA 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 therapies and physical comorbidities that place patients at increased risk for safety events. Biases resulting from channeling may present as increased rates of safety events in tofacitinib-treated patients. Lower safety event rates within internal comparator groups may reflect such channeling. Stratification on or adjustment for key indicators of disease severity, patient characteristics and past therapies will be done to mitigate the effects of channeling.

The pcJIA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing safety events. The rates of safety events and their distribution among patients may have changed over time. However, the comparators in this study will be contemporaneous to tofacitinib-treated patients. Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. The CARRA Registry has an established system of targeted remote data monitoring processes for all critical outcomes, including safety events. Each reported event is systematically reviewed for completeness of essential data elements as well as for clinical accuracy. Events of particular concern are verified via medical records.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves secondary data that exist in anonymized structured format and contain no patient personal information.

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/assent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

The data used for this study will be collected under the CARRA Registry protocol which is approved at each participating site.

The analyses to be conducted fall under the CARRA Registry IRB approval (Duke University IRB Pro00054616). This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. The data used for this study will not involve interaction or interviews with any subjects and the data do not include any personal identifiers (e.g., do not include names, addresses, social security or medical record numbers or other obvious identifiers). The study will use only aggregate, de-identified data and the investigator(s) will report data in a way that subjects cannot be identified.

10.4. 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), 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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator 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.

The study will be registered in the EU PAS before the start of data collection. Interim and final reports will be submitted to FDA. An interim report will summarize the patient characteristics and crude event rates for the first 5 years of the study period. A final dataset, to include up to approximately 9 years of follow-up, will be the basis for the final report. Manuscripts based on specific outcomes of interest may be developed in collaboration with CARRA for external publication purposes.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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